POST-ORLANDO 2025
Novità dal Meeting della Società Americana di Ematologia

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Torino
Centro Congressi Lingotto
19-21 febbraio 2026

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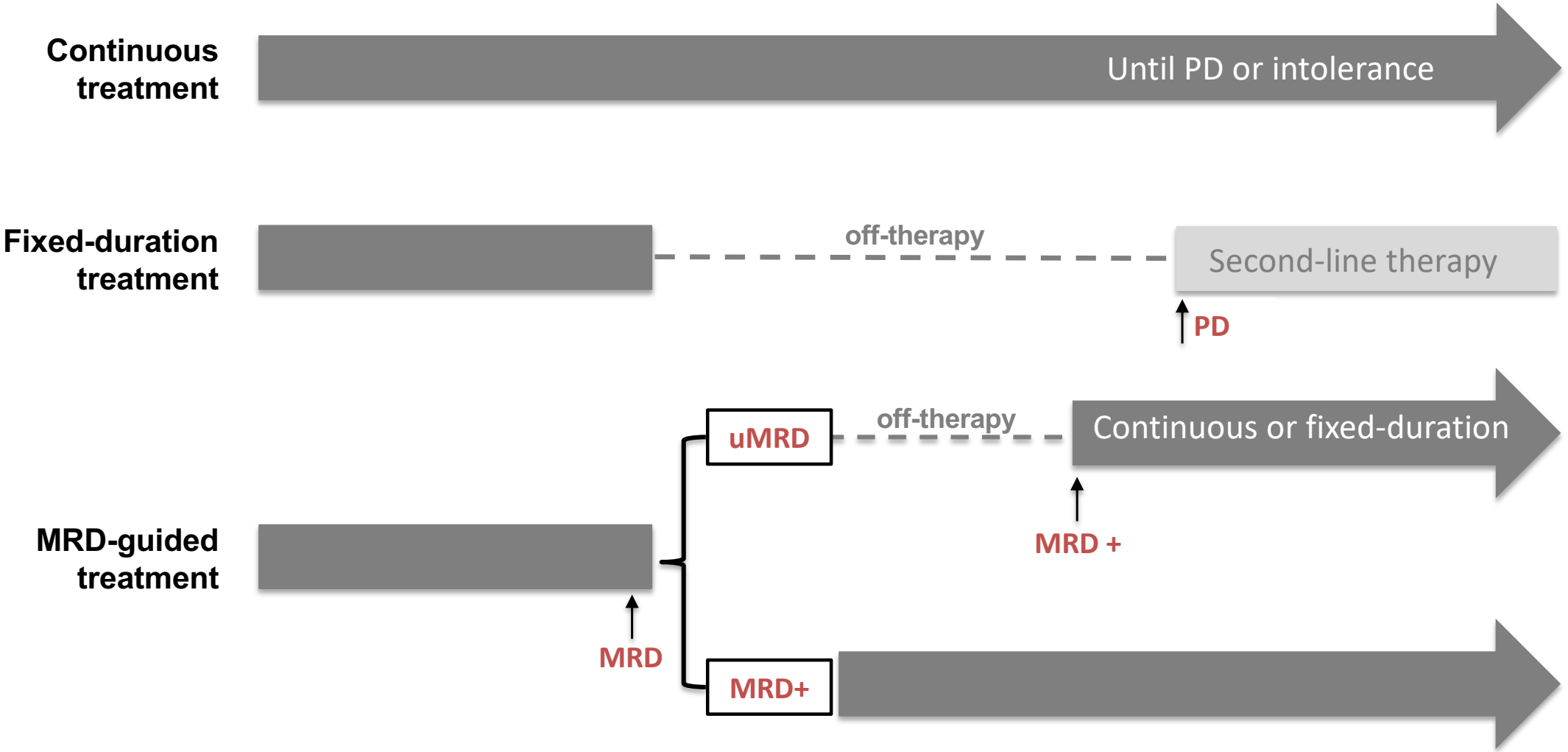
Sessione 3 Leucemia Linfatica Cronica: Trattamento di prima linea

Università degli Studi dell'Insubria, Varese

DICHIARAZIONE MARTA COSCIA

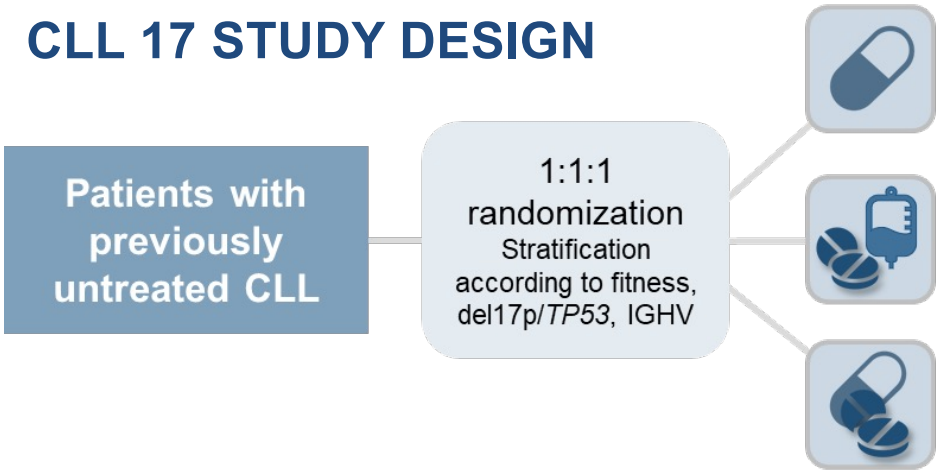
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie	X				X	X	
AstraZeneca					X	X	
Behring						X	
Beigene					X	X	
GSK	X		X			X	
Johnson&Jhonson	X				X	X	

TREATMENT PARADIGMS CURRENTLY UNDER INVESTIGATION IN TN CLL



Fixed-duration versus continuous targeted treatment for previously untreated chronic lymphocytic leukemia: Results from the randomized CLL17 trial

CLL 17 STUDY DESIGN

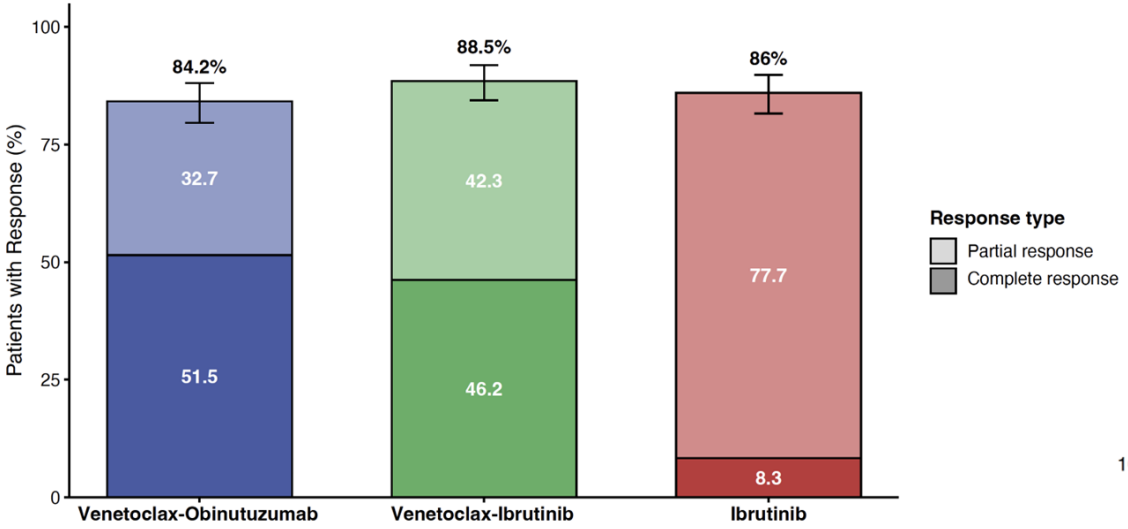


Primary objective: Testing PFS non-inferiority of **fixed-duration venetoclax-obinutuzumab (VO) versus continuous ibrutinib (I)** and **fixed-duration venetoclax-ibrutinib (VI) versus continuous I**

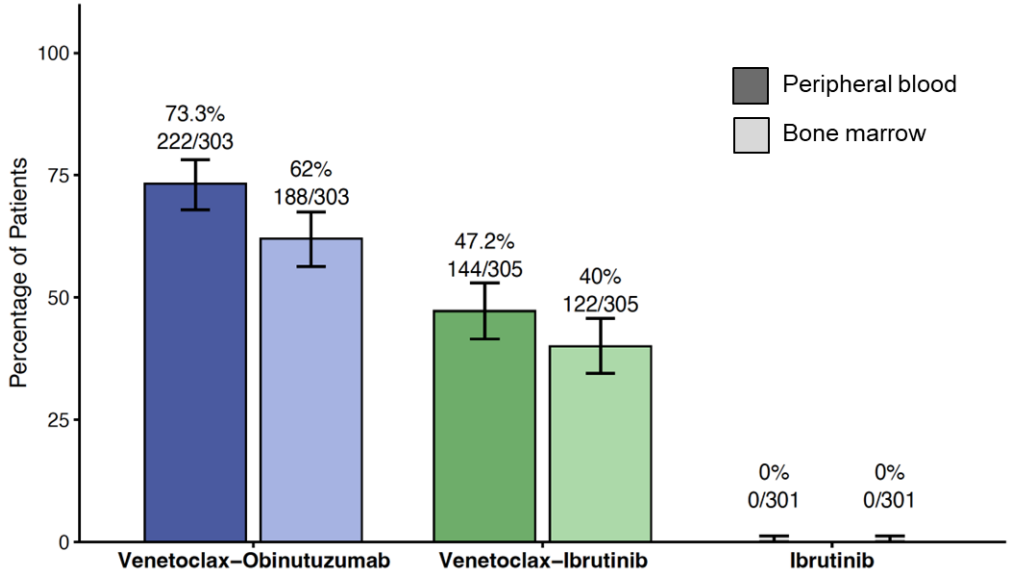
Al-Sawaf O et al., oral presentation, Plenary Scientific session, ASH 2025

