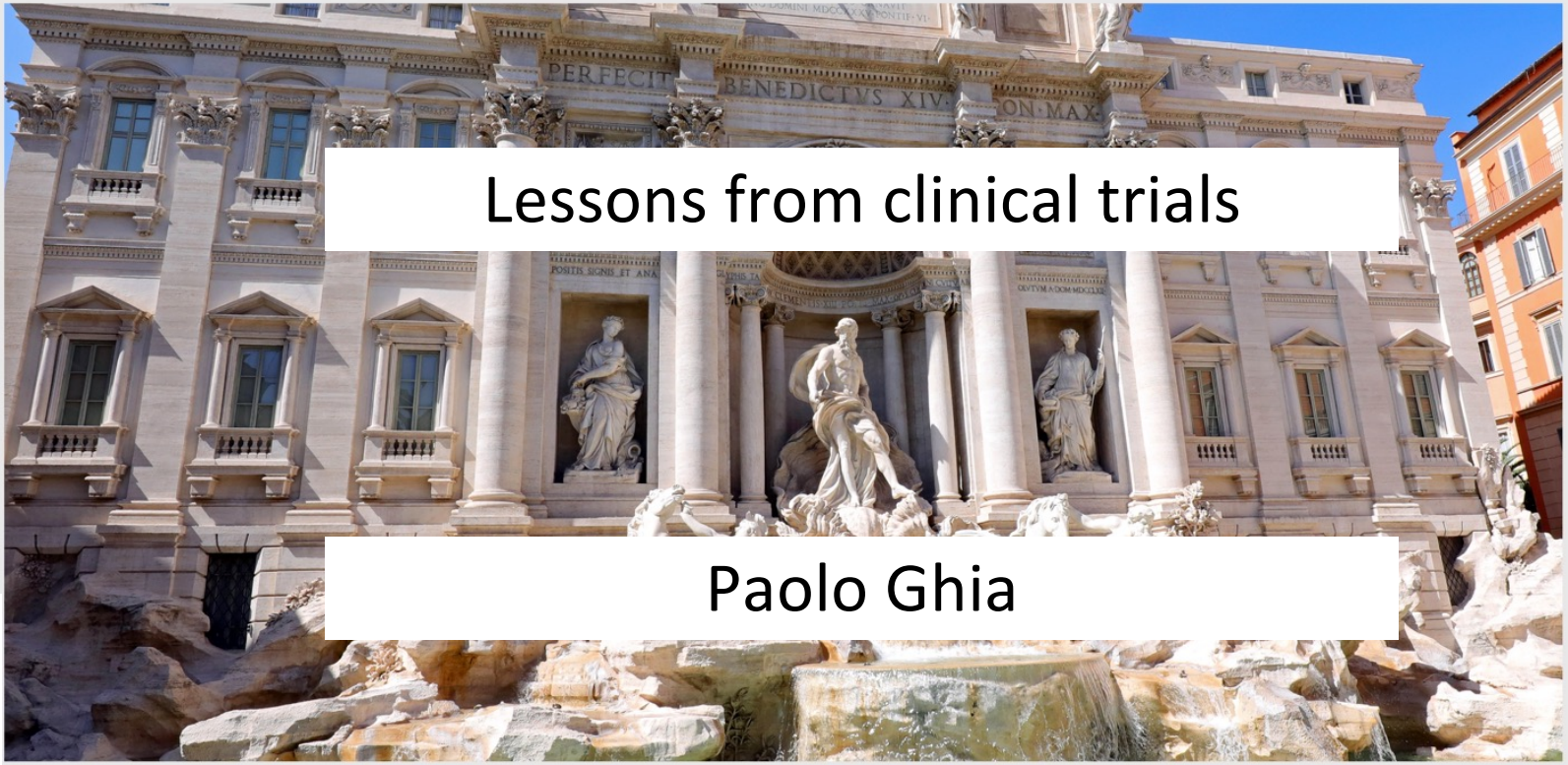
LEUKEMIA2022

Rome, Hotel NH Collection - Vittorio Veneto

May 5-6, 2022

AIL President: G. Toro
Coordinators: A.M. Carella, S. Amadori



Lessons from clinical trials

Paolo Ghia

UNDER THE AUSPICES OF:

fondazione GIMEMA onlus per la promozione e lo sviluppo della ricerca scientifica sulle malattie ematologiche. FRANCO MANDELLI

