POST-SAN DIEGO 2023
Novità dal Meeting della Società Americana di Ematologia

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Verona
Palazzo della Gran Guardia
15-16-17 Febbraio 2024

COORDINATORI
Angelo Michele Carella
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3° SESSIONE
LEUCEMIA LINFATICA CRONICA

Terapia di prima linea

Antonio Cuneo

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DA SEICENTO ANNI GUARDIAMO AVANTI.

Disclosures of Antonio Cuneo

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					X	X	
Astrazeneca					X	X	
Beigene					X	X	
Janssen					X	X	
Lilly						X	

Overall survival advantage with target therapy	Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR ---------- First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 55-Month Follow-up from the Glow Study ---------- ELEVATE-TN 6-Yr Update: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive CLL	BEST OF ASH Hillmen abs #631 ---------- Moreno C abs #634 ---------- Sharman JP Abs#636
PFS advantage with longer follow-up and by genetic subgrouos	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 Broad Superiority of Zanu Over BR Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With TN CLLwithout del(17p)	Furstenau M abs#635 Ramakrishnan V Abs#1902
Adherence to treatment	Impact of Ibrutinib Dose Reduction on Duration of Therapy in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Shadman M Abs#269
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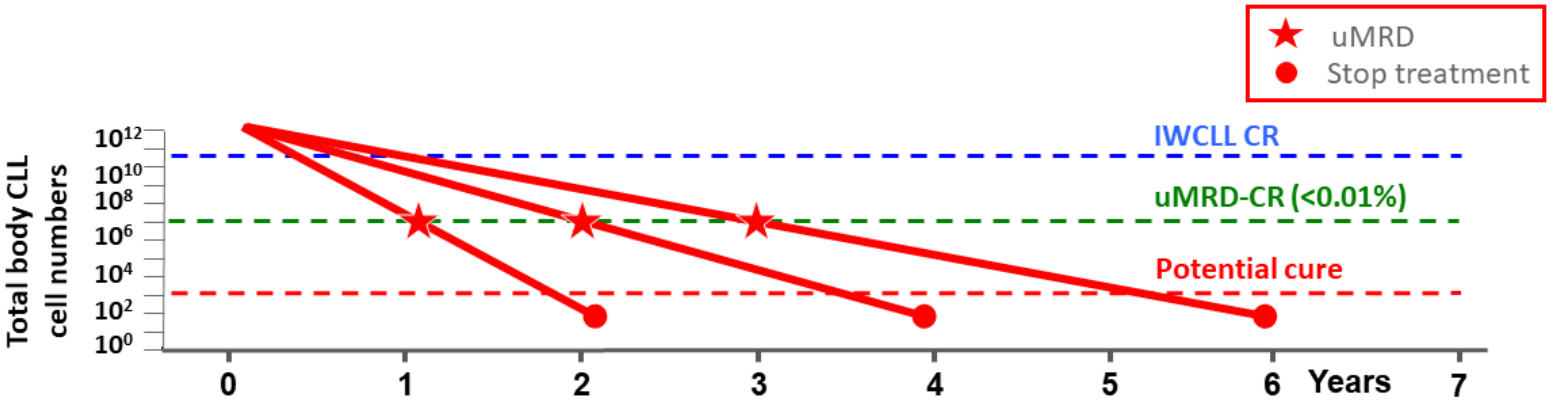
Flair

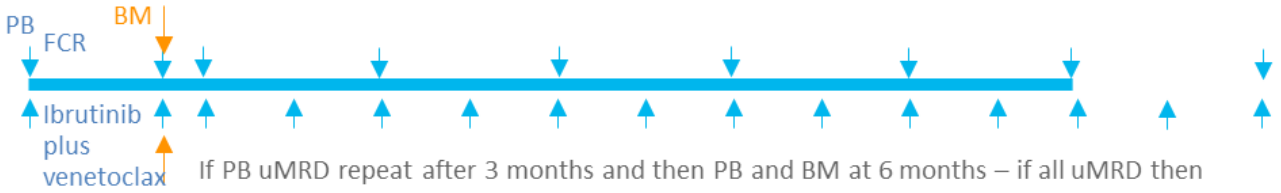
FCR vs I+V: Trial design

Best of ASH

Stopping rules for ibrutinib + venetoclax in Flair



Testing schedule
(Central lab, MRD flow, uMRD <1 CLL cell in 10^4)



If PB uMRD repeat after 3 months and then PB and BM at 6 months – if all uMRD then first PB uMRD result is time to uMRD

Stopping rules
2 to 6 years ibrutinib plus venetoclax
Double time after uMRD

Restart treatment if detectable MRD prior to Year 6

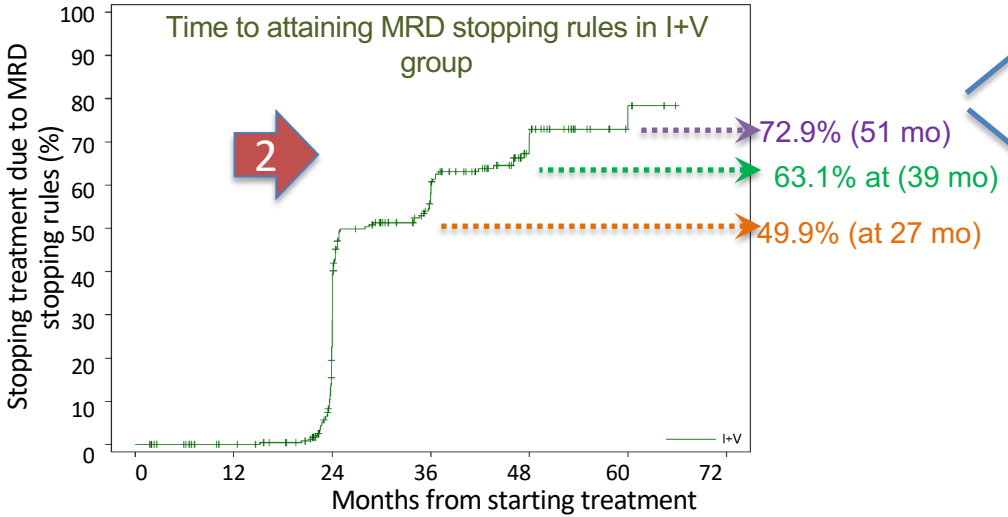
Flair

iwCLL response and MRD stopping rules

iwCLL Responses

1	Complete Response/CRi		Overall Response		BM uMRD
	9 months	Anytime	9 months	Anytime	Anytime
FCR	49%	71.5%	76.4%	83.7%	40.3%
I+V	59.2%	92.3%	86.5%	95.4%	61.9%

