UNIKLINIK KÖLN
Department I of Internal Medicine
University Hospital of Cologne

DEUTSCHE CLL STUDIENGRUPPE

Cardiovascular Toxicity of Contemporary First-Line CLL Treatment Regimens: A Pooled Analysis of the German CLL Study Group

Florian Simon[1], Rudy Ligtvoet[1], Moritz Fürstenau[1], Othman Al-Sawaf[1], Henriette Huber[2], Julia von Tresckow[3], Thomas Nösslinger[4], Christian B. Poulsen[5], Thomas Illmer[6], Lothar Müller[7], Ursula Vehling-Kaiser[8], Liliya Sivcheva[9], Javier Loscertales[10], Kathleen Jentsch-Ullrich[11], Holger Hebart[12], Christof Schneider[13], Eugen Tausch[13], Stephan Stilgenbauer[13], Sandra Robrecht[1], Anna-Maria Fink[1], Kirsten Fischer[1], Arnon P. Kater[14], Carsten U. Niemann[15], Michael Hallek[1], Barbara Eichhorst[1], Petra Langerbeins[1]

[1]University Hospital Cologne, Germany · [2]Städtisches Klinikum Karlsruhe · [3]Katholisches Klinikum Bochum · [4]Hanusch Krankenhaus Wien · [5]Zealand University Hospital, Roskilde · [6]Hematology Practice, Dresden · [7]Practice for Oncology and Hematology, Leer · [8]Outpatient Clinic, Landshut · [9]Multiprofile Hospital, Vratsa · [10]Hospital Universitario de La Princesa, Madrid · [11]Hämatologie und Onkologie, Magdeburg · [12]Stauferklinikum, Mutlangen · [13]Ulm University · [14]Cancer Center Amsterdam · [15]Rigshospitalet, Copenhagen

INTRODUCTION

- Current first-line options for CLL include BTK inhibitors, venetoclax-based combinations and in certain situations chemoimmunotherapy (CIT)
- While the distinct side-effect profile of BTKis regarding cardiac, bleeding and hypertensive events is well-established, data on other treatment classes – including placebo - remains sparce
- This analysis aims to evaluate the cardiovascular toxicity profile of contemporary first-line CLL treatment regimen across organ classes from pooled data of multicenter trials by the German CLL Study Group (GCLLSG)

PATIENTS AND METHODS

Study Design
- Pooled analysis of 4 GCLLSG first line trials: CLL12 (ibrutinib vs. placebo in asymptomatic, high-risk CLL), CLL13 (GVe vs. RVe vs. GIVe vs. FCR/BR in fit patients), CLL14 (GVe vs. GCIb in unfit patients), CLL2-GIVe (phase II, GIVe in TP53 mut. CLL)
- Pooling of 4 different treatment groups Ven+CD20ab, BTKi (ibrutinib), Triplet (Ven+Ibru+CD20ab), CIT (FCR/BR/GCIb) and placebo

Observation frame
- First dose of study medication until end of treatment plus 28 days

Events of interest
- Coded per MedDRA SOC/PT, grading by CTC
- Cardiac, vascular, bleeding and thrombotic events combined as CV events and separately

Statistics
- Case- and patient-level incidence and severity of CV events
- Exposure-adjusted incidence rates per 1,000 patient months
- Kaplan-Meier estimates of time to first CV event
- Univariate logistic regression for baseline factors associated with CV events

RESULTS – PATIENTS AND TREATMENT

Table 1. Treatment Groups & Baseline Characteristics

Characteristic	Venetoclax +CD20ab*	Ibrutinib	Triplet	CIT	Placebo
N (%)	677 (39.4)	170 (9.9)	272 (15.8)	430 (25)	168 (9.8)
Age (years)					
Median (IQR)	65 (57–72)	64 (55–69)	61 (54–69)	67 (59–73)	65 (56–70)
Sex, n (%)					
Male	488 (72.1)	125 (73.5)	182 (66.9)	295 (68.6)	120 (71.4)
ECOG performance status, n (%)					
= 0	425 (62.8)	151 (88.8)	191 (70.2)	256 (59.5)	148 (88.1)
= 1	219 (32.3)	19 (11.2)	68 (25.0)	146 (34.0)	20 (11.9)
≥ 2	33 (4.9)	0 (0.0)	13 (4.8)	28 (6.5)	0 (0.0)
Binet stage, n (%)					
A	165 (24.4)	169 (99.4)	72 (26.5)	105 (24.4)	168 (100.0)
B	259 (38.3)	1 (0.6)	101 (37.1)	156 (36.3)	0 (0.0)
C	253 (37.4)	0 (0.0)	99 (36.4)	169 (39.3)	0 (0.0)
Severe constitutional symptoms, n (%)					
Yes	276 (40.9)	4 (2.4)	112 (41.2)	197 (45.8)	3 (1.8)
Creatinine clearance (mL/min)					
< 70, n (%)	222 (32.9)	32 (18.9)	58 (21.3)	157 (36.8)	37 (22.0)
Total CIRS score					
Median (IQR)	4 (1–7)	3 (1–5)	2 (1–4)	5 (2–8)	3 (1–4)
Range	0–23	0–14	0–8	0–28	0–12
> 6, n (%)	184 (27.2)	19 (11.2)	4 (1.5)	175 (40.7)	19 (11.3)
CIRS Heart (organ class)					
≥ 2, n (%)	90 (13.3)	12 (7.1)	17 (6.3)	69 (16.0)	12 (7.1)
≥ 1 (any cardiac), n (%)	166 (24.5)	26 (15.3)	39 (14.3)	106 (24.7)	17 (10.1)
CIRS Blood Pressure (organ class)					
≥ 2, n (%)	200 (29.5)	49 (28.8)	53 (19.5)	143 (33.3)	44 (26.2)
≥ 1 (any hypertension), n (%)	309 (45.6)	96 (56.5)	103 (37.9)	201 (46.8)	89 (53.0)
CIRS Vascular (organ class)					
≥ 2, n (%)	49 (7.2)	6 (3.5)	15 (5.5)	46 (10.7)	6 (3.6)
≥ 1 (any vascular), n (%)	116 (17.1)	18 (10.6)	24 (8.8)	99 (23.0)	19 (11.3)