GITMO

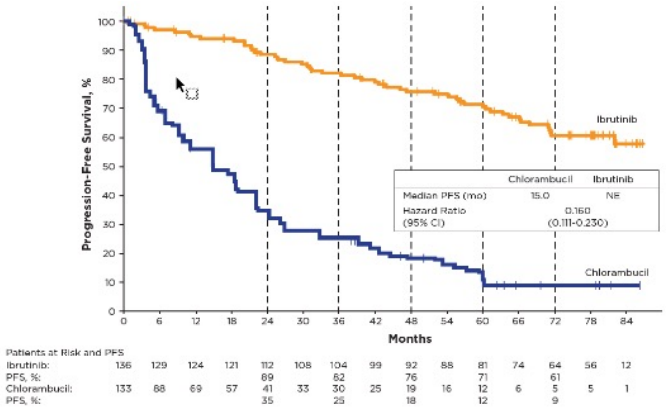
SIE - Società Italiana di Ematologia

Disclosures of PAOLO GHIA

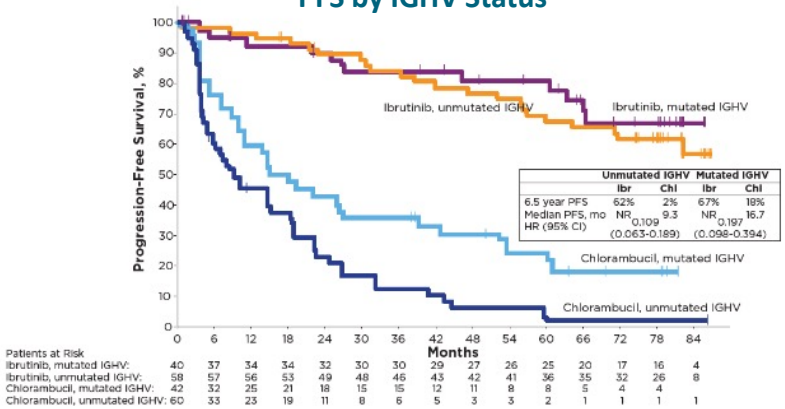
Company name	Research support	Employee	Consultant	Stockholder	Speakers fees	Advisory board	Other
AstraZeneca	x		x		x	x	
AbbVie	x		x		x	x	
ArQule/MSD			x			x	
BeiGene			x		x	x	
CelGene/Juno/BMS			x			x	
Janssen	x		x		x	x	
Lilly/Loxo			x		x	x	
Sanofi			x			x	
Roche			x			x	