RESPONSE TO TREATMENT

iwCLL response at final restaging (C18D1)

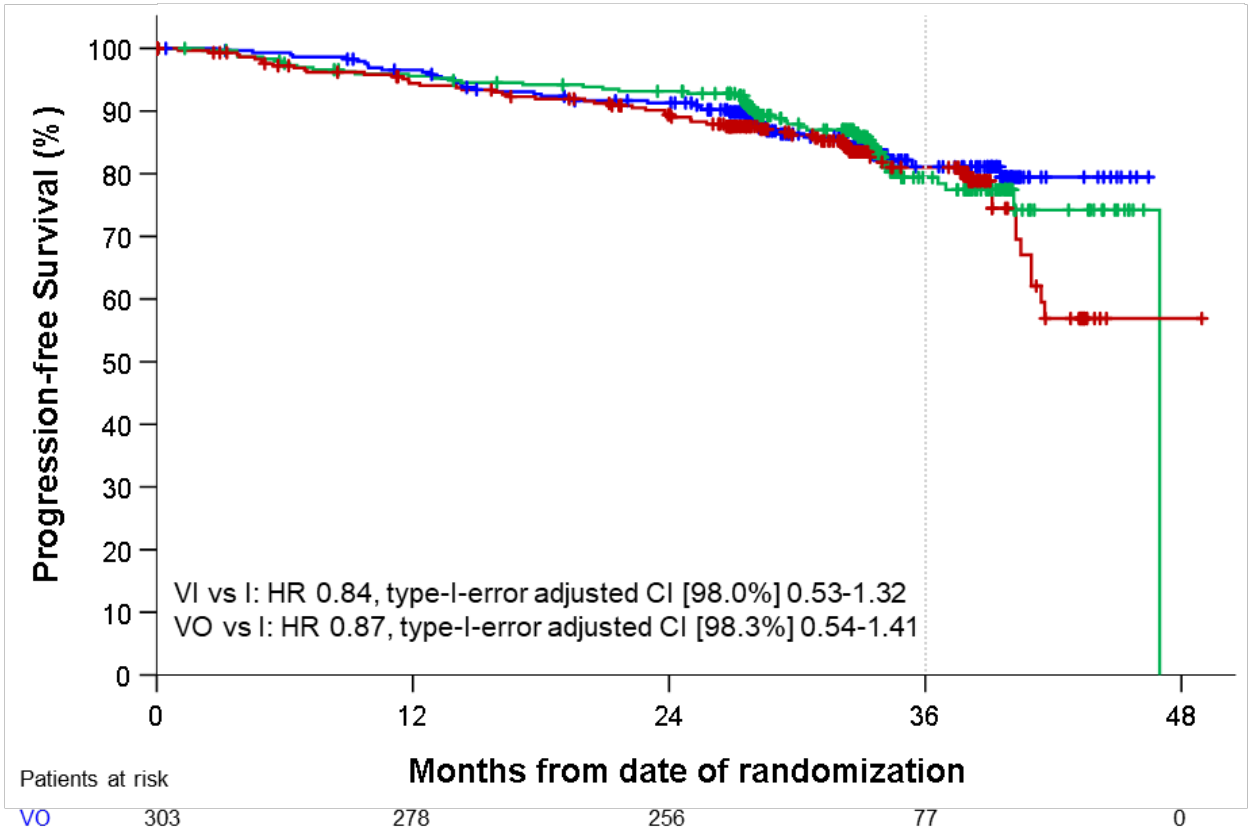


uMRD <10^{-4} in **peripheral blood** and **bone marrow**, by flow cytometry, at final restaging



Al-Sawaf O et al., oral presentation, Plenary Scientific session, ASH 2025

PROGRESSION-FREE SURVIVAL



3-year-PFS

I 81.0%

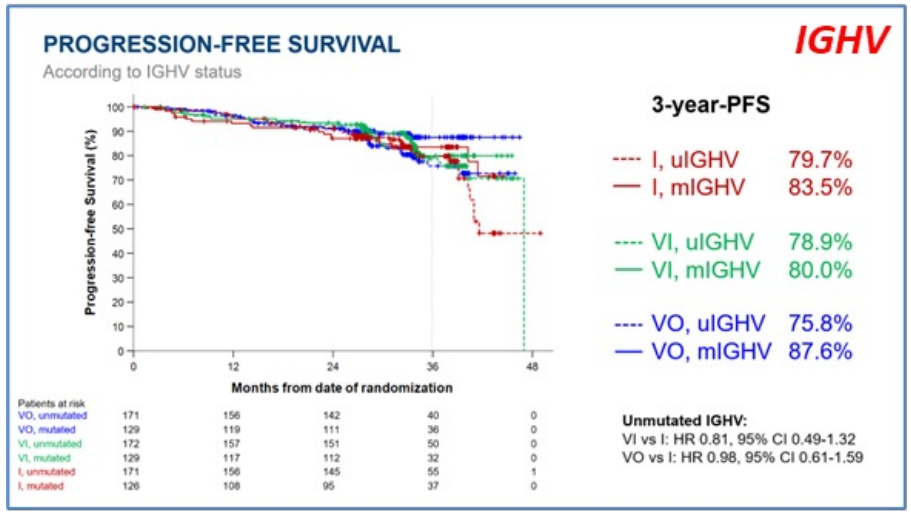
VI 79.4 %

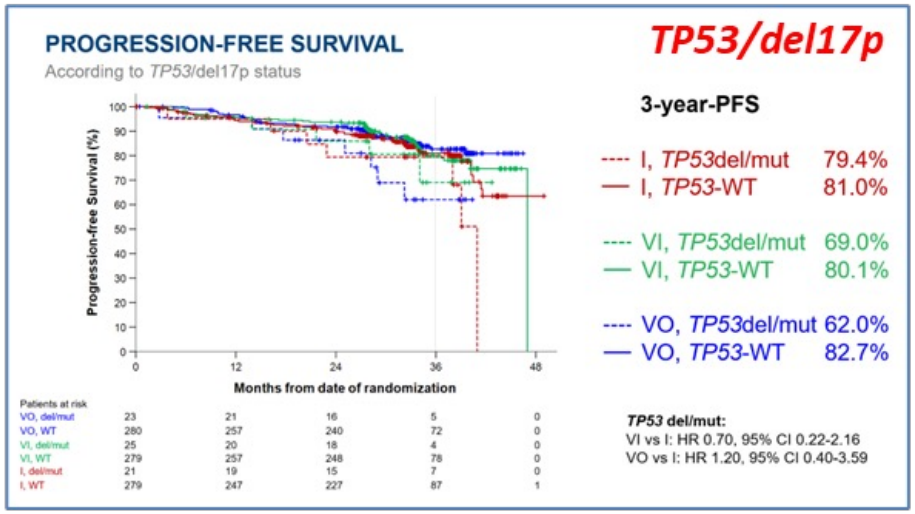
VO 81.1%

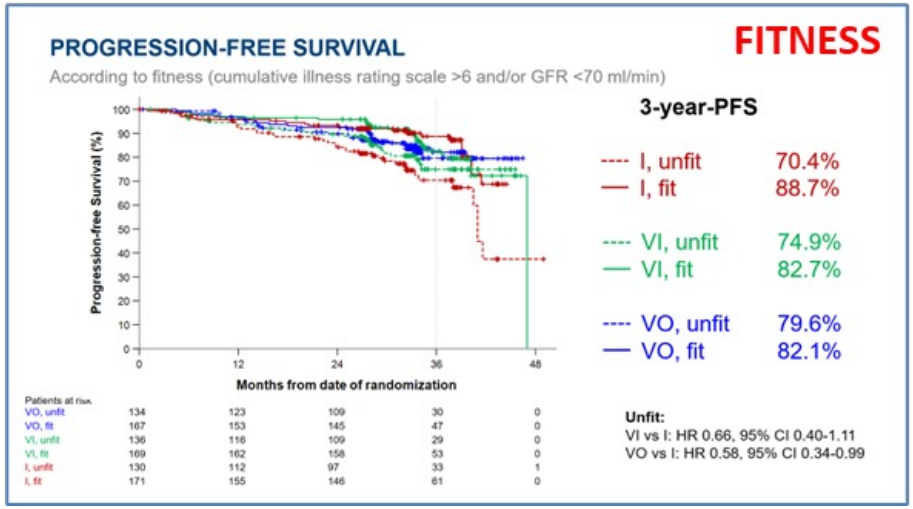
	PD	Death
I	46	11
VI	37	13
VO	25	21

Al-Sawaf O et al., oral presentation, Plenary Scientific session, ASH 2025

PROGRESSION-FREE SURVIVAL – according to disease and patient characteristics







Al-Sawaf O et al., oral presentation, Plenary Scientific session, ASH 2025

ADVERSE EVENTS

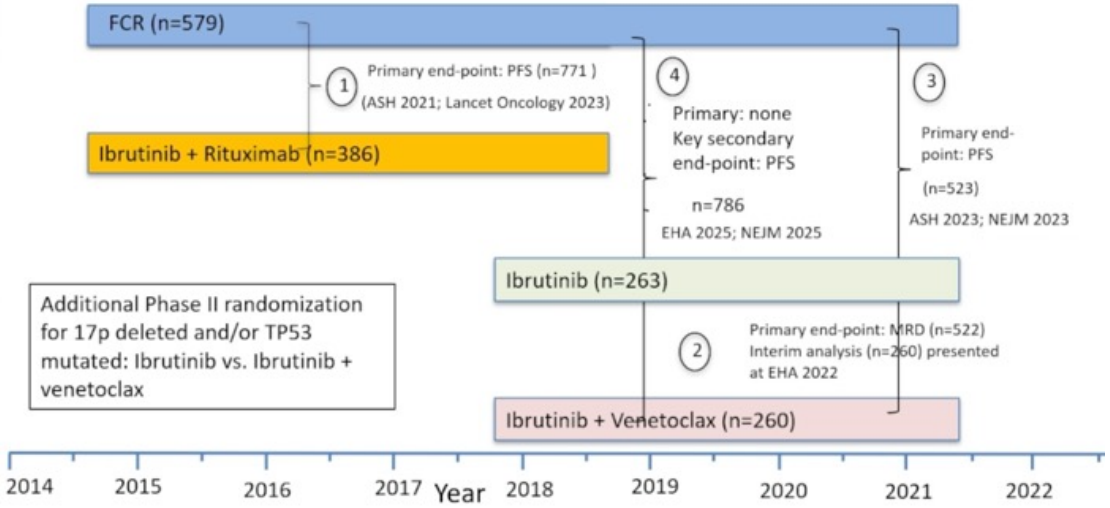
Selected adverse events of interest, all CTC grades

