Second primary malignancies in patients with chronic lymphocytic leukemia treated with targeted therapies in three phase-III trials of the German CLL Study Group

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INTRODUCTION

Background:
Despite advancements in targeted therapies, second primary malignancies (SPM) remain a major challenge for patients (pts) with chronic lymphocytic leukemia (CLL) contributing to morbidity.
Aims:
The aim of this pooled analysis is to identify risk factors for the development of SPM in pts with treatment-naïve CLL treated in phase-III trials of the German CLL Study Group.

METHODS

Data from phase-III trials (CLL12, CLL13, CLL14) were pooled in 5 cohorts:
•venetoclax-based (ven) (n=677),
•Bruton tyrosine kinase inhibitor (BTKi) (n=170),
•BTKi-ven-based (n=231),
•chemoimmunotherapy (CIT) (n=430)
•untreated (n=320).

SPM (including benign neoplasia) were reported until end of study. Follow-up adjusted incidence rates (FUAIR) of SPM were calculated based on time from study entry to first SPM or last observation while alive and reported per 1,000 patient-months (pt-mo). Multivariable logistic regression was used to identify prognostic factors for SPM development. Overall survival was assessed using Cox regression with SPM as a time-dependent covariate with onset at the time of first SPM from study entry.

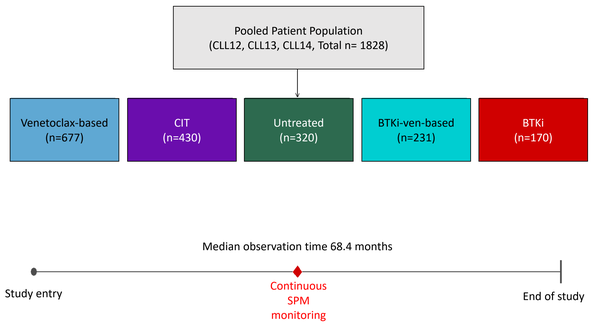


Figure 1. Study population and observation time

RESULTS

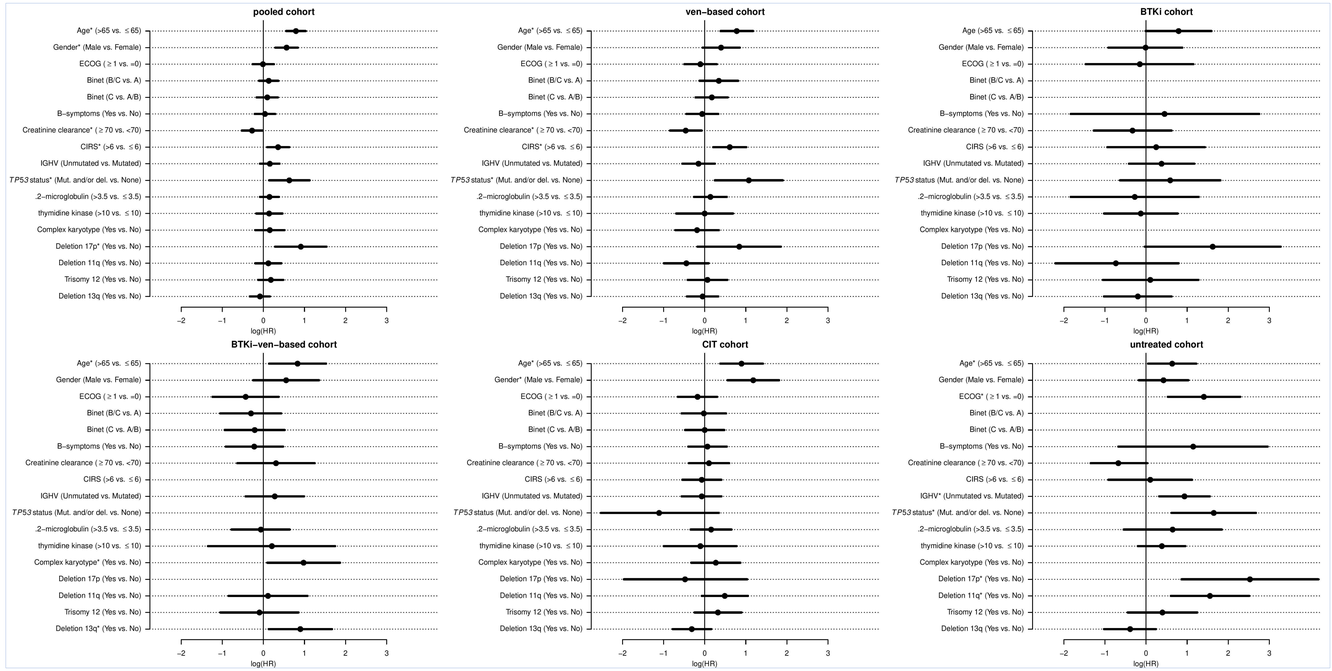


Figure 2. Forest plot of risk factors for each treatment cohort analyzed by univariable analysis. ECOG: Eastern Cooperative Oncology Group; CLL-IPI: international prognostic index for patients with chronic lymphocytic leukemia; *: significant risk factors for SPM in multivariable analysis.