Odds ratio: 1.51 P<0.05 Odds ratio: 2.0 P<0.005



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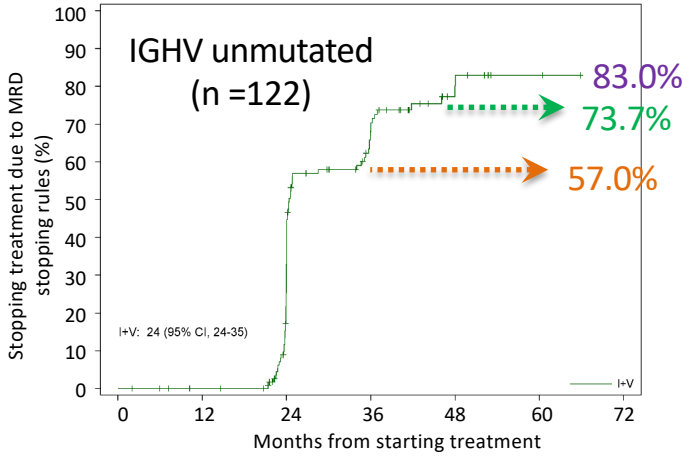

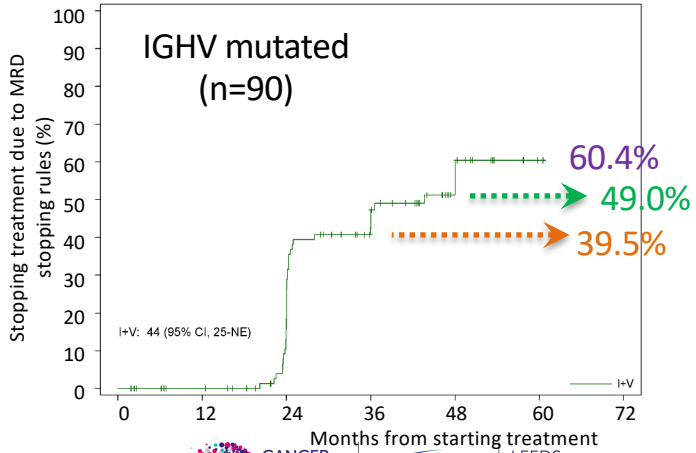

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Hillmen *et al.*, Abstract 631, ASH 2023

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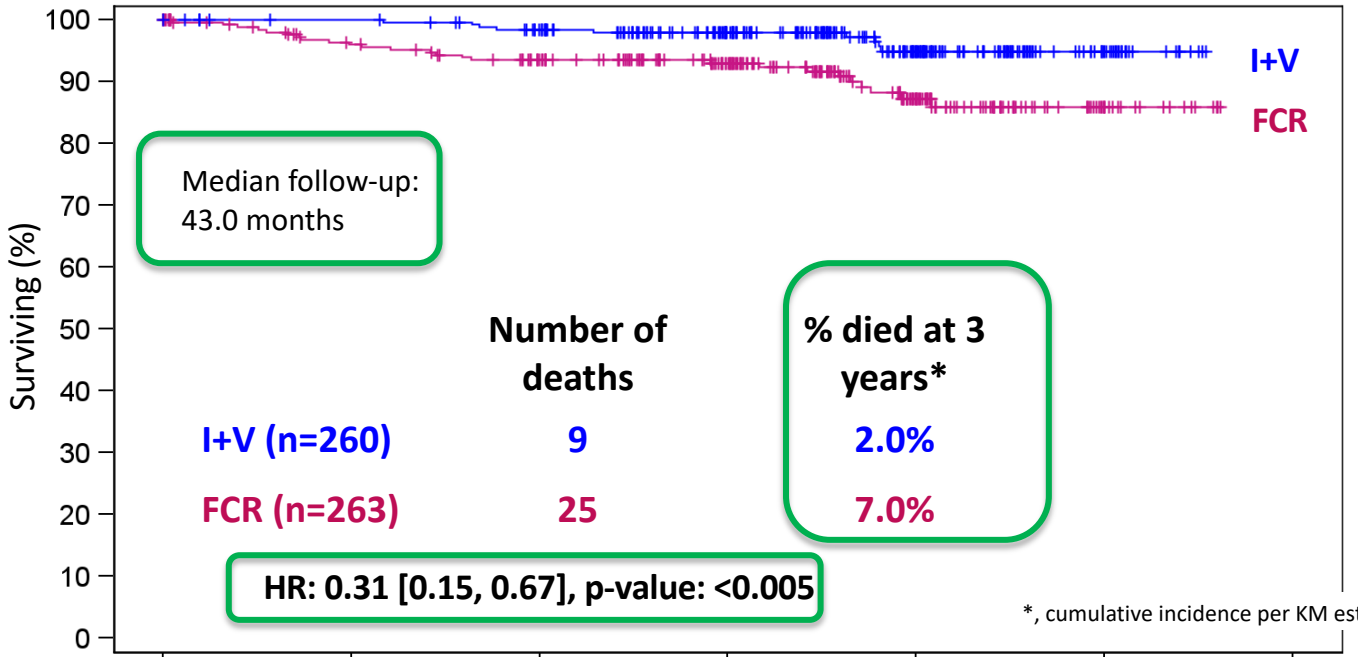
Overall Survival in FCR versus I+V



No. at risk	0	12	24	36	48	60	Months 72
I+V	260	254	240	185	100	22	0
FCR	263	234	213	166	79	15	0

National Cancer Research Institute

Hillmen *et al.*, Abstract 631, ASH 2023

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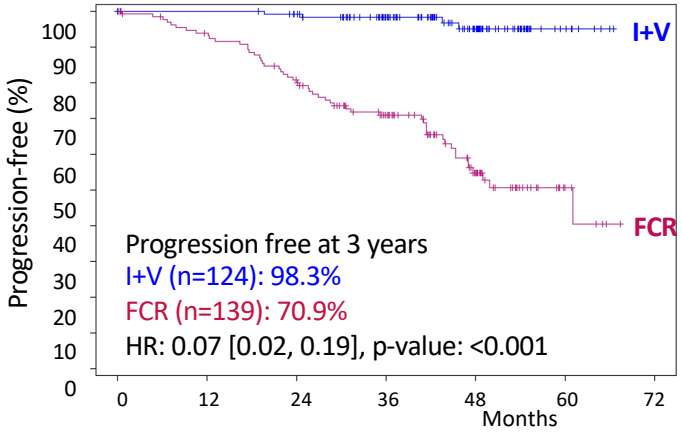
Flair

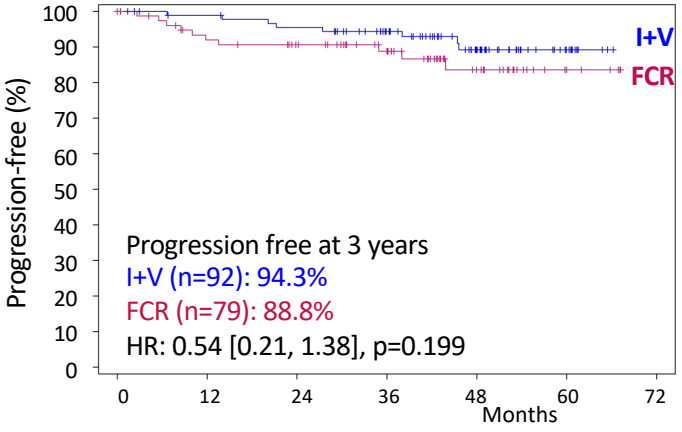
Outcome by IGHV mutation status

IGHV unmutated (excl. Subset 2)