	VO	VI	I
Safety population – No. (%)	**295**	**303**	**298**
Blood and lymphatic system disorders	174 (59.0)	130 (42.9)	85 (28.5)
Febrile neutropenia	14 (4.7)	7 (2.3)	0 (0)
Neutropenia	155 (52.5)	110 (36.3)	49 (16.4)
Cardiac disorders	41 (13.9)	72 (23.8)	103 (34.6)
Atrial fibrillation	11 (3.7)	38 (12.5)	50 (16.8)
Gastrointestinal disorders	176 (59.7)	225 (74.3)	189 (63.4)
Diarrhea	80 (27.1)	143 (47.2)	104 (34.9)
Infections and infestations	225 (76.3)	243 (80.2)	238 (79.9)
COVID-19	113 (38.3)	128 (42.2)	117 (39.3)
Pneumonia	41 (13.9)	28 (9.2)	40 (13.4)

Grade 3-5 Infections	**VO**	**VI**	**I**
	295	**303**	**298**
Infections and infestations	103 (34.9)	76 (25.1)	74 (24.8)
COVID-19	47 (15.9)	26 (8.6)	20 (6.7)
Pneumonia	29 (9.8)	22 (7.3)	22 (7.4)

Al-Sawaf O et al., oral presentation, Plenary Scientific session, ASH 2025

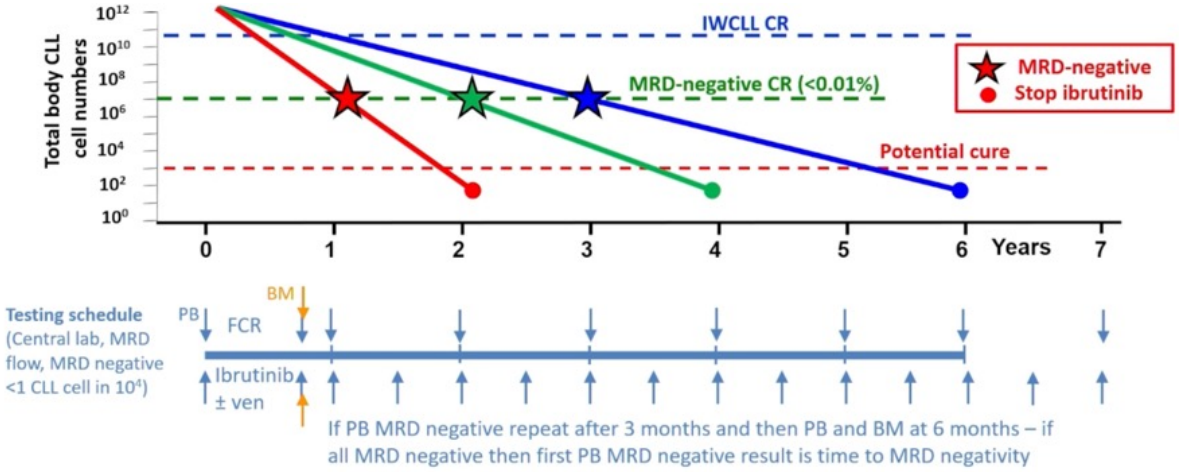
Selected Oral Presentations from the FLAIR Trial



ABS ID 679 - Efficacy of MRD-guided I+V in standard-risk (IGHV UM) and poor-risk (e.g.TP53dis) CLL *(Dalal S. oral presentation)*

ABS ID 794 - Half-way uMRD4 as a parameter of delayed MRD relapse in IGHV M and UM *(Hillmen P. oral presentation)*

ABS ID 796 - Acquired BTK mutations in ibrutinib containing arms *(Evans C. oral presentation)*

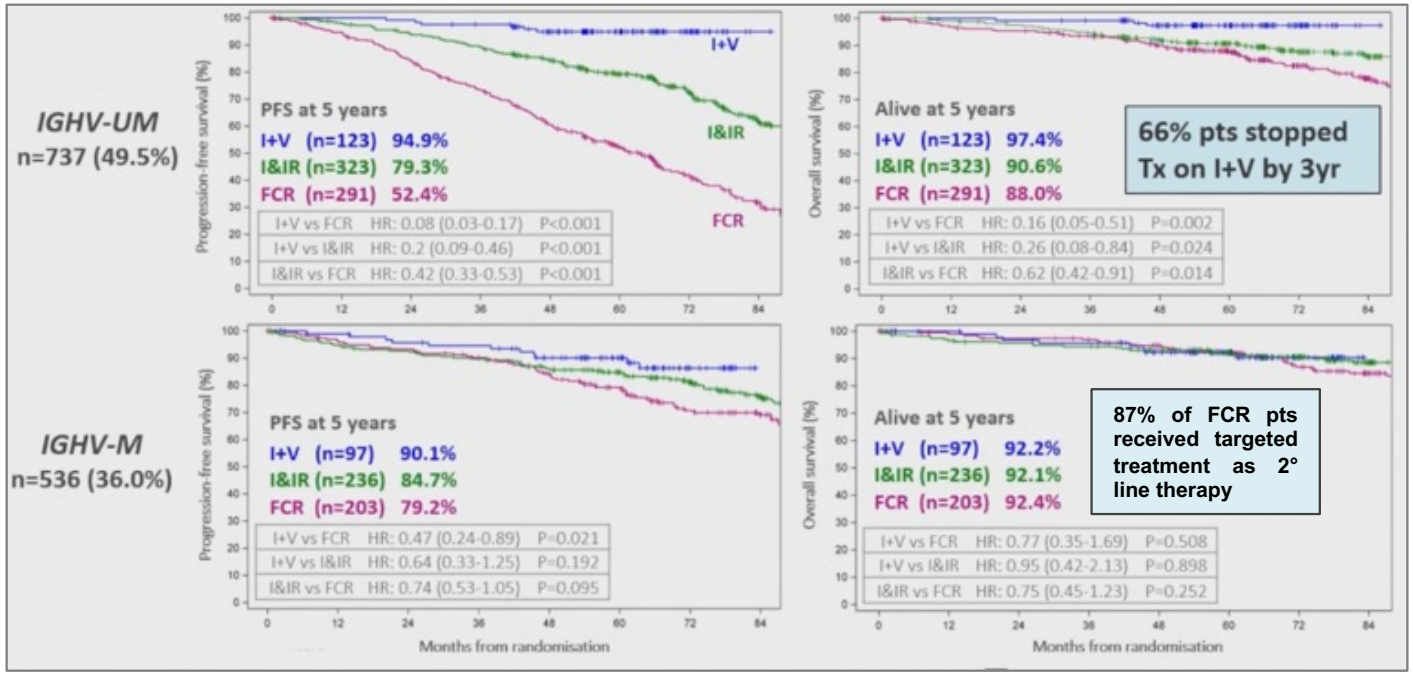


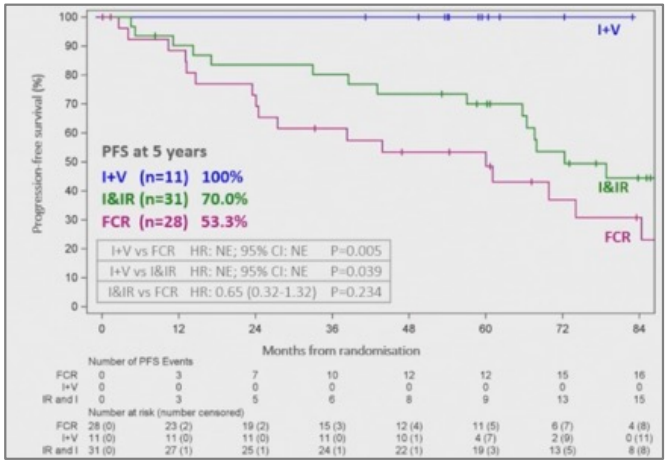
Defining treatment duration:
- 2 to 6 yrs I or I+V
- double time after MRD negative
- restart I+V if becomes MRD+ prior to 6 yrs

Dalal S et al., Abstract N. 679, oral presentation, ASH 2025
Rawstron A et al., Abstract N. 794, oral presentation, ASH 2025
Evans C et al., Abstract N. 796, oral presentation, ASH 2025

Selected Oral Presentations from the FLAIR Trial

1. MRD-guided I+V is effective in intermediate- and poor-risk CLL





TP53^{mut} n=70 (4.7%) [n=11 in I+V arm]

- ❑ MRD-guided I+V is highly effective in overcoming the adverse prognostic effect associated with IGHV-UM status
- ❑ Similar efficacy also in subset #2 and ATM aberrations (Del11q and ATM^{mut})
- ❑ 100% 5-year PFS in 11 patients with TP53 mutations treated with I+V