Phase 3 RESONATE-2 study with up to 7 years of follow-up: 1L ibrutinib

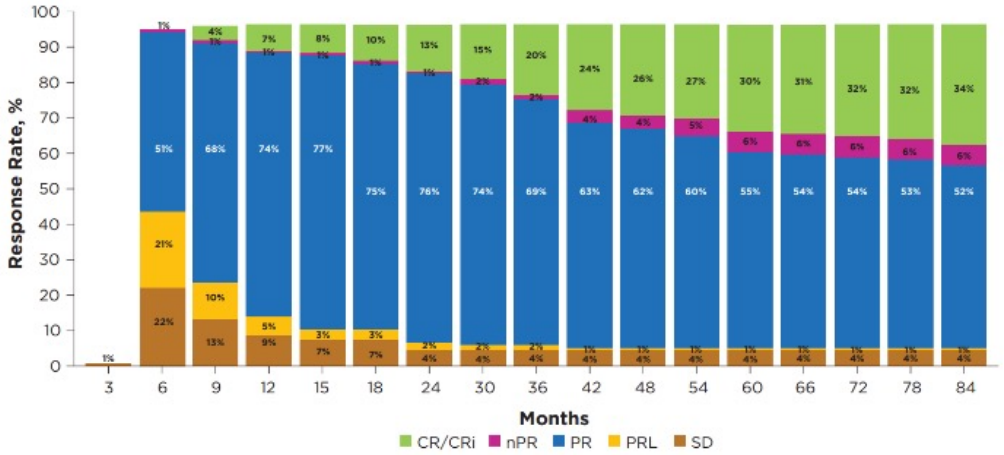
PFS: Ibrutinib vs chlorambucil



PFS by IGHV Status



Response increase over time: CR/CRi 34%



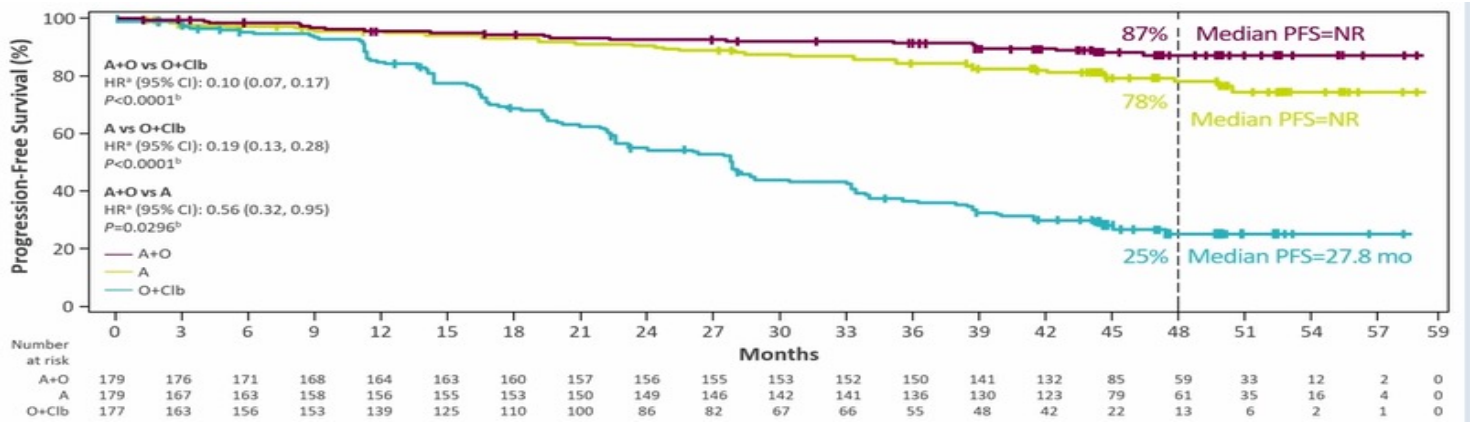
- **Longest follow-up of any Ph3 1L studies of targeted agents**
- **61% of patients are alive and progression-free at 6.5 years. 6.5-year OS: 78%.**
- Ibr benefit similar in pts with mIGHV and uIGHV, and response including CR/CRi continued to deepen over time.
- **Only 16 (12%) pts progressed while receiving ibr.**
- Close to 50% of pts remain on therapy; dose adjustments effectively managed most AEs

Median Follow-up: 74.9 months

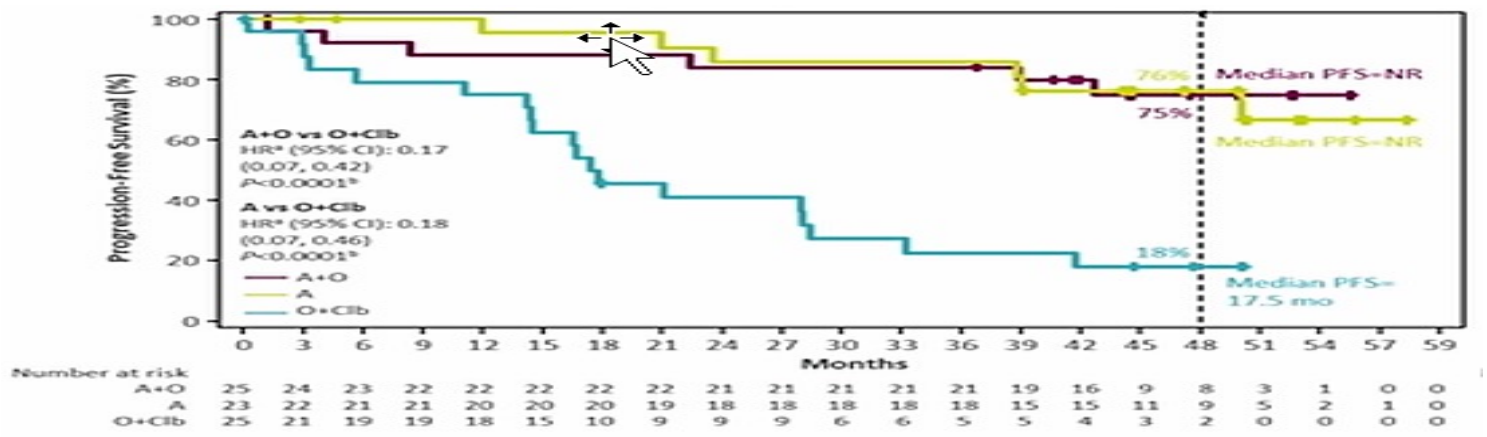
Ghia et al., EHA 2021; EP636 (poster presentation)