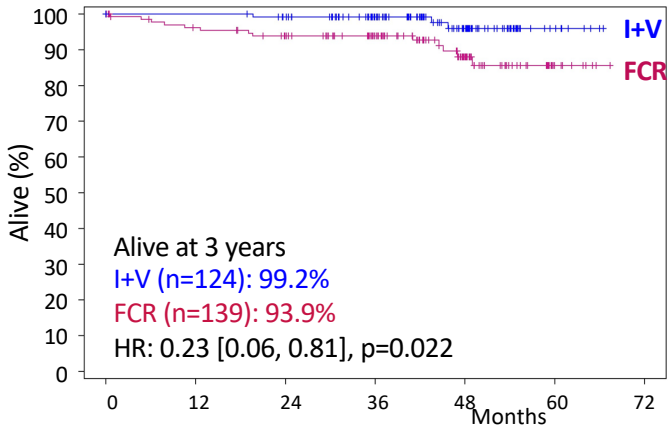
IGHV mutated (excl. Subset 2)

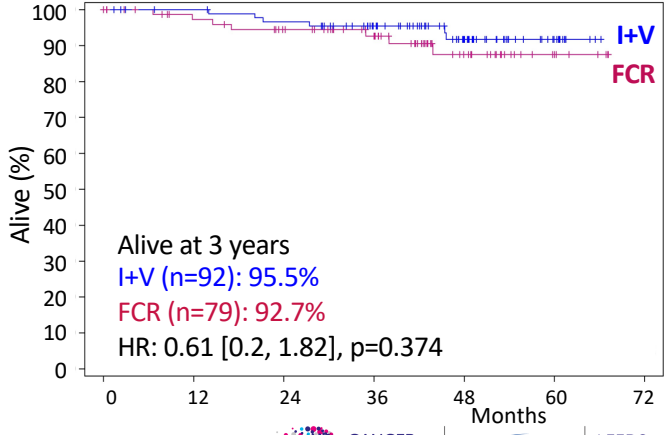
Progression Free





Overall Survival





Hillmen *et al.*, Abstract 631, ASH 2023

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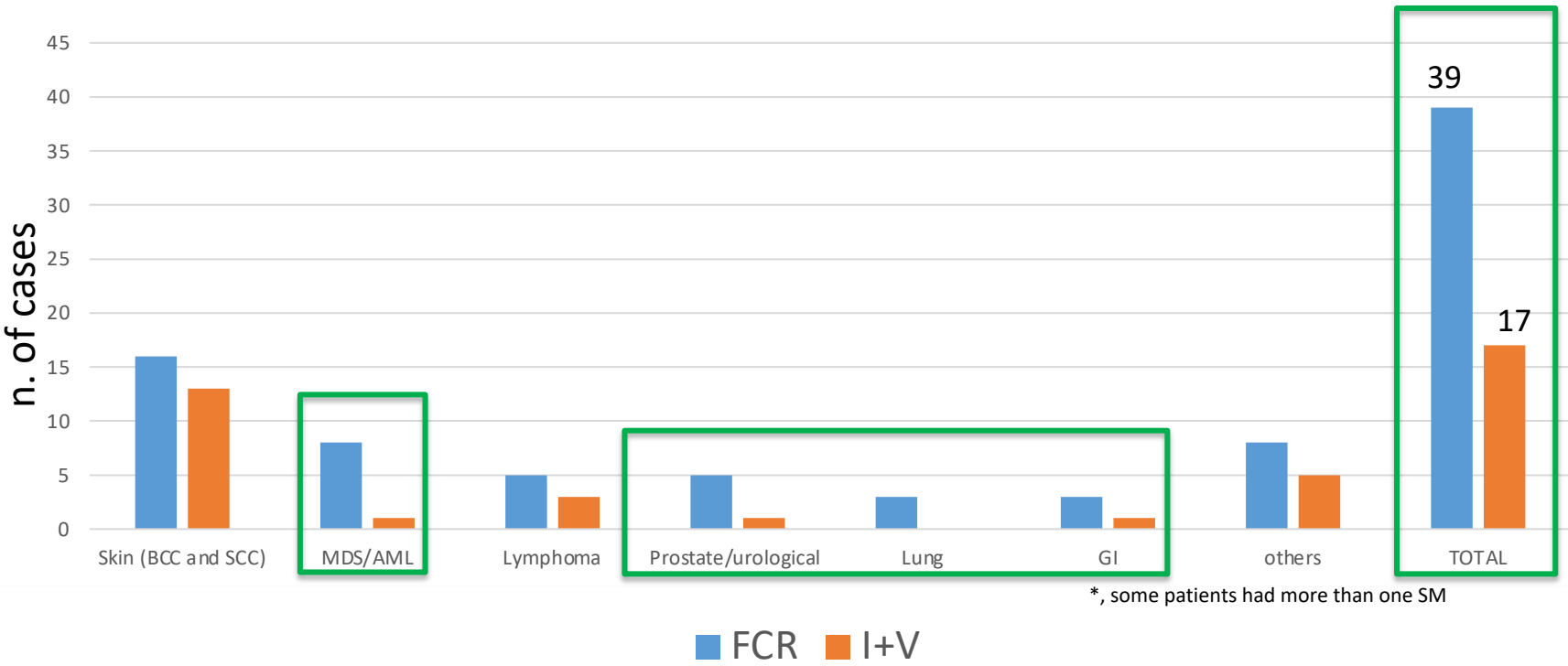
Safety and Toxicity: Deaths

	FCR	I+V
Infection	7	1
Sudden/Cardiac	2	3*
COVID-19	2	2
Richter's transformation	2	1
Non-haem malignancy	2	1
Allogeneic SCT – infection	1	0
Allogeneic SCT – GvHD	1	0
Disease progression	1	0
Hemorrhage	1	0
Lymphoma	1	0
Treatment related MDS/BMF	3	0
Total:	**23**	**8**