Dalal S et al., Abstract N. 679, oral presentation, ASH 2025

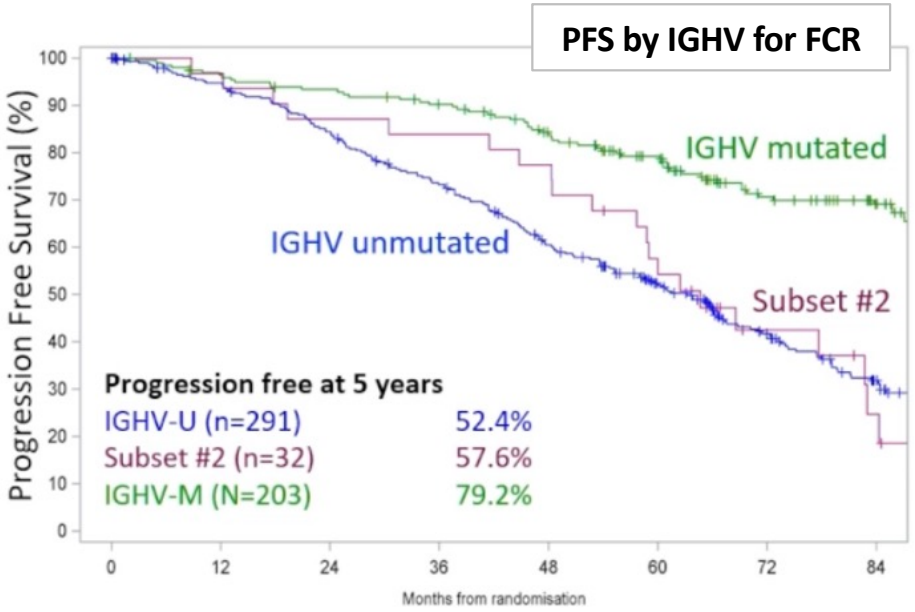
Selected Oral Presentations from the FLAIR Trial

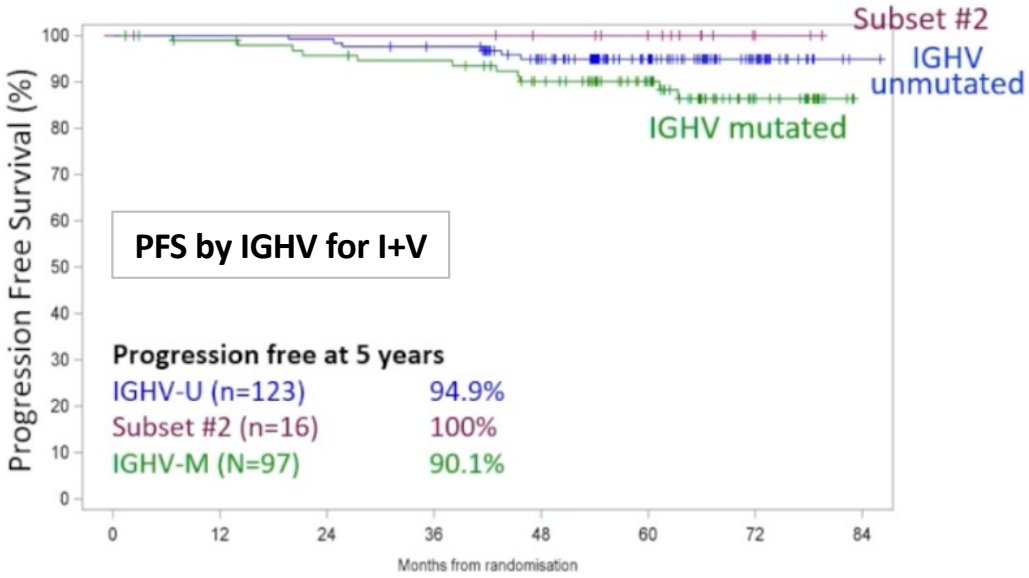
2. MRD data in follow up for FCR and I+V (i.e. arms in which uMRD was achieved)

Eight-color flow cytometry on PB (two consecutive samples collected three months apart) and confirmed on BM uMRD4 (<1 CLL cell in 10^4 leucocytes) is stopping threshold

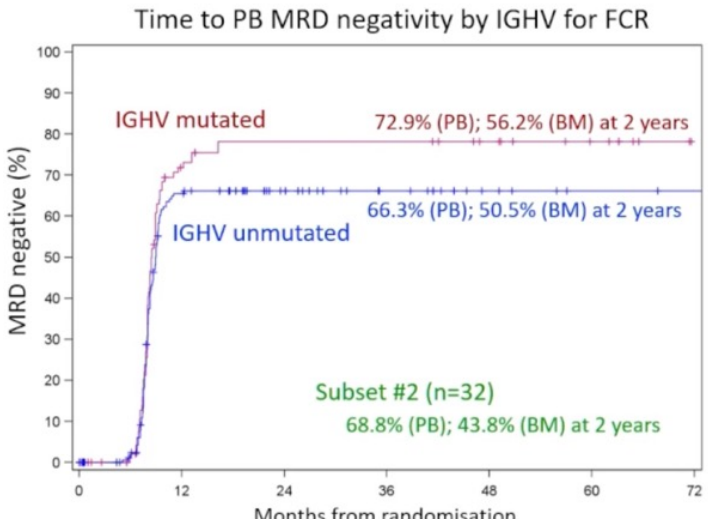
Ibrutinib + Venetoclax

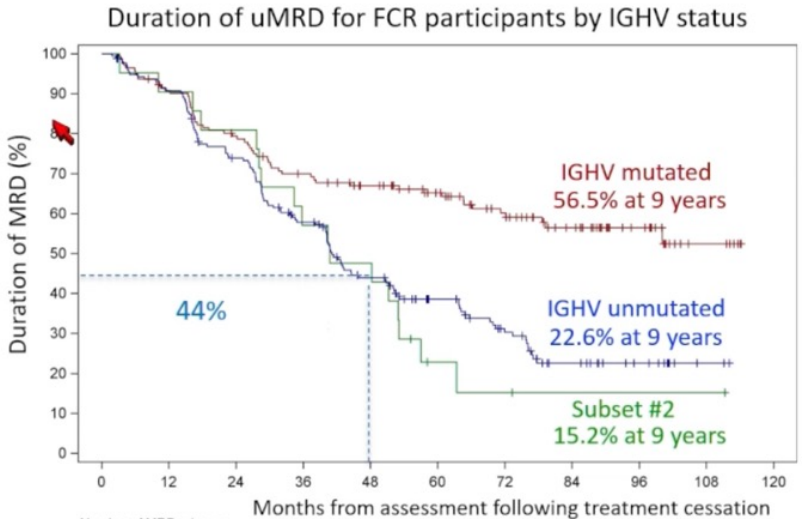
- MRD assessed in PB every 6 months throughout stopping I+V double the time taken to achieve MRD4
- In follow-up MRD becomes detectable (MRD4) then patient will restart I+V at that point (before progression) and complete 6 yrs of therapy





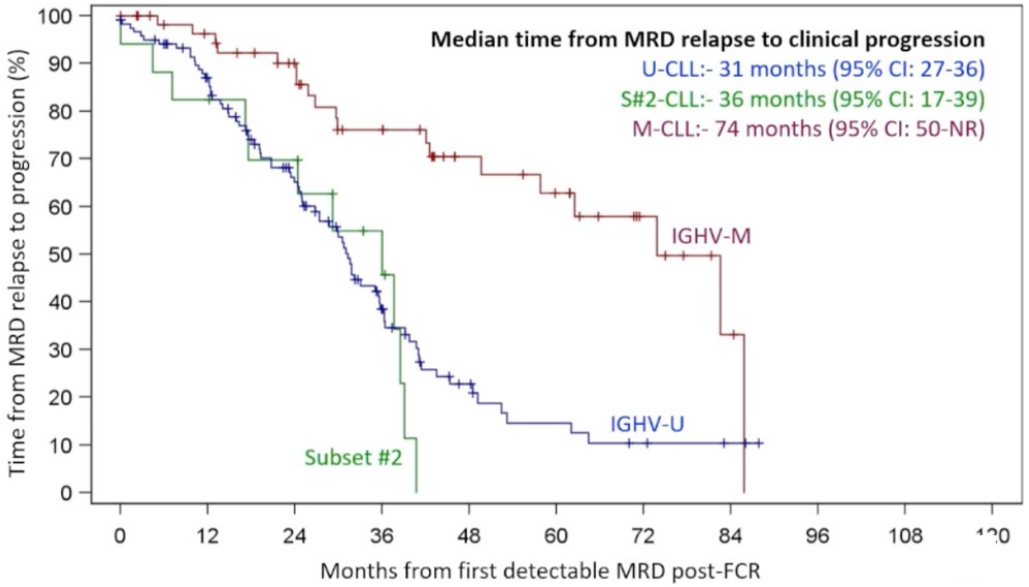
Rawstron A et al., Abstract N. 794, oral presentation, ASH 2025





FCR MRD response

- A higher proportion of IGHV-M patients achieve uMRD at 2 yrs
- A higher proportion of IGHV-M patients mantain a persistent uMRD