CD20ab = anti-CD20 monoclonal antibody (rituximab, obinutuzumab)

- 1,717 patients overall included from 4 first-line trials
- Median age was similar across cohorts (range 61–67 yrs)
- CLL12 cohorts (placebo and ibrutinib monotherapy) included only **Binet A patients** — lower CIRS, but **highest prevalence of baseline hypertension** (CIRS BP ≥ 1: 56.5% ibrutinib, 53.0% placebo).
- The **BTKi+Ven triplet cohort was the youngest** (median age 61 yrs) and **least comorbid** (median CIRS 2; only 1.5% > 6) — reflecting CLL13/CLL2-GIVe eligibility criteria favoring fit patients.

RESULTS – EVENT RATES AND SURVIVAL

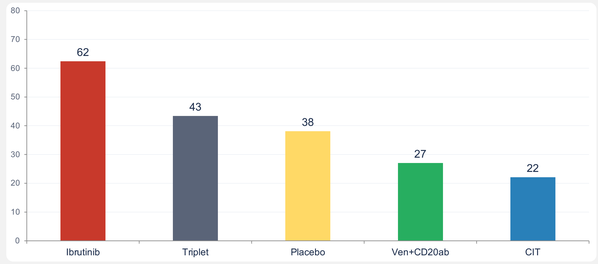

Figure 1: Proportion of Patients with Any CV Event (%)

- Ibrutinib and Triplet arms showed highest rate of CV events on a patient-level

Table 2. CV Event Rates by Treatment Group

Group	Any CV	Cardiac	Grade ≥3 Cardiac	Exp-adj rate*
Ibrutinib	**62.4%**	29.4%	12.9%	27.7
Triplet	43.4%	17.3%	6.3%	**54.9**
Placebo	38.1%	17.3%	6.5%	20.4
Ven+CD20ab	27.0%	8.0%	1.8%	32.9
CIT	22.1%	6.7%	2.3%	41.0

**per 1,000 patient-months*

- Treatment durations differ substantially across arms (5.5–36.1 mo). Cumulative rates favor short-duration regimens; exposure-adjusted rates better capture intensity of CV risk per unit time.

Table 3: Median CV Event-Free Survival

Group	Median	12-mo rate (95% CI)
Ibrutinib	17.0 mo	58.0% (50.2–65.8%)
Triplet	18.7 mo	57.8% (51.9–63.8%)
Placebo	58.1 mo	79.7% (73.4–86.0%)
Venetoclax+CD20ab	Not reached	72.5% (69.1–76.0%)
CIT	Not reached	74.7% (69.6–79.5%)

- Ibrutinib-containing arms showed the shortest event-free survival, with placebo serving as a benchmark for occurrence of regular or non-agent-associated cardiovascular risk in untreated CLL

RESULTS – EVENT SUBTYPES & PREDICTORS

Table 4: Patient-Level Rate (% of patients)

SOC	Ven +CD20ab	Ibrutinib	Triplet	CIT	Placebo
Cardiac	8.0%	29.4%	17.3%	6.7%	17.3%
Atrial fib.	1.3%	15.3%	8.8%	1.9%	1.8%
Vascular	17.9%	37.6%	28.3%	14.0%	19.6%
Hypertension	7.7%	18.2%	12.1%	4.0%	7.7%
Bleeding/Haematoma	2.2%	17.1%	12.1%	1.6%	5.4%
Thrombotic (PE/DVT)	1.2%	0%	1.1%	0.7%	1.2%
CNS (stroke/TIA)	0.7%	2.4%	1.1%	0.7%	3.6%

Table 5: Exposure-Adjusted Rate (per 1,000 pt-months)

SOC	Ven +CD20ab	Ibrutinib	Triplet	CIT	Placebo
Cardiac	8.6	9.5	18.0	12.9	9.6
Atrial fib.	1.5	3.8	8.0	2.3	1.8
Vascular	18.1	13.7	28.6	22.7	7.0
Hypertension	7.5	5.0	9.5	6.0	2.3
Bleeding/Haematoma	1.9	6.0	10.6	2.3	2.0
Thrombotic (PE)	0.6	0	0.5	0.3	0.2
CNS (stroke/TIA)	0.6	0.6	0.8	0.9	1.3

Figure 2: Univariate Predictors of CV Events

Ibrutinib
Baseline hypertension
OR 2.56 (CI 1.35–4.83, *p = 0.004*)

Triplet
CIRS heart ≥1
OR 3.07 (1.50–6.27, *p = 0.002*)
CIRS overall >3
OR 1.78 (1.07–2.95, *p = 0.026*)

No significant associations between baseline CV comorbidities and CV events in placebo, venetoclax+CD20ab, or CIT cohorts.

CONCLUSIONS

- Class-associated CV toxicity of ibrutinib-containing regimens confirmed; ibrutinib monotherapy shows highest cumulative CV event rate (62.4%).
- Bleeding events scale with BTKi exposure (highest in ibrutinib and triplet arms), reflecting a class effect distinct from cardiac toxicity.
- Venetoclax-based regimens show lower CV burden (27%) — supporting them as a preferred option for patients with elevated CV risk.
- CV risk assessment should be an integral component of first-line treatment selection in CLL.

For correspondence: florian.simon@uk-koeln.de