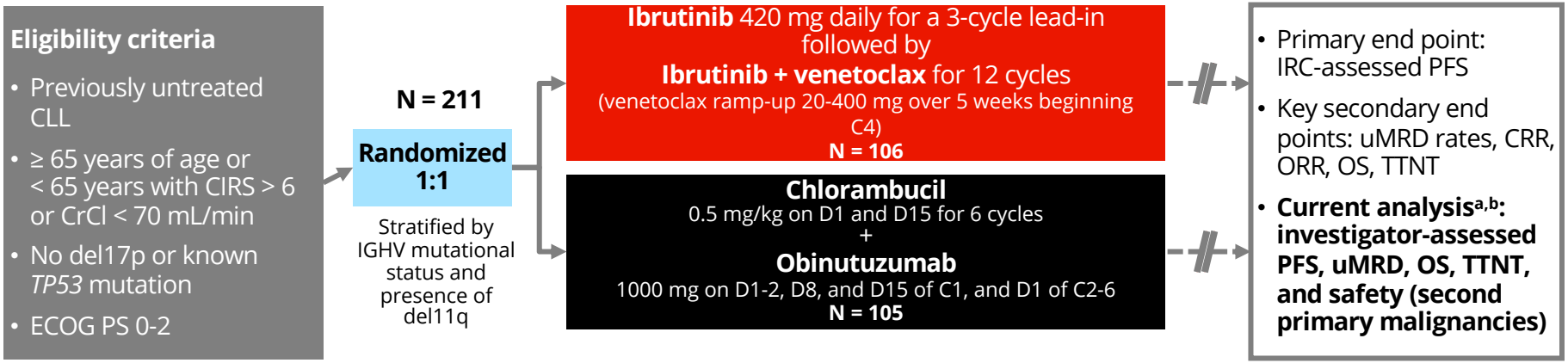
***2 of the 3 cardiac deaths in the I+V arm occurred after treatment was completed (35 days and 411 days later)**

Malignancies
(n. of cases in 239 pts treated with FCR and 252 with I+V)



Data from Hillmen P et al, Abstract 631, ASH 2023

GLOW: Phase 3 Study (NCT03462719) Evaluating Fixed-Duration Ibr+Ven in Previously Untreated CLL



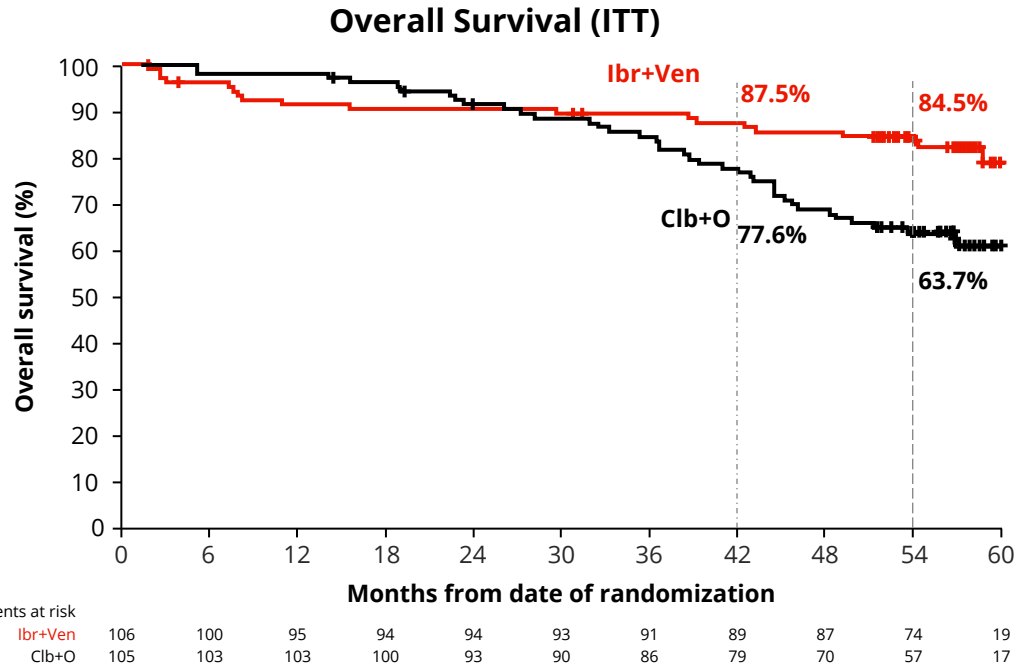
- **Here we present the updated clinical outcomes at a median follow-up of 57.3 months (range, 1.7-65.2)**
- Baseline characteristics (presented previously) were generally balanced between arms and reflective of an elderly and/or comorbid population[1]
- IGHV status at baseline:
  - Ibr+Ven arm: mIGHV 30.2%, uIGHV 63.2%
  - Clb+O arm: mIGHV 33.3%, uIGHV 54.3%

[a]All *p* values are nominal. [b]uMRD in PB by NGS via Clonoseq assay.
C, cycle (28 days); CIRS, Cumulative Illness Rating Scale score; CrCl, creatinine clearance; CRR, complete response rate; D, day; ECOG PS, Eastern Cooperative Oncology Group performance status; IRC, independent review committee; mIGHV, mutated IGHV; NGS, next-generation sequencing; ORR, overall response rate; PB, peripheral blood; uIGHV, unmutated IGHV.

1. Niemann CU, et al. *Lancet Oncol*. 2023;24:1423-1433.

Presented by G. Follows at the 65th ASH Annual Meeting and Exposition; December 9-12, 2023; San Diego, CA, USA

GLOW: Ibr+Ven Remained Associated With Improved Overall Survival at 57 Months of Study Follow-up



- **Ibr+Ven reduced the risk of death by 55%** versus Clb+O
  - HR 0.453 (95% CI, 0.261-0.785); *p* = 0.0038
- Estimated 54-month OS rates:
  - **84.5%** for patients treated with Ibr+Ven
  - **63.7%** for patients treated with Clb+O

p value is nominal.