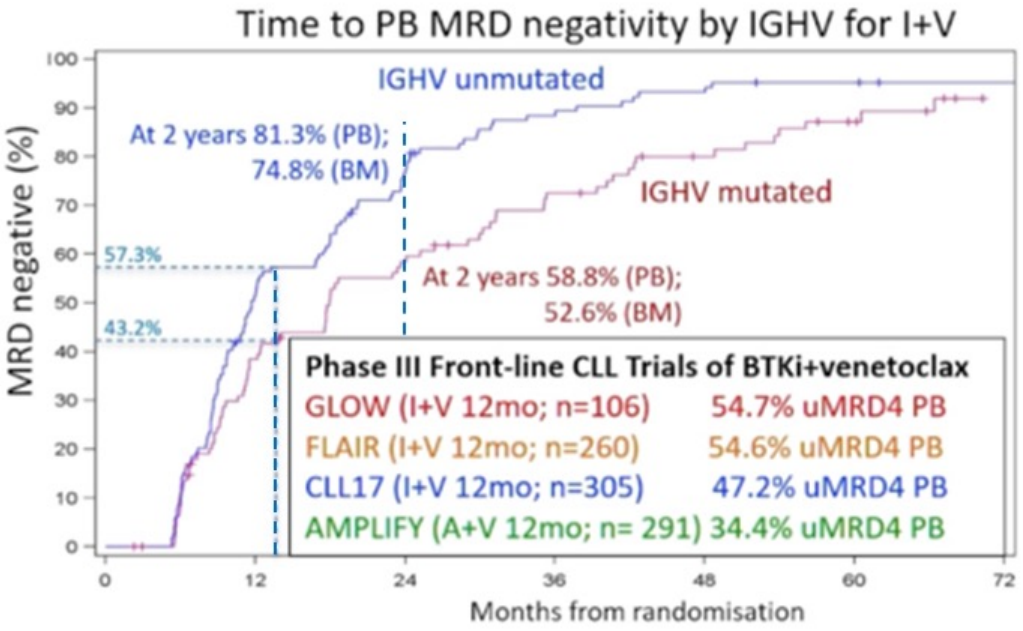


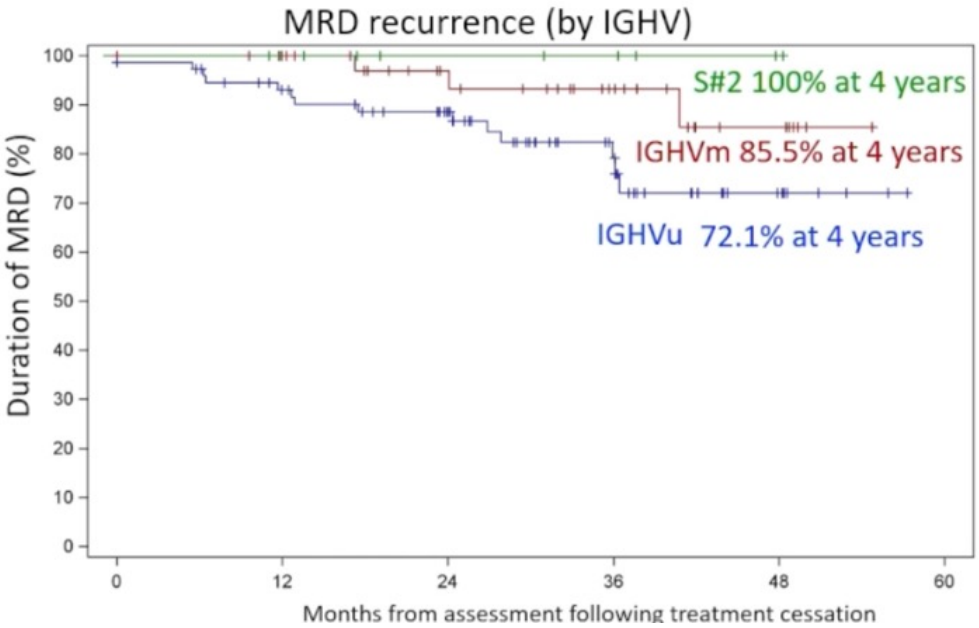
Time from MRD recurrence to PD in FCR group

- ❑ IGHV-M → average of 6 yrs from MRD recurrence to PD
- ❑ IGHV-UM → average of 3 yrs from MRD recurrence to PD

Rawstron A et al., Abstract N. 794, oral presentation, ASH 2025

MRD response and uMRD duration for I+V participants by IGHV status





I+V MRD response

A higher proportion of **IGHV-UM** patients achieve uMRD at 2 yrs

Duration of uMRD for I+V (by IGHV status)

A higher proportion of **IGHV-M** patients mantain a persistent uMRD

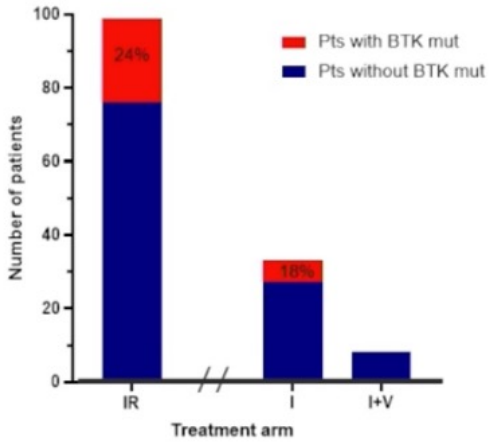
- In I+V group, 19/143 patients experience MRD relapse
- Patients respond to re-introduction of I+V after MRD recurrence

Rawstron A et al., Abstract N. 794, oral presentation, ASH 2025

Selected Oral Presentations from the FLAIR Trial

3. Acquired BTK mutations in ibrutinib-containing arms

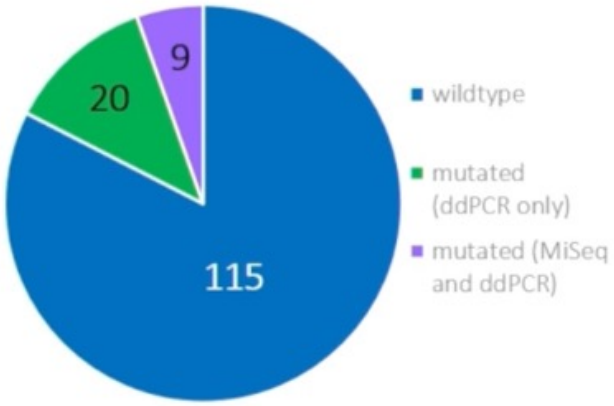
BTK mutation in patients with PD



Arm	Number Enrolled	Number Progressed	Median Time on treatment (years)	Available Samples
IR	386	114	5.9	96
I	263	37	4.8	33
I+V	260	7	2.1	7

- **23/96 (24%) IR patients had 1 or more BTK mutation**
- **6/33 (18%) I patients had 1 or more BTK mutation**
- **No I+V patient had a BTK mutation, 1 did have a BCL2 G101V**

Detection of BTK^{mut} via Miseq and ddPCR



- **Total number of disease progression samples investigated for BTK mutation:- 136**
- **9 relapsing patients found to have BTK muts using Miseq.**
- **ddPCR detected BTK mutations in a further 20 patients.**
- **ddPCR can detect mutations <0.01%**

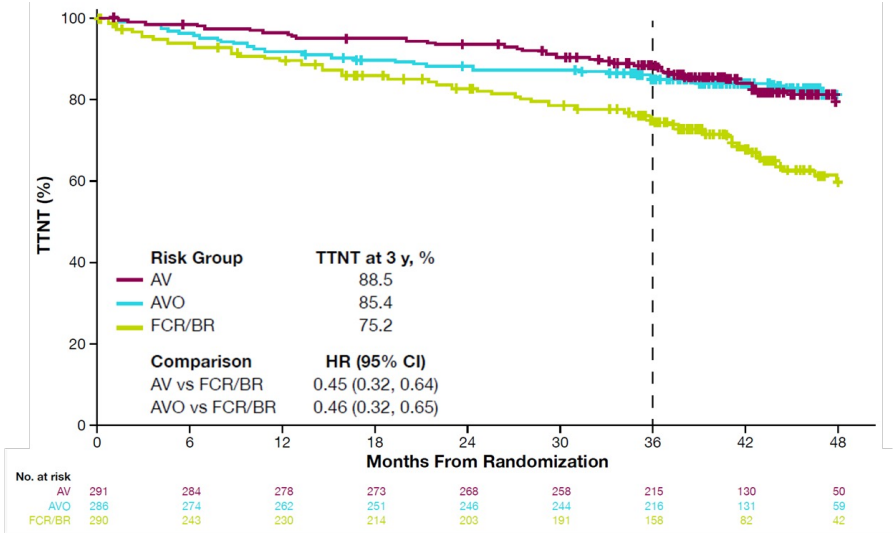
- **The majority of pts had more than 1 BTK^{mut}**
- **No BTK^{mut} was found at baseline**
- **Most BTK^{mut} pts were IGHV UM**

Evans C et al., Abstract N. 796, oral presentation, ASH 2025

Impact of prognostic mutations on outcome with Fixed-Duration Acalabrutinib-Venetoclax Combinations Versus CIT – AMPLIFY TRIAL

- In the ITT population, the 36-month **PFS rate was 76.5% (AV), 83.1% (AVO)**, and 66.5% (FCR/BR)
- In patients with uIGHV, PFS was improved with AV and AVO vs FCR/BR

TTNT by Treatment Arm

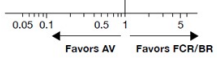


- In the ITT population, the 36-month **TTNT rate** was **88.5% (AV), 85.4% (AVO),** and 75.2% (FCR/BR)
- Forest plots showed a consistent **TTNT benefit with AV and AVO** vs FCR/BR **in IGHV-M and UM pts**, and in pts with or without ATM, SF3B1 and NOTCH1 mutations.