ELEVATE TN: Acalabrutinib ± obinutuzumab vs CHL+Obinu

Investigator assessed PFS



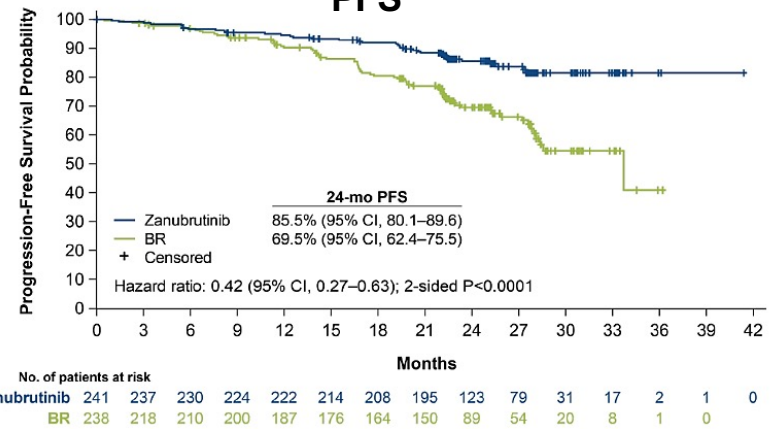
PFS del(17p)/*TP53*mut



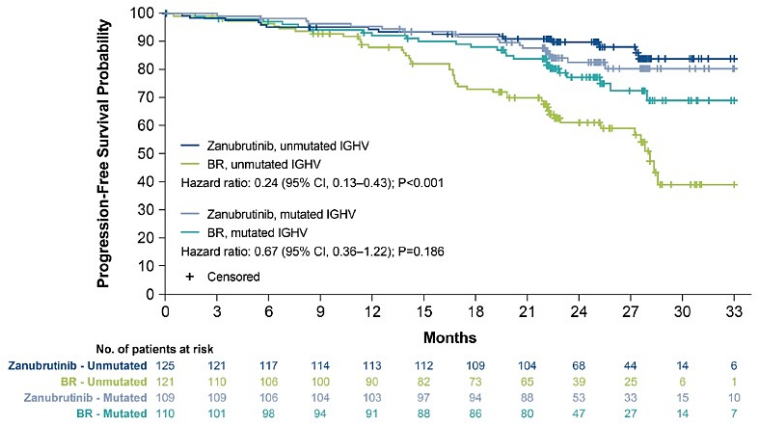
Sharman et al., EHA 2021; S148 (oral presentation)

