Second primary malignancies in patients with chronic lymphocytic leukaemia treated with combined targeted agents in four phase-II trials of the German CLL Study Group (GCLLSG)

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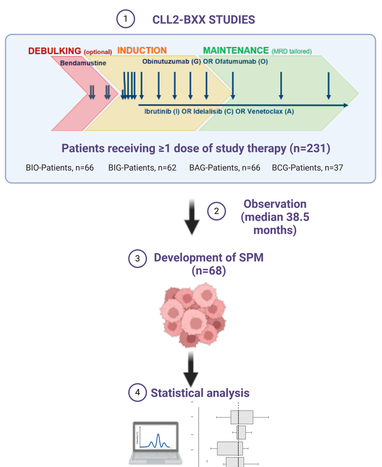
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INTRODUCTION

- Chronic lymphocytic leukemia (CLL) is associated with an increased risk for second primary malignancies (SPMs) due to both CLL- and treatment-related immune dysfunction.
- Targeted therapies have considerably improved the survival of patients with CLL, therefore long-term side effects and comorbidities gain importance.
- The impact of different targeted agents on the risk of SPMs is still unknown.

The aim of this analysis is to assess the frequency and prognostic factors of SPMs in four similar phase-II-trials evaluating different combinations of targeted drugs (including obinutuzumab, venetoclax, ibrutinib, ofatumumab and idelalisib) in an all-comer population with treatment-naïve or relapsed/ refractory CLL.

METHODS



- All pts with **≥1 dose** of antibody/targeted agent from the four so-called "**BXX trials**" combining **ibrutinib** with either **obinutuzumab or ofatumumab** (CLL2-BIG and -BIO), **venetoclax with obinutuzumab** (-BAG) as well as **idelalisib with obinutuzumab** (-BCG). In all four trials, patients with high tumour-burden received **optional bendamustine debulking**.
- Targeted treatment was continued until achievement of a **deep remission or for up to 32 months**.
- Patients participating in >1 of the trials were only evaluated once.
- **Odds ratios** and 95% confidence intervals were calculated by **logistic regression. Multivariate logistic regression** modelling was used to identify **independent prognostic factors** for developing a SPM using forward and backward selection.
- SPMs were reported until end of study.

RESULTS

Logistic regression SPM	Univariate comparison		Odds ratio	95% CI
Stratum	Relapsed/refractory	vs. first-line	1.127	0.590-2.151
Debulking	Debulking	vs. no debulking	1.226	0.565-2.661
Age	**>65**	**vs. ≤ 65**	**3.080**	**1.567-6.053**
Sex	Male	vs. female	1.070	0.531-2.155
Fitness status	**Unfit**	**vs. fit**	**2.445**	**1.265-4.724**
Binet stage	B	vs. A	0.573	0.235-1.394
	C	vs. A	0.980	0.449-2.137
Severe constitutional symptoms	Yes	vs. no	0.964	0.498-1.868
Total CIRS score	**>6**	**vs. ≤ 6**	**4.165**	**1.952-8.888**
ECOG performance status	>0	vs. 0	1.275	0.655-2.483
Creatinine clearance	**< 70 ml/min**	**vs. ≥ 70 ml/min**	**2.304**	**1.193-4.446**
Serum β2-microglobulin	>3.5 mg/dl	vs. ≤ 3.5 mg/dl	2.118	0.987-4.547
Serum thymidine kinase	>10 u/l	vs. ≤ 10 u/l	0.855	0.172-4.263
Cytogenetic subgroup by hierarchical model	del(17p)	vs. del(13q)	0.597	0.231-1.545
	del(11q)	vs. del(13q)	0.389	0.147-1.026
	Trisomy 12	vs. del(13q)	0.519	0.171-1.580
	No abnormalities	vs. del(13q)	0.466	0.183-1.189
IGHV status	Unmutated	vs. mutated	0.773	0.384-1.554
TP53 status	Mutated and/or deleted	vs. none	1.298	0.654-2.577
CLL-IPI risk group	Intermediate	vs. low	2.204	0.254-19.117
	High	vs. low	3.259	0.402-26.449
	Very high	vs. low	3.907	0.466-32.787
Complex karyotype	CKT	vs. NCKT	0.992	0.471-2.091
Duration of CLL	>10 years	vs. ≤ 10 years	1.816	0.904-3.647
Number of previous treatments	1	vs. 0	0.795	0.328-1.928
	≥ 2	vs. 0	1.424	0.685-2.961
Previous treatment with chemo(immune)therapy	Yes	vs. no	1.202	0.630-2.295
Study treatment	Venetoclax-containing treatment	vs. Ibrutinib-containing treatment	1.821	0.868-3.823
	Idelalisib-containing treatment	vs. Ibrutinib-containing treatment	2.140	0.892-5.134

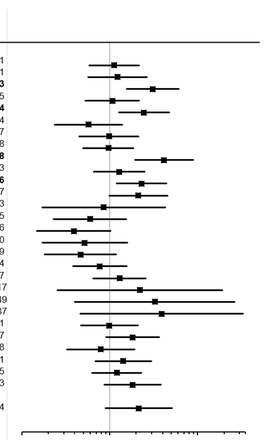
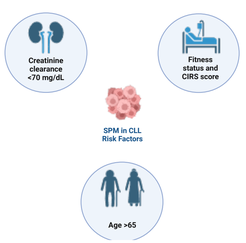


Figure 1: Forest Plot showing odds ratios (including 95% confidence intervals [CI] for development of a SPM in subgroups

Sixtysix, 62, 66 and 37 evaluable pts in BIO, BIG, BAG and BCG, respectively, were analyzed. The median age was **64** years; 115 (49.8%) had relapsed CLL with a median of 2 prior therapies, 71.1% of 228 evaluable pts had an unmutated IGHV, 30.3% of 228 pts a *TP53* deletion/mutation and 39% of 187 pts a complex karyotype. The median observation time was **38.5 months** (BIO: 37.7, BIG: 37.7, BAG: 66.6, and BCG: 38.1 months).
Overall, **68 SPM** occurred among 46 of the 231 pts, resulting in an incidence rate of 5.9 cases per 1000 patient-months. The incidence rates for non-melanoma skin cancers, solid tumours, benign tumours and melanomas were 3.0, 2.3, 0.7, and 0.3 cases per 1000 patient-months. Additionally, eleven Richter's transformations, but no other haematological malignancies were observed.
Several factors were associated with a higher risk for SPMs (see figure 1), only **age >65 years**, and higher burden of comorbidities with a **cumulative illness rating scale (CIRS) score >6** were independent prognostic factors in a multivariate analysis. No significant differences were seen regarding *TP53* deletion/mutation and IGHV status, number of prior therapies, prior chemo(immune)therapy or administration of bendamustine debulking in the study.

CONCLUSION

- higher age (>65 years), creatinine clearance (<70 mg/dL), fitness status and burden of comorbidity (CIRS >6) were risk factors for the development of a SPM.
- No significant differences were seen for prior CLL therapy (bendamustine debulking, number, type) and genetic risk factors.



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