Figure 6. Forest Plots of TTNT Comparison for AV (A) and AVO (B) vs FCR/BR Based on Key Genetic Mutations

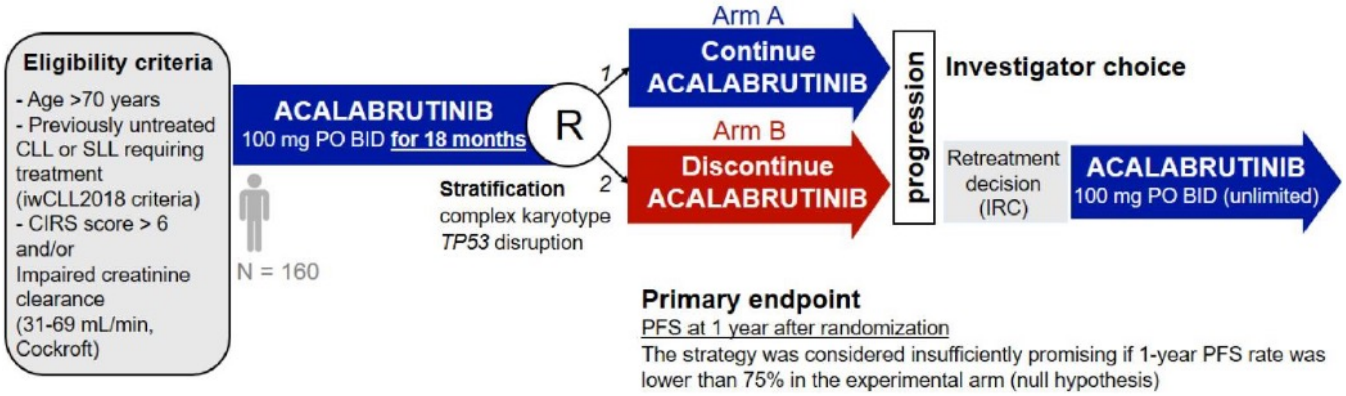
A

Mutation Status	Events/Patients, n AV (N=291)	FCR/BR (N=290)	Hazard Ratio (95% CI)
Overall			
All subjects	52/290	84/289	0.46 (0.32, 0.64)
IGHV mutational status			
Mutated	13/124	23/118	0.43 (0.21, 0.83)
Unmutated	39/167	61/172	0.50 (0.33, 0.74)
ATM			
Mutated	17/70	23/59	0.45 (0.24, 0.84)
Unmutated	34/199	51/207	0.56 (0.36, 0.86)
Missing	1/21	10/23	NC (NC, NC)
BIRC3			
Mutated	6/18	4/12	NC (NC, NC)
Unmutated	45/251	70/254	0.49 (0.34, 0.72)
Missing	1/21	10/23	NC (NC, NC)
CARD11			
Mutated	3/9	1/9	NC (NC, NC)
Unmutated	48/260	73/257	0.50 (0.35, 0.72)
Missing	1/21	10/23	NC (NC, NC)
MYD88			
Mutated	1/11	1/11	NC (NC, NC)
Unmutated	50/258	73/255	0.52 (0.36, 0.75)
Missing	1/21	10/23	NC (NC, NC)
NOTCH1			
Mutated	15/41	17/50	0.80 (0.40, 1.61)
Unmutated	36/228	57/216	0.47 (0.31, 0.71)
Missing	1/21	10/23	NC (NC, NC)
SF3B1			
Mutated	9/45	19/46	0.31 (0.13, 0.67)
Unmutated	42/224	55/220	0.61 (0.40, 0.91)
Missing	1/21	10/23	NC (NC, NC)



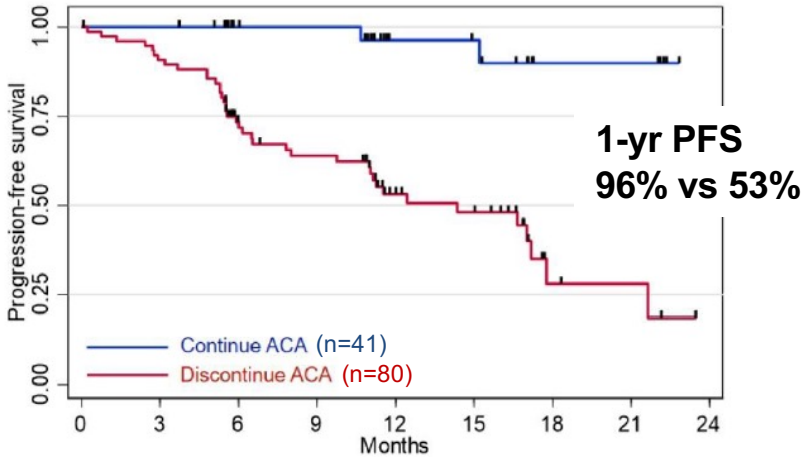
Ghia P et al., Poster n. 3898, ASH2025

Time-Limited Acalabrutinib Monotherapy in Frail Patients with Previously Untreated CLL: Primary endpoint analysis of the randomized STAIR trial

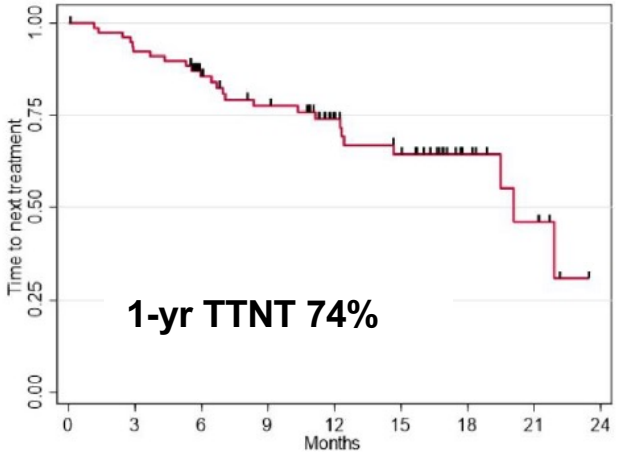


Median age 77 yrs
CIRS score >6 in ≈60% of pts
CrCl <70 in 78% of pts

PFS



TTNT



Among pts who discontinued Acala → 1-year PFS 90% in IGHV-M and 34% in IGHV-UM

Response to retreatment (n=25)
→24 restarted Acala per protocol, ORR 87.5% (21/24)

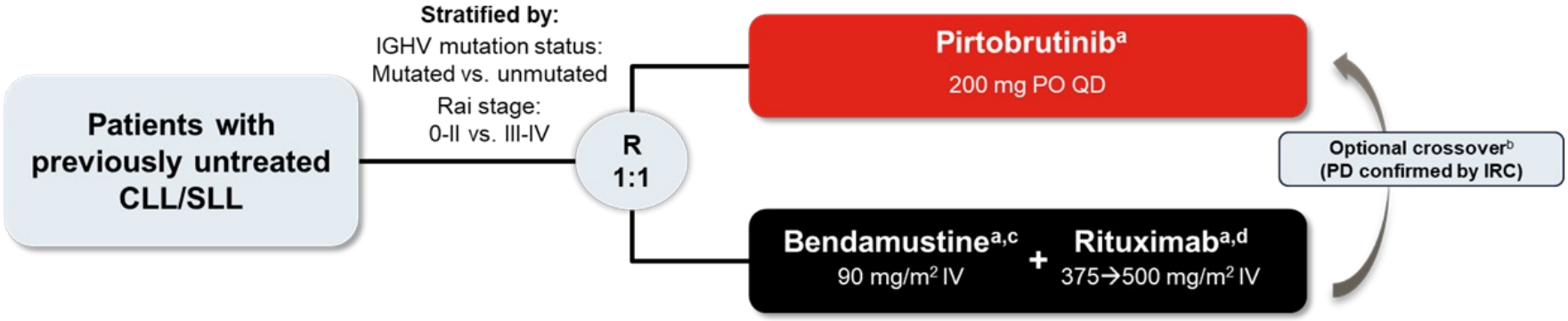
AEs (in the whole cohort)

AF 6.9%, Hypertension 2.5%, Bleeding 1.9%

Lower burden of AEs in the group who discontinued Acala

Guièze R et al., Abstract N. 684, oral presentation, ASH 2025

Pirtobrutinib vs BendaR in TN CLL: First Results from BRUIN CLL-313



Key Eligibility Criteria

- Confirmed diagnosis of CLL/SLL, with requirement for therapy (per iwCLL 2018 criteria)
- ECOG PS 0 to 2
- Naïve to systemic therapy for CLL/SLL
- No 17p deletion
- Platelets ≥75 × 10^9/L (≥50 × 10^9/L for patients with evidence of bone marrow infiltrate)
- Hemoglobin ≥8 g/dL
- Absolute neutrophil count ≥0.75 × 10^9/L

Endpoints

Primary
- PFS[e,f] (per iwCLL 2018 criteria)

Key secondary
- OS[f]

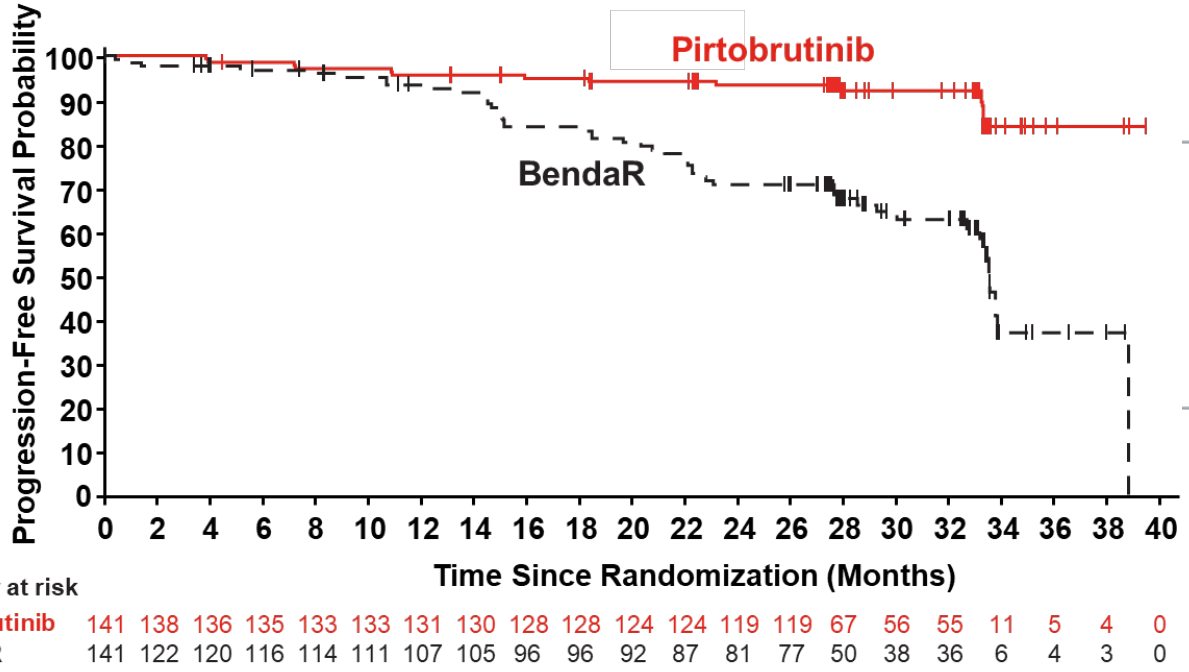
Secondary
- ORR[g] (per iwCLL 2018 criteria)
- Safety measures

[a]Treatment was given in 28-day cycles. [b]Patients who were randomly assigned to BendaR could crossover to pirtobrutinib treatment after IRC-confirmed progressive disease according to iwCLL 2018 criteria. [c]Administered on Days 1 and 2 of each 28-day cycle, cycles 1 through 6. [d]Administered at 375 mg/m² for the first cycle and then at 500 mg/m² on Day 1 of each 28-day cycle, cycles 2 through 6. [e]The primary endpoint of PFS was assessed by a blinded IRC. [f]A sequential gate-keeping strategy was used to control the overall 2-sided type I error rate at 0.05 when testing primary and key secondary endpoints. [g]ORR is defined as the proportion of patients who achieve a best overall response of CR, CRi, nPR, or PR at or before the initiation of subsequent anti-cancer therapy.