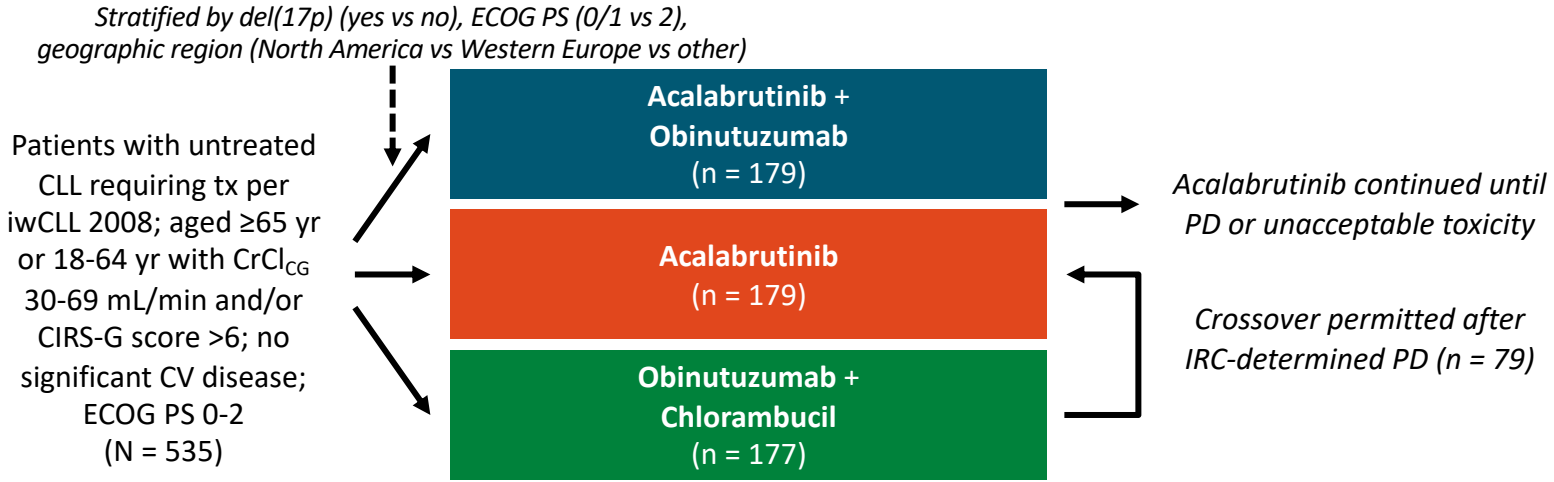
GLOW: Summary of Deaths

	Ibr+Ven (n = 106)		Clb+O (n = 105)	
Total number of deaths	**19**		**39**	
Reasons for deaths	**On treatment**	**Post randomized treatment[a]**	**On treatment**	**Post randomized treatment[a]**
Infection related[b]	1	3	1	13
SPM	1	1	0	7
Cardiac	2[c]	0	0	4
Sudden/unknown	2	3	0	4
Progressive disease	0	1	0	2
Vascular disorders	1	2	0	3
Other	0	2	1	4
Total	**7**	**12**	**2**	**37**

[a]Either before or after initiation of subsequent antileukemic therapy. [b]Including 2 and 7 deaths due to COVID-19 in the Ibr+Ven and Clb+O arm, respectively. [c]1 patient had 3 causes of death: tachy-brady syndrome, cardiac failure, and pneumonia. SPM: second primary malignancies

ELEVATE-TN 6-Yr Update: Study Design

- International, randomized, open-label phase III trial (data cutoff: March 3, 2023)



- **Primary endpoint:** IRC-assessed PFS for A + O vs O + Clb; after interim analysis, PFS assessed by investigator
- **Secondary/other endpoints:** IRC-assessed PFS for A vs O + Clb; investigator-assessed PFS, ORR (IRC-assessed and investigator-assessed), TTNT, OS, uMRD, and safety

ELEVATE-TN 6-Yr Update: Patient Disposition

Characteristic, n (%)	A + O (n = 179)	A (n = 179)	O + Clb (n = 177)
Treated with ≥1 dose of study drug	179 (100.0)	178 (99.4)	169 (95.5)
Randomized but not treated	0	1 (0.6)	8 (4.5)
Treatment status*			
▪ Ongoing	96 (53.6)	84 (46.9)	0
▪ Completed regimen	-	-	136 (76.8)
▪ Discontinued regimen	83 (46.4)	95 (53.1)	41 (23.2)
— Death	5 (2.8)	16 (8.9)	3 (1.7)
— AE	38 (21.2)	32 (17.9)	25 (14.1)
— Acalabrutinib-related AE	9 (5.0)	13 (7.3)	-
— Lost to follow-up	2 (1.1)	1 (0.6)	1 (0.6)
— CLL progressive disease	10 (5.6)	25 (14.0)	4 (2.3)
— Consent withdrawal	5 (2.8)	3 (1.7)	6 (3.4)
— Investigator's discretion	13 (7.3)	13 (7.3)	0
— Other	10 (5.6)	5 (2.8)	2 (1.1)
Duration of Follow-up, mo (range)	**A + O**	**A**	**O + Clb**
Median follow-up	74.6 (1.7-89.0)	74.5 (0.1-88.8)	73.3 (0.0-88.8)

Sharman. ASH 2023. Abstr 636.

Slide credit: clinicaloptions.com

ELEVATE-TN 6-Yr Update: OS

OS	A + O (n = 179)	A (n = 179)	O + Clb (n = 177)
Median OS, mo	NR	NR	NR
6-yr OS rate, %	87	79	80

Comparison of OS Among Arms	HR (95% CI)	*P* Value
A + O vs O + Clb	0.62 (0.39-0.97)	.0349
A vs O + Clb	0.89 (0.58-1.35)	.5868
A + O vs A	0.69 (0.44-1.09)	.1220

Sharman. ASH 2023. Abstr 636.

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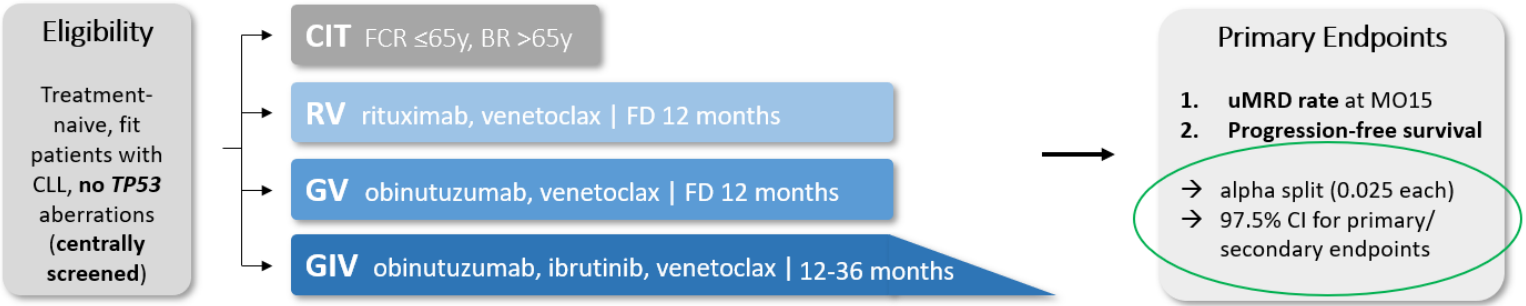
Four-year follow-up

Study Design - GAIA/CLL13



Key patient characteristics

Randomized patients (=ITT population): **n= 926**

Median age:	**61 years** (range: 27-84)
Median CIRS score:	**2** (range: 0-7)
Unmutated IGHV:	**56%** of all patients
Complex karyotype:	**17%** of all patients

Follow-up analysis (data cut-off: 01/2023)

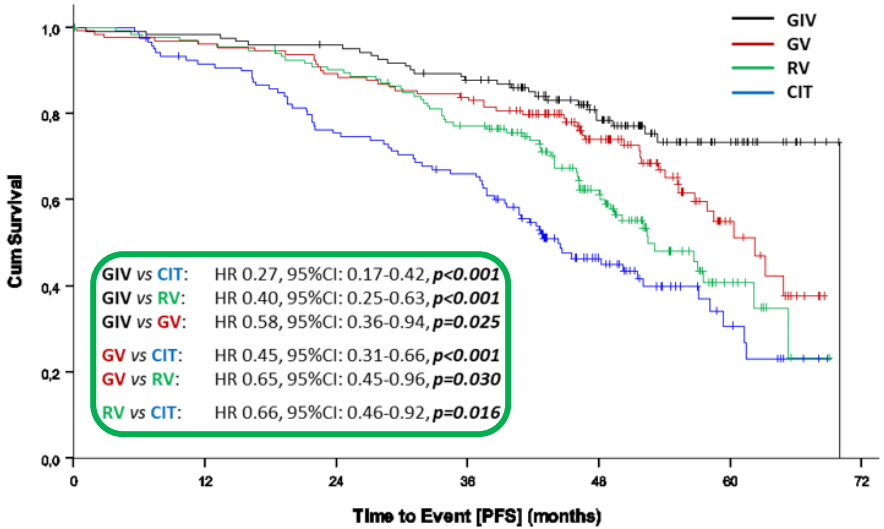
Median observation time
50.7 months (IQR: 44.6-57.9)