Cohort	Total SPM	Pts with SPM (%)	Overall FUAIR (per 1,000 pt-mo)	Solid	NMSC	Benign	RT	Hem
ven	163	133 (19.6%)	3.5	1.3	1.2	0.6	0.4	0.1
BTKi	35	30 (17.6%)	3.1	1.3	0.5	1.1	0.1	0.0
BTKi-ven	50	40 (17.3%)	3.1	1.3	0.6	0.7	0.2	0.6
CIT	133	89 (20.7%)	3.9	1.4	1.7	0.4	0.5	0.3
untreated	72	57 (17.8%)	3.0	1.3	1.0	0.4	0.3	0.1

Table 1. Details on Follow-up adjusted incidence rates and SPM frequency per treatment cohort

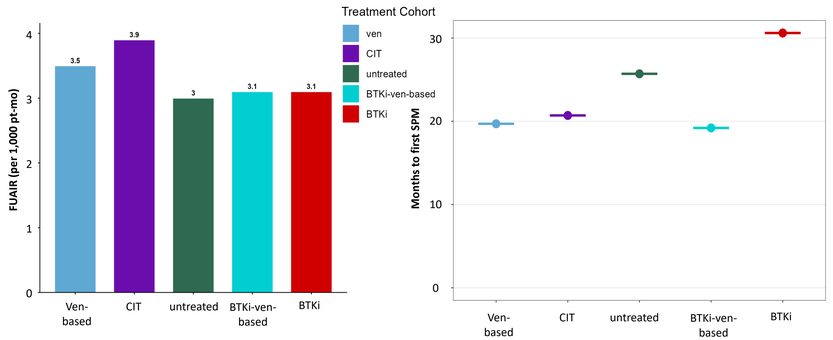
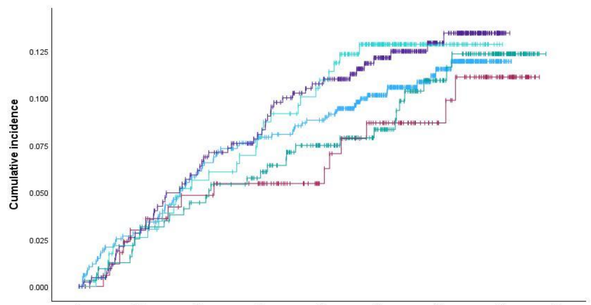


Figure 3A. Follow-up adjusted incidence rates of SPM by treatment cohort

Figure 3B. Median time to first SPM by treatment cohort



Patients at risk		12 MO	24 MO	36 MO	48 MO	60 MO	72 MO	84 MO
Cohort								
Venetoclax-based cohort	677	611	565	539	517	372	191	15
BTKi-based cohort	170	156	147	136	107	92	65	37
Ven-BTKi-based cohort	231	211	198	192	183	127	42	3
CIT cohort	430	375	354	323	293	220	128	15
Untreated cohort	320	298	281	259	223	181	116	70

Figure 4. Cumulative incidence of SPM with death as competing risk factor

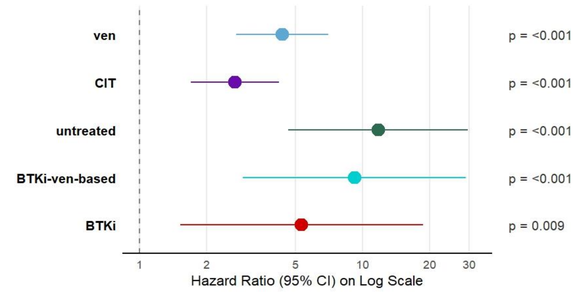


Figure 5. Forest plot of hazard ratios of overall survival for patients with SPM compared to patients without SPM.

CONCLUSIONS

In this pooled analysis of 1,828 CLL pts treated within 3 phase-III trials, SPM occurred in 19.1% of pts with FUAIR ranging from 3.1 to 3.9 per 1,000 pt-mo across various treatment cohorts with the highest incidence in the CIT cohort, and 3.0 in the untreated cohort, suggesting a comparable SPM rate in the untreated and treated cohorts.

Significant risk factors for SPM included **higher age, *TP53* aberration, high burden of comorbidity** and **male gender**. With a mortality rate of 9.1%, SPMs remain a challenge in the era of targeted therapies and a continuous surveillance for SPM is recommended.

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