Abbreviations: BendaR, bendamustine plus rituximab; CLL, chronic lymphocytic leukemia; CR, complete response; CRi, CR with incomplete bone marrow recovery; ECOG PS, Eastern Cooperative Oncology Group performance status; IGHV, immunoglobulin heavy-chain variable region; IRC, independent review committee; IV, intravenous; iwCLL, International Workshop on Chronic Lymphocytic Leukemia; nPR, nodular partial response; ORR, overall response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PO, by mouth; PR, partial response; QD, once daily; R, randomized; SLL, small lymphocytic lymphoma.

Jurczak et al., oral presentation, Late Breaking Abstract, ASH 2025

Primary Endpoint: Progression-Free Survival



Number at risk

Pirtobrutinib	141	138	136	135	133	133	131	130	128	128	124	124	119	119	67	56	55	11	5	4	0
BendaR	141	122	120	116	114	111	107	105	96	96	92	87	81	77	50	38	36	6	4	3	0

	Pirtobrutinib (n=141)	BendaR (n=141)
Number of events, n (%)	13 (9.2)	48 (34.0)
24-month PFS rate, (95% CI)	**93.4** (87.6, 96.5)	**70.7** (61.5, 78.1)
Median follow-up, months	28.1	28.3
Hazard ratio (95% CI)	**0.20 (0.11, 0.37)**	
p-value[a]	<0.0001[a]	

The PFS results presented are IRC assessed

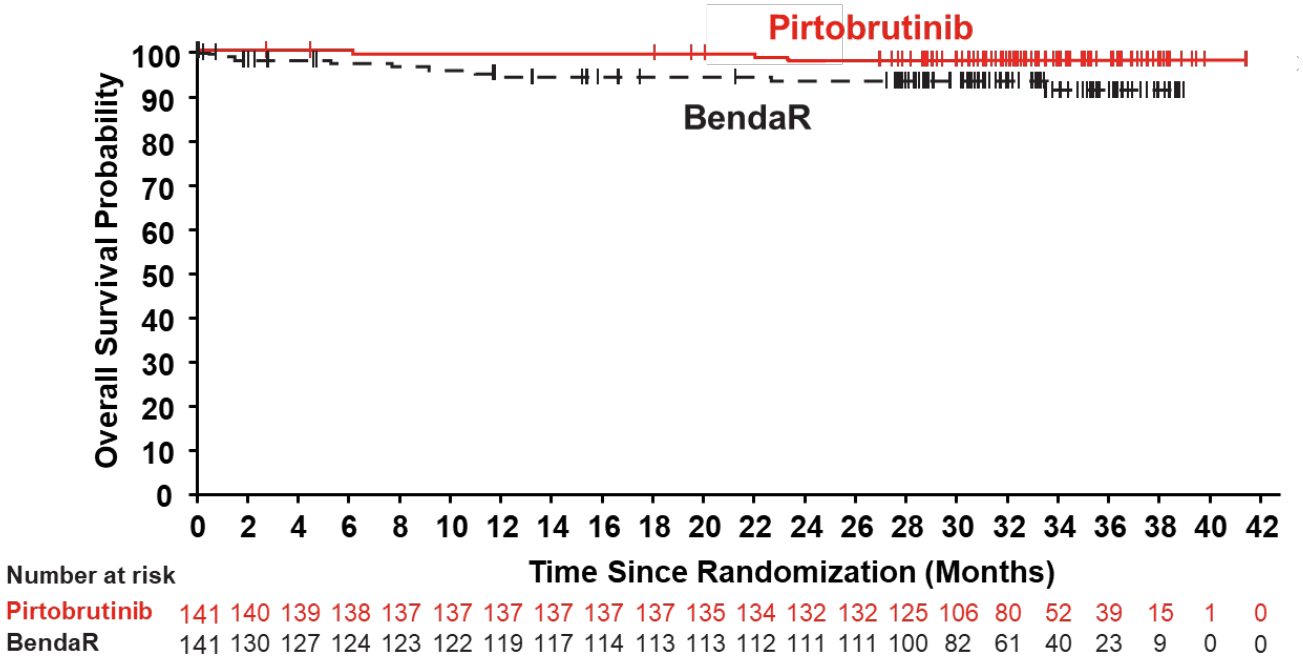
ORR with pirtobrutinib was >90% and higher than with BendaR (81.5%)

Pirtobrutinib demonstrated a statistically significant and clinically meaningful PFS improvement, with an 80% reduction in risk of PD or death compared with BendaR

PFS favored Pirtobrutinib across all prespecified subgroups, included IGHV UM

Jurczak et al., oral presentation, Late Breaking Abstract, ASH 2025

Overall Survival



	Pirtobrutinib n=141	BendaR n=141
Number of events, n (%)	3 (2.1)	10 (7.1)
24-month OS rate, (95% CI)	**97.8** (93.3, 99.3)	**93.0** (87.0, 96.3)
Median follow-up, months	32.7	31.7
Hazard ratio (95% CI)	**0.26 (0.07, 0.93)**	
p-value	0.0261[a]	

Effective crossover rate[b]:

52.9% (18/34)

OS data were immature, but trended in favor of pirtobrutinib, despite a high effective crossover rate

[a]Stratified log-rank 2-sided p-value; the 2-sided alpha level was 0.000001 at this interim OS analysis. [b]Uses the number of patients with investigator-assessed PD as the denominator; eligible patients receiving BendaR could crossover to receive pirtobrutinib monotherapy upon confirmation of PD by IRC per protocol.

Abbreviations: BendaR, bendamustine plus rituximab; CI, confidence interval; IRC, independent review committee; OS, overall survival; PD, progressive disease.

Jurczak et al., oral presentation, Late Breaking Abstract, ASH 2025

Adverse Events of Interest

	Pirtobrutinib (n=140)		BendaR (n=132)		EAIR per 100 Person-Years		
	Any Grade n (%)	Grade ≥3 n (%)	Any Grade n (%)	Grade ≥3 n (%)	Pirtobrutinib Any Grade EAIR[g]	BendaR Any Grade EAIR[g]	EAIR Ratio (95% CI)[h]
Infection[a]	80 (57.1)	19 (13.6)	44 (33.3)	11 (8.3)	38.3	89.7	0.43 (0.30, 0.62)
Infection without COVID-19	72 (51.4)	19 (13.6)	38 (28.8)	9 (6.8)	30.9	74.9	0.41 (0.28, 0.61)
Bleeding[b]	36 (25.7)	1 (0.7)	2 (1.5)	0 (0)	12.5	3.3	3.73 (0.90, 15.50)
Hemorrhage	17 (12.1)	1 (0.7)	2 (1.5)	0 (0)	5.2	3.3	1.55 (0.36, 6.69)
Bruising	16 (11.4)	0 (0)	0 (0)	0 (0)	4.8	0	NE
Petechiae and purpura	8 (5.7)	0 (0)	0 (0)	0 (0)	2.3	0	NE
Neutropenia[c]	21 (15.0)	13 (9.3)	68 (51.5)	60 (45.5)	6.5	169.5	0.04 (0.02, 0.06)
Anemia[d]	14 (10.0)	6 (4.3)	21 (15.9)	10 (7.6)	4.1	37.7	0.11 (0.06, 0.21)
Thrombocytopenia[e]	12 (8.6)	4 (2.9)	23 (17.4)	9 (6.8)	3.5	43.1	0.08 (0.04, 0.16)
Atrial fibrillation and atrial flutter	2 (1.4)	1 (0.7)	2 (1.5)	1 (0.8)	0.5	3.3	0.17 (0.02, 1.17)
≥75 years old[f]	1 (5.0)	0	1 (4.3)	0	2.2	10.0	0.22 (0.01, 3.46)
Hypertension	11 (7.9)	4 (2.9)	6 (4.5)	4 (3.0)	3.2	10.2	0.31 (0.11, 0.84)