Median observation time after end of treatment
40.7 months (IQR: 34.5-47.9)

Furstenau M abs#635

Efficacy – PFS

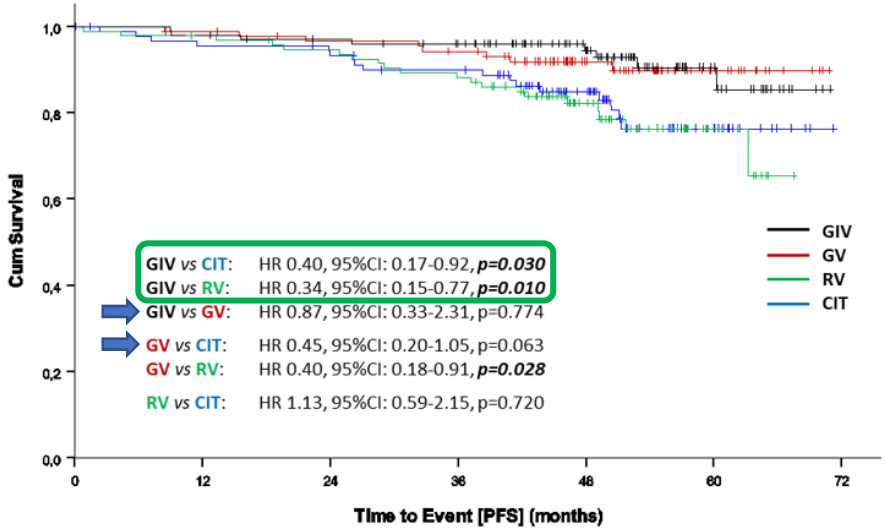
PFS, patients with **unmutated IGHV**



Pts at risk

CIT	131	108	89	77	34	9
RV	134	128	119	100	56	10
GV	130	125	116	108	67	15
GIV	123	121	117	105	65	24

PFS, patients with **mutated IGHV**

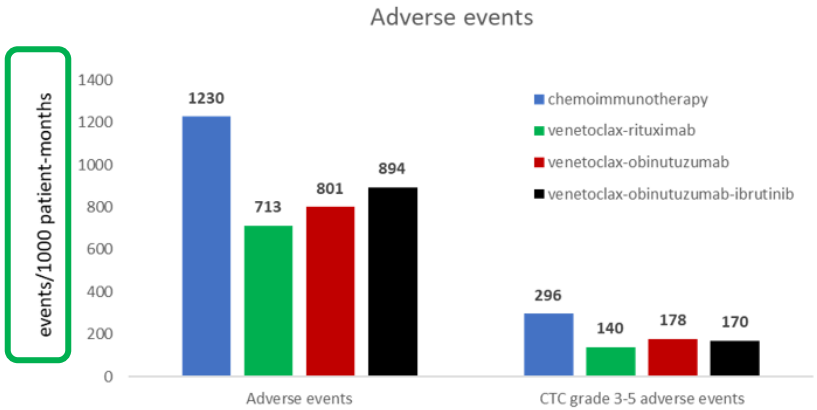


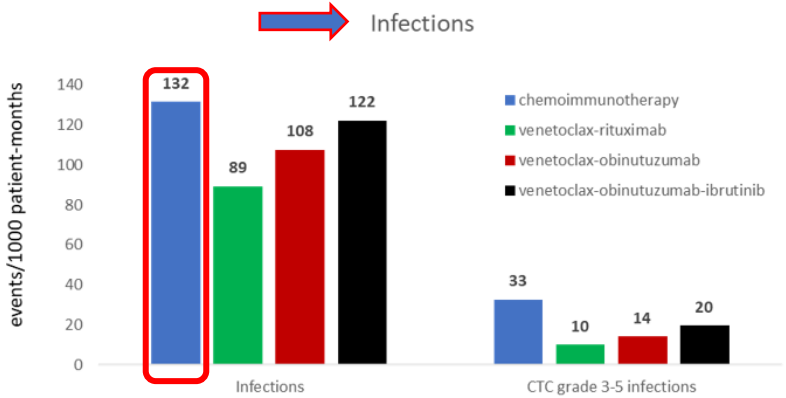
Pts at risk

CIT	95	86	83	78	50	15
RV	95	92	88	82	47	11
GV	89	87	83	80	48	15
GIV	101	99	95	90	60	20

Furstenau M abs#635

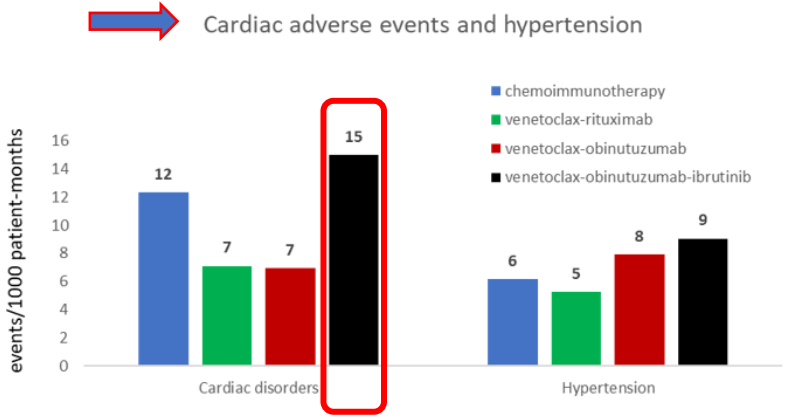
Safety





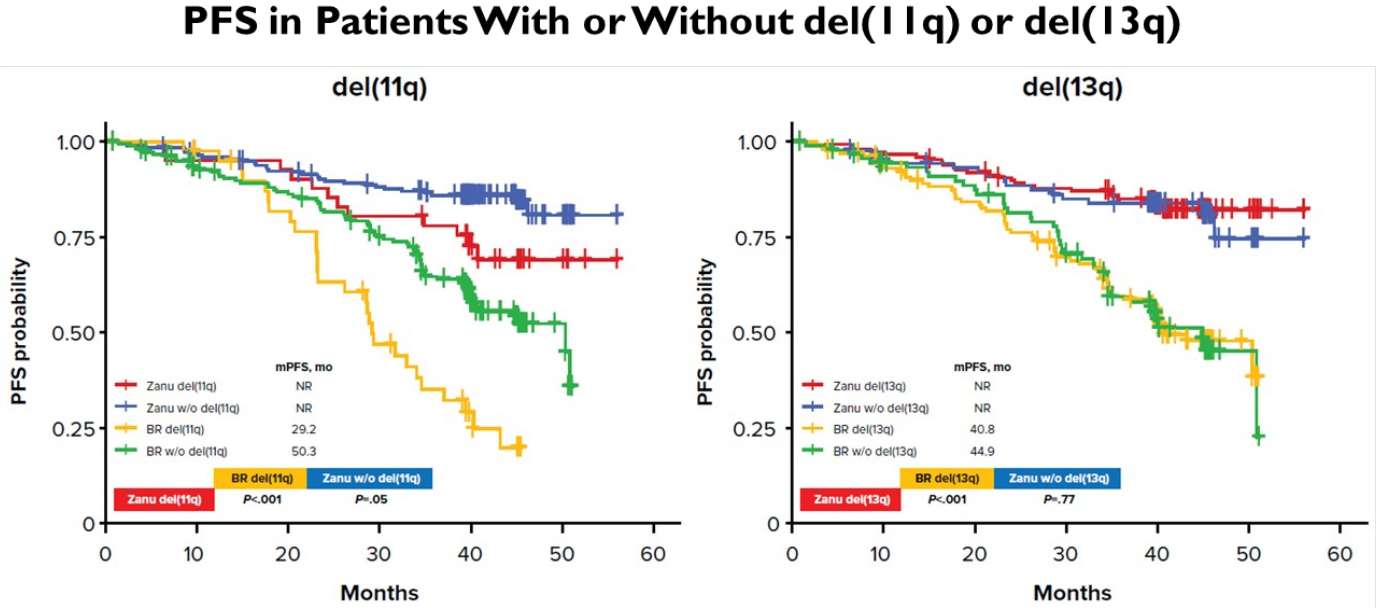
Exposure-adjusted incidence rates

- Events per 1000 patient-months **based on the treatment period**
- Treatment period = **start of treatment until the end of treatment + 84 days** or until start of first subsequent treatment whichever occurred first



Furstenau M abs#635

BROAD SUPERIORITY OF ZANUBRUTINIB OVER BENDAMUSTINE + RITUXIMAB ACROSS MULTIPLE HIGH-RISK FACTORS: BIOMARKER SUBGROUP ANALYSIS IN THE PHASE 3 SEQUOIA STUDY IN PATIENTS WITH TREATMENT-NAIVE CHRONIC LYMPHOCYTIC LEUKEMIA/SMALL LYMPHOCYTIC LYMPHOMA WITHOUT DEL(17P)