Phase 3 SEQUOIA (BGB-3111-304): Zanubrutinib vs bendamustine + R

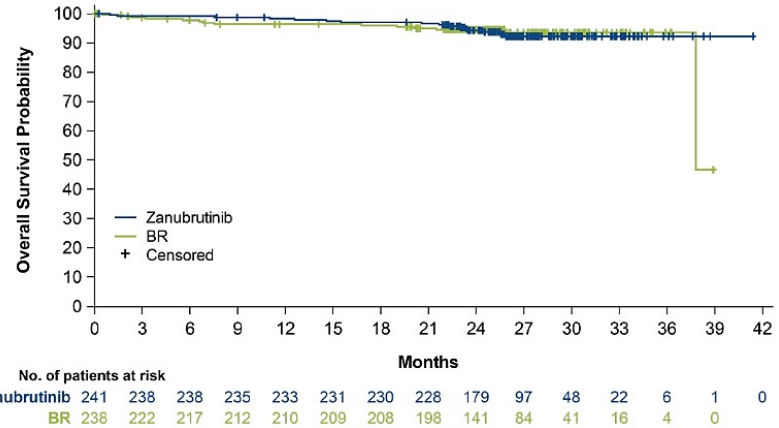
PFS



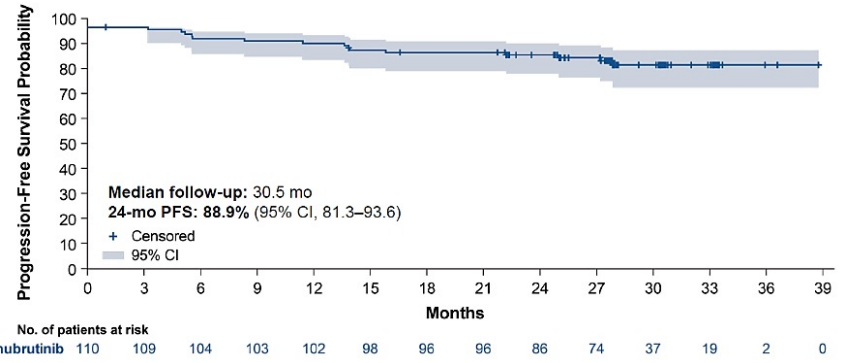
PFS by IGHV status



OS

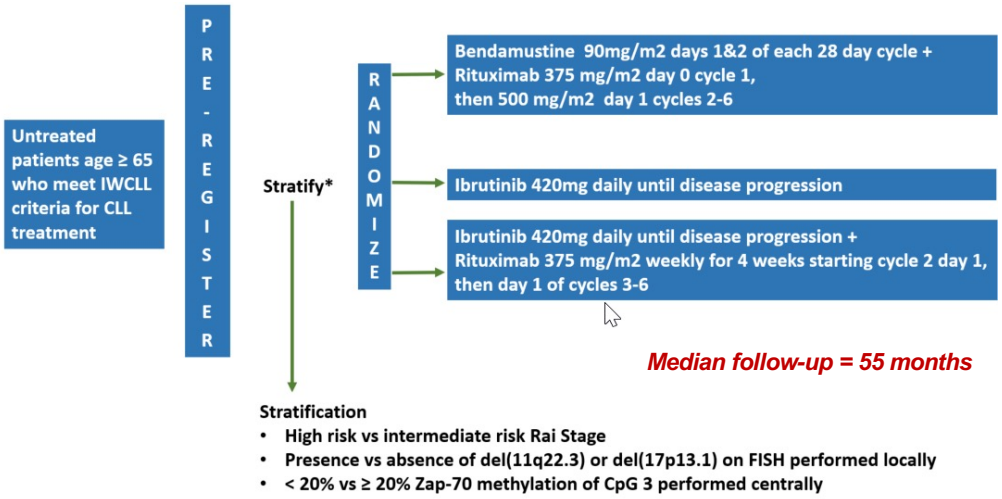


Cohort 2: PFS in patients with del(17p)

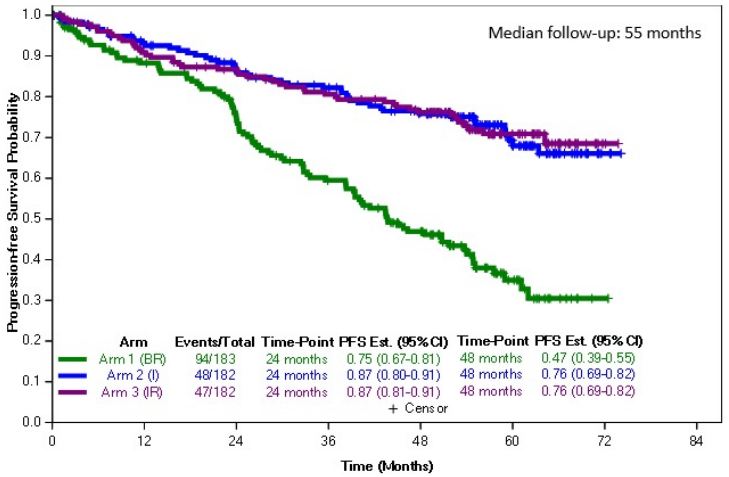


Tam et al., ASH 2021; abstract 396

Alliance A041202 : long term results of ibrutinib-based regimens vs bendamustine + rituximab



PFS



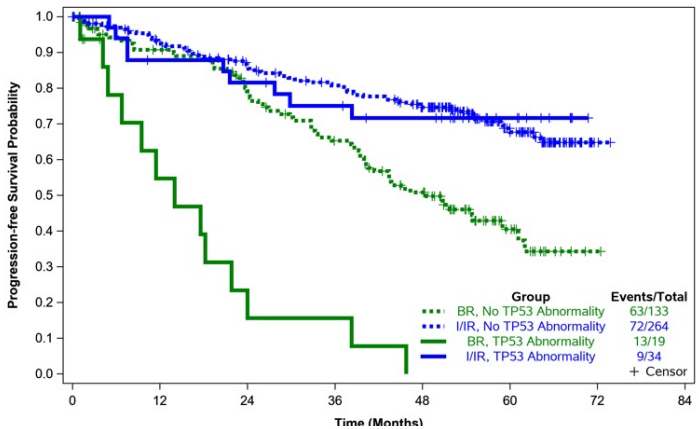
Pairwise Comparisons

I vs BR:
Hazard Ratio 0.36
95% CI: 0.26-0.52
P <0.0001

IR vs BR:
Hazard Ratio 0.36
95% CI: 0.25-0.51
P <0.0001

IR vs I:
Hazard Ratio 0.99
95% CI: 0.66-1.48
P = 0.96

PFS: *TP53* abnormalities