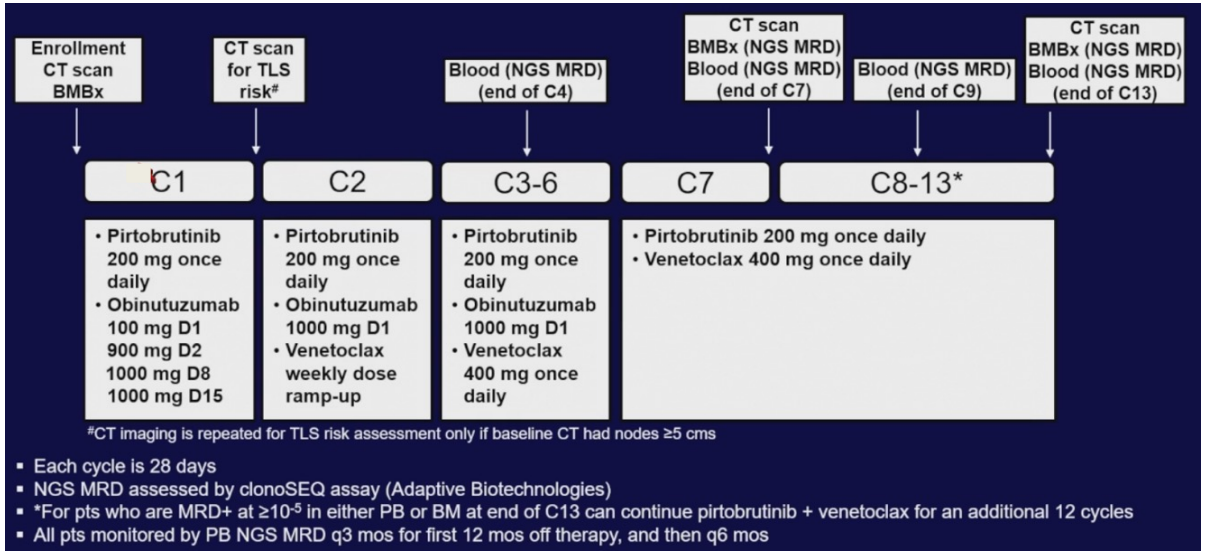
Incidence of atrial fibrillation/flutter remains low in older patients aged ≥75 years (5.0% with pirtobrutinib and 4.3% with BR

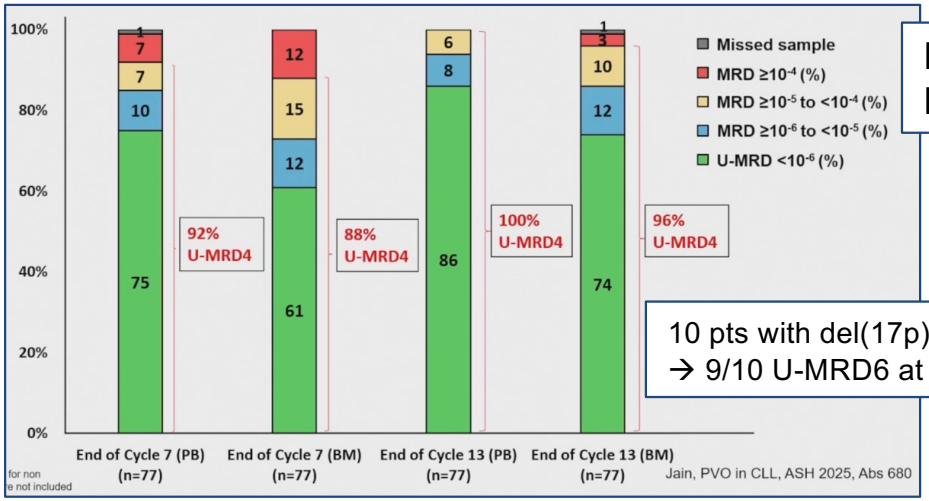
[a]Aggregate of all preferred terms indicating infection and including COVID-19. [b]Aggregate of all preferred terms indicating bleeding. [c]Includes neutropenia, neutrophil count decreased, and febrile neutropenia. [d]Includes anemia and iron deficiency anemia. [e]Includes thrombocytopenia and platelet count decreased. [f]Pirtobrutinib, n=20; BendaR, n=23. [g]EAIR per 100 person-years is based on the first occurrence of an event and is calculated as the number of events divided by the sum of years at risk for a TEAE across all patients times 100. [h]EAIR ratio and 95% CI were estimated using Poisson regression and based on the EAIR with pirtobrutinib relative to the EAIR with BendaR.

Abbreviations: BendaR, bendamustine plus rituximab; CI, confidence interval; COVID-19, coronavirus disease of 2019; EAIR; exposure-adjusted incidence rate; NE, not estimable.

Jurczak et al., oral presentation, Late Breaking Abstract, ASH 2025

Time Limited Pirtobrutinib, Venetoclax and Obinutuzumab combination in TN CLL





NGS MRD in PB and BM

10 pts with del(17p) and/or TP53^{mut}
→ 9/10 U-MRD6 at EOC13

80 pts enrolled
Median follow up 21.6 mo

Safety analysis

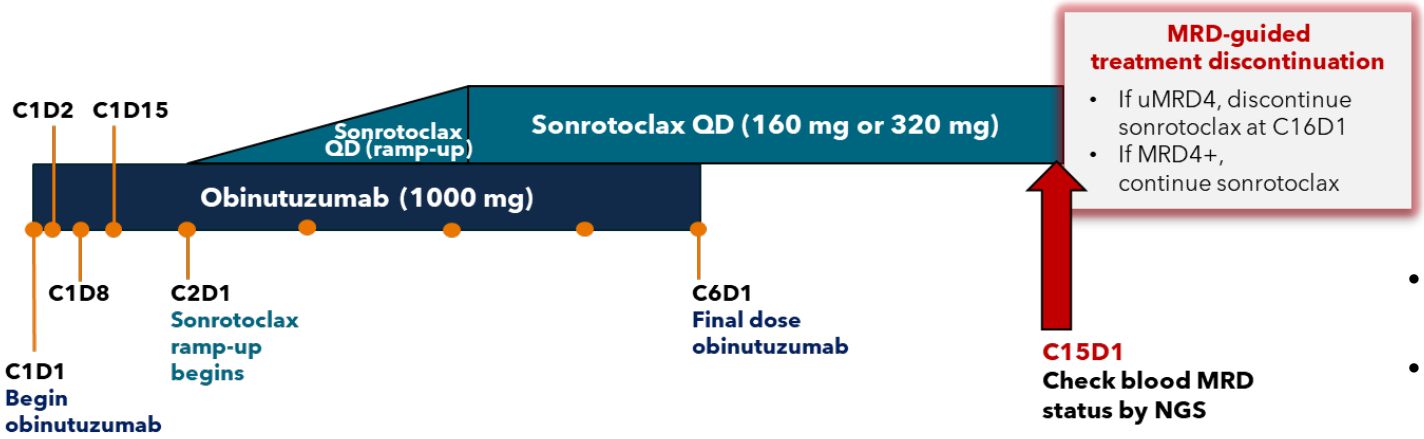
67% of pts had ≥G3 neutropenia or thrombocytopenia
5% of pts had neutropenic fever
2 pts (2%) developed AF

Patient disposition

- No pt had PD, 1 pt died
- 66/77 pts completed all therapy
- No pt had MRD recurrence at a median follow up of 10.4 months after completing treatment
- 11/77 pts were eligible for additional 12 cycles of PV due to ≥MRD5 at EOC13

Jain N et al., Abstract N. 680, oral presentation, ASH 2025

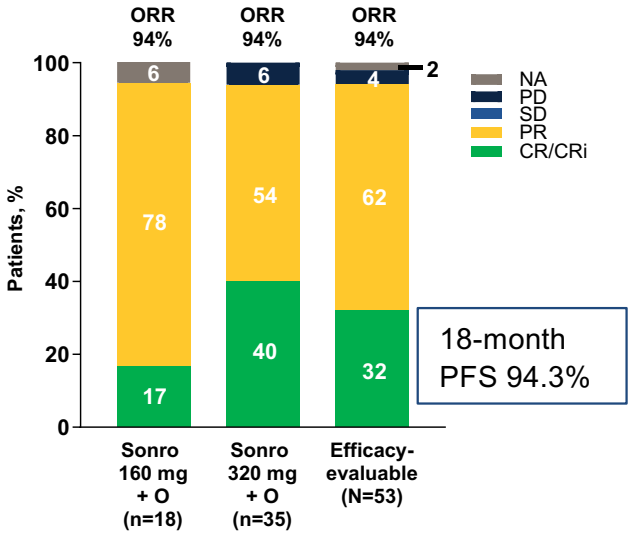
MRD-guided therapy of sonrotoclax + obinutuzumab in patients with TN CLL: Initial results from an ongoing phase 1/1b study, BGB-11417-101

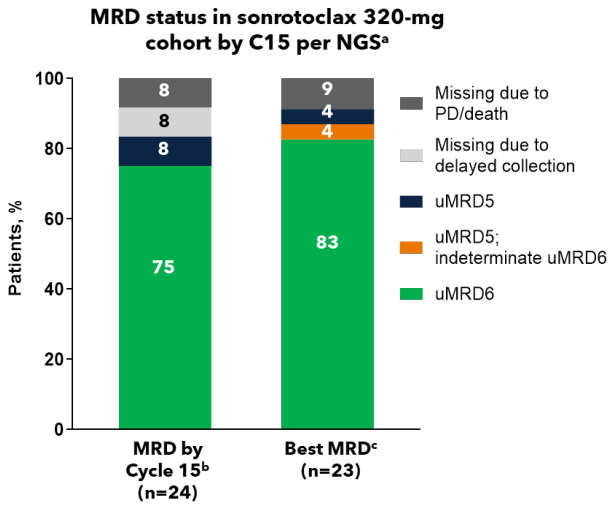


Overall, 55 pts enrolled
Median age 62 yrs
Median follow up 12.3 mo

- No treatment discontinuations attributable to sonrotoclax
- No deaths due to adverse events

- Most frequent TEAEs were Thrombocytopenia, neutropenia and IRR
- Grade 3+ neutropenia did not translate to serious or life-threatening infections





All analyzed patients who reached C15 (n=21) achieved at least uMRD5

All patients in remission with a median time off treatment of 7.2 months

Hoffmann MS, et al. abstract N. 7489, Oral Presentation, ASH 2025

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Varese

Grazie per la vostra attenzione!