Xu L et al. Poster presented at ASH 2023; poster number: 1902

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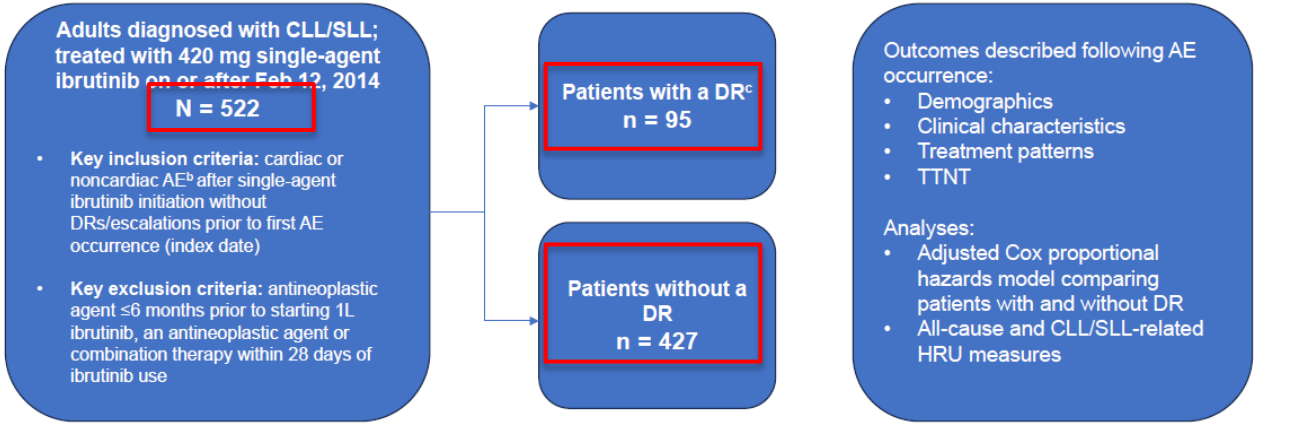
Impact of ibrutinib dose reductions on duration of therapy in CLL

Assessment of real-world impact of DR following an AE on duration of therapy and HRU

- Data from previously untreated adults with CLL/SLL were analyzed using EMRs from the Concert AI database
- AEs[a] were identified based on ICD-9-CM and ICD-10-CM codes; causality cannot be determined



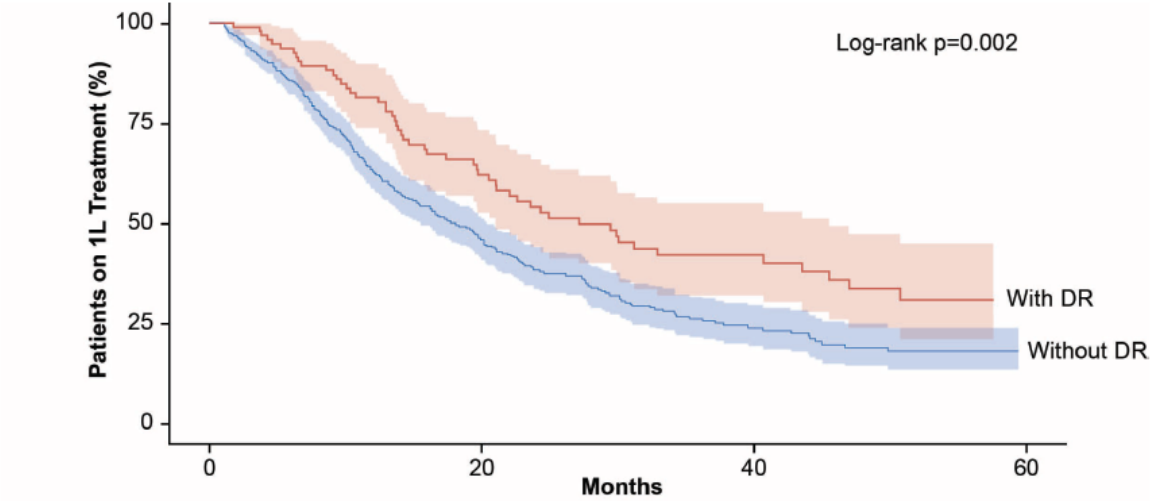
HRU, health resource utilization; ICD-9-CM, International Classification of Diseases 9 Clinical Modification; ICD-10-CM, International Classification of Diseases 10 Clinical Modification.
[a]Study was not intended to assess AEs or report their frequency. [b]Cardiac AEs included atrial fibrillation, ischemic heart disease, heart failure, hypertension, and cardiomyopathy. Noncardiac AEs included febrile neutropenia, anemia, neutropenia, pancytopenia, thrombocytopenia, diarrhea, abdominal pain, musculoskeletal pain, rash, and pneumonia. [c]Defined as a dose lower than 420 mg per day on or after the date of first AE post-ibrutinib initiation, per pharmacy records.

