Impact of Sex on Treatment Outcomes, Tolerability, and Patient-Reported Outcomes in First-Line Therapy for Chronic Lymphocytic Leukemia: Results from the CLL13/GAIA Study

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Background

- The phase 3 CLL13/GAIA trial showed superior progression-free survival for venetoclax-obinutuzumab (GV) and GV + ibrutinib (GIV) compared to chemoimmunotherapy (CIT) and venetoclax-rituximab (RV) in fit, previously untreated patients with CLL and without *TP53* aberrations.
- CLL shows marked sex-based disparities in incidence and outcomes:
  - Male predominance (M ≈ 1.8:1), particularly pronounced in patients aged 40–60 years
  - Female (F) sex is an independent favorable prognostic factor with improved overall survival (OS) and treatment response
  - F patients achieve superior outcomes despite lower cumulative treatment exposure and higher toxicity rates
  - Differential response to CIT (Fludarabin, Cyclophosphamid and Rituximab (FCR) vs. Bendamustin and Rituximab (BR)) in first-line setting
  - Sex influences time to relapse after rituximab-based CIT, but not after obinutuzumab-based regimens
- Biological differences contributing to outcome disparities:
  - Lower frequency of high-risk features in F (e.g., unmutated IGHV, *TP53* aberrations)
  - BTK gene located on X chromosome → potential differences in resistance mechanisms to BTK inhibitors
- Here, we present an exploratory analysis of the impact of sex on clinical and patient-reported outcomes (PRO) in the CLL13/GAIA trial.

Methods

- Patients received six cycles of CIT or 12 cycles of RV, GV or GIV, with I discontinued according to undetectable minimal residual disease (uMRD, < 10-4) status.
- Efficacy and PRO were post-hoc analyzed in all randomized patients and safety in all patients with ≥1 dose of study treatment, grouped by sex.
- Categorical and continuous outcomes were compared between sexes using Chi-Square tests and Mann-Whitney U tests. Kaplan-Meier estimates were used to analyze time to event data.
- All reported p values are descriptive without adjustment for multiple testing (test level at 5%).

Results

Patient characteristics

Table 1. Demographics and baseline characteristics according to sex

	Female	Male	Total
All patients [ITT], N	259	667	926
Age group (years), N (%)			
≤ 65	164 (63.3)	433 (64.9)	597 (64.5)
Time between first diagnosis and randomization (months)			
Median	32.2	27.5	29.0
Binet stage, N (%)			
A	90 (34.7)	155 (23.2)	245 (26.5)
Severe constitutional symptoms, N (%)			
Yes	106 (41.1)	257 (38.6)	363 (39.3)
ECOG performance status			
Median (Range)	0 (0-1)	0 (0-2)	0 (0-2)
CIRS score			
Median (Range)	2 (0-7)	2 (0-7)	2 (0-7)
Creatinine clearance (Cockroft-Gault) (ml/min)			
Median	75.6	89.1	85.7
Cytogenetic subgroup by hierarchical order, N (%)			
Deletion 11q	38 (14.7)	124 (18.6)	162 (17.5)
Trisomy 12	36 (13.9)	115 (17.2)	151 (16.3)
No abnormalities	47 (18.1)	153 (22.9)	200 (21.6)
Deletion 13q	138 (53.3)	275 (41.2)	413 (44.6)
IGHV mutational status, N (%)			
Unmutated	135/259 (52.1)	383/666 (57.5)	518/925 (56.0)
Complex karyotype, N (%)			
≥ 5 aberrations	5/244 (1.9)	38/651 (5.8)	43/895 (4.8)
CLL-IPI risk group, N (%)			
High	116/255 (45.5)	339/637 (53.2)	455/892 (51.0)

Patient reported outcomes

- F reported lower physical functioning in the RV and GIV arms and higher symptom burden in the RV arm during early treatment phases.
- No consistent differences in CIT and GV arms.
- Global health status was unaffected by sex.

Efficacy

- **Overall response rates** at month 15 were comparable between F and M (CIT 84.8 vs 79.1%, RV 96.8 vs 92.0%, GV 96.6 vs 95.9%, GIV 97.3 vs 93.0%).
- Significantly higher **complete response rates** in F in the V-containing arms (RV 64.5 vs 42.3%, p=0.003; GV 67.2 vs 52.0%, p=0.044; GIV 75.3 vs 51.9%, p<0.001).
- Statistically significant higher **uMRD rates** at month 15 in peripheral blood in F in the GV arm (94.8 vs 83.6%, p=0.031).
- No significant differences **in survival outcomes** between sexes were observed (Figure 1/2).

Figure 1. Progression-free survival according to sex and treatment arm

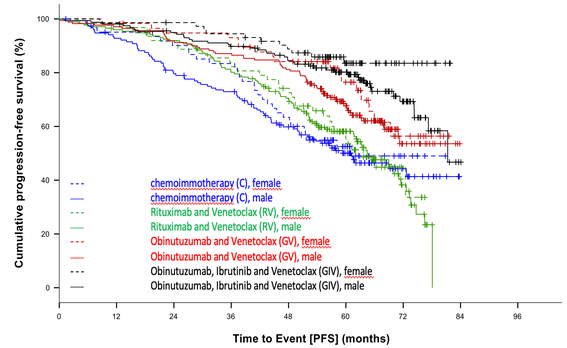
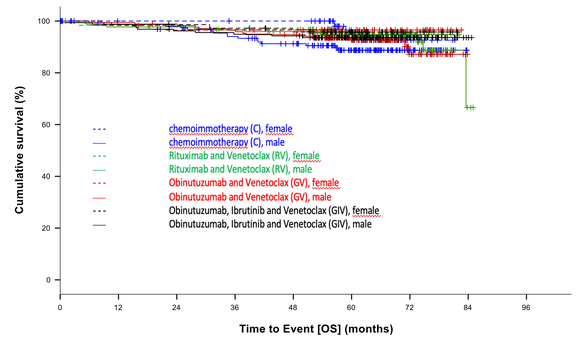


Figure 2. Overall survival according to sex and treatment arm



Safety

Table 2. Median number of adverse events per patient of the safety population (SP, patients with at least one dose of study drug)

	Female	Male	p-value
SCIT [SP], N	**62**	**154**	
Median	9	8	0.118
RV [SP], N	**62**	**175**	
Median	10.5	8.5	0.049
GV [SP], N	**58**	**170**	
Median	11	10	0.114
GIV [SP], N	**73**	**158**	
Median	16	12	<0.001

Early treatment discontinuations did not differ significantly between F and M across treatment arms (CIT 21.0 vs 17.5%, RV 8.1 vs 7.4%, GV 5.2 vs 6.5%, GIV 11.0 vs 15.2%)

F had a lower follow-up adjusted incidence rate of **secondary primary malignancies** in the CIT arm (1.4 vs 5.0 patients per 1000 patient-months, p=0.003), primarily driven by a lower incidence of non-melanoma skin cancer (0.8 vs. 2.8; p=0.033).

Summary/Conclusion

- In the CLL13/GAIA trial, F experienced a higher number of toxicities and reported worse PRO during early treatment phases in selected scales in the RV and GIV arms.
- F achieved higher CRR in V containing arms and a higher uMRD rate in the GV arm, respectively.
- Sex may influence treatment tolerability, depth of remission and patients experience in CLL, warranting further investigation regarding treatment optimization according to sex.

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