Baseline and demographic characteristics were generally well-balanced between groups

Older age and shorter time between first AE and end of follow-up were more frequent in the DR group (P = 0.003 and P = 0.002), respectively

Shadman M Abs#269

Median TTNT[a] was significantly longer in patients with DR[b]



Patients at risk				
With DR	95	48	22	7
AEs	0	33	47	52
Without DR	427	143	37	10
AEs	0	206	262	270

[a]TTNT defined as the time from the first incident AE to either the first dose of a next treatment (any nonibrutinib therapy), a gap of >90 days between the last day of supply of ibrutinib and the date of the next ibrutinib claim, or death. [b]DR defined as a dose lower than 420 mg per day on or after the date of first AE post-ibrutinib initiation, per pharmacy records.

Overall survival advantage with target therapy	Ibrutinib Plus Venetoclax with MRD-Directed Duration of Treatment Is Superior to FCR and Is a New Standard of Care for Previously Untreated CLL: Report of the Phase III UK NCRI FLAIR --- First-Line Fixed-Duration Ibrutinib Plus Venetoclax (Ibr+Ven) Versus Chlorambucil Plus Obinutuzumab (Clb+O): 55-Month Follow-up from the Glow Study --- ELEVATE-TN 6-Yr Update: Acalabrutinib ± Obinutuzumab vs Obinutuzumab + Chlorambucil in Treatment-Naive CLL	BEST OF ASH Hillmen abs #631 --- Moreno C abs #634 --- Sharman JP Abs#636
PFS advantage with longer follow-up and by genetic subgrouos	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 Broad Superiority of Zanu Over BR Across Multiple High-Risk Factors: Biomarker Subgroup Analysis in the Phase 3 SEQUOIA Study in Patients With TN CLLwithout del(17p)	Furstenau M abs#635 Ramakrishnan V Abs#1902
Adherence to treatment	Impact of Ibrutinib Dose Reduction on Duration of Therapy in Patients with Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma	Shadman M Abs#269
New combinations	Combination Treatment with Sonrotoclax (BGB-11417), a Second-Generation BCL2 Inhibitor, and Zanubrutinib, a Bruton Tyrosine Kinase Inhibitor, is Well Tolerated and Achieves Deep Responses in Patients with Treatment-Naive Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma: Data From an Ongoing Phase 1/2 Study	Tam C abs#327

Background

BGB-11417-101

- **Sonrotoclax is a BH3 mimetic that binds and inhibits BCL2**
  - **>10-fold potency compared to venetoclax[1] and better in vitro activity against BCL2 mutations, including BCL2 G101V**
  - **Demonstrated high selectivity**
  - **Short half life (4 hours)**
- The combination of BCL2 and BTK inhibitors has shown synergistic activity in preclinical CLL models[2-5]
- Ibrutinib with venetoclax in patients with CLL/SLL is effective, however, toxicities can limit use[6]
- Zanubrutinib is highly effective in patients with TN and RR CLL including those with high-risk diseases[7,8]
  - Zanubrutinib demonstrated a superior efficacy and safety profile, including less cardiovascular toxicity than ibrutinib in R/R CLL[8]
- **Here, we report preliminary results of the BGB-11417-101 trial (NCT04277637) in patients with TN CLL/SLL treated with sonrotoclax in combination with zanubrutinib**

1. Hu N, et al. AACR 2020. Abstract 3077; 2. Soumerai JD, et al. Lancet Haematol. 2021;8(12):e879-e890; 3. Hillmen P, et al. J Clin Oncol. 2019;37(30):2722-2729; 4. Jain N, et al. N Engl J Med. 2019;380(22):2095-2103; 5. Wierda WG, et al. J Clin Oncol. 2021;39(34):3853-3865; 6. Kater AP, et al. NEJM Evidence. 2022;1(7); 7. Tam CS, et al. Lancet Oncol. 2022;23(8):1031-1043; 8. Brown JR, et al. Clin Lymphoma Myeloma Leuk. 2022;22:S266.
BCL2=B-cell lymphoma 2, BTK=Bruton tyrosine kinase, CLL=chronic lymphocytic leukemia, R/R=relapsed/refractory, SLL=small lymphocytic lymphoma, TN=treatment naïve.
Tam CS, et al. Oral Presentation at ASH 2023; abstract number 327.

Author Conclusions

BGB-11417-101

- Sonrotoclax 160 or 320 mg in combination with zanubrutinib 320 mg QD was safe and well tolerated
  - **106/107 of patients remain on treatment**
  - **No TLS and no cardiac toxicity were observed**; low rates of GI AEs (predominantly Grade 1)
  - The most commonly reported grade ≥3 AE was **neutropenia** which was mostly transitory, and not requiring dose modifications or interruptions
- Efficacy was promising in this all-comer TN CLL/SLL population
  - ORR was 100% (32% CR and 58% PR) – **response rates improved with time**
  - High blood MRD negativity by Week 24, with deepening response by Week 48 of combination therapy
  - No PFS events were observed as of the data cut off
- Based on these data, **sonrotoclax 320 mg was selected for the phase 3 study in combination with zanubrutinib in patients with TN CLL**

AE=adverse event, CLL=chronic lymphocytic leukemia, GI=gastrointestinal, MRD=minimal residual disease, ORR=overall response rate, PFS=progression-free survival, QD=once daily, RP2D=recommended phase 2 dose, TLS=tumor lysis syndrome, TN=treatment-naïve.
Tam CS, et al. Oral Presentation at ASH 2023; abstract number 327.

First line therapy at ASH 2023: Salient take home messages

I+V (FLAIR + GLOW)	OS advantage in fit and unfit patients as compared with CIT (FCR or Chlor + O) Well tolerated with no unexpected toxicities - Excess of SPM with CIT (FCR) I+V regimen reimbursed as per Glow study (15 months)
Acalabrutinib + obinutuzumab (ELEVATE-TN 6 yr f.u.)	OS advantage compared with Chlor+O (not reimbursed in Italy)
Venetoclax-based regimens (4-yr f.u. GAIA)	uIGHV: significantly longer PFS with GIV vs GV (p=0.025) GIV: more cardiac events CIT (FCR/BR): more infections
Ibrutinib: dose reduction	Longer time on treatment in pts with dose reduction (hypothesis generating study)
BCL2i sonrotoclax + Zanubutinib (Phase I-II)	Safe, well tolerated and effective (short follow-up) – Phase 3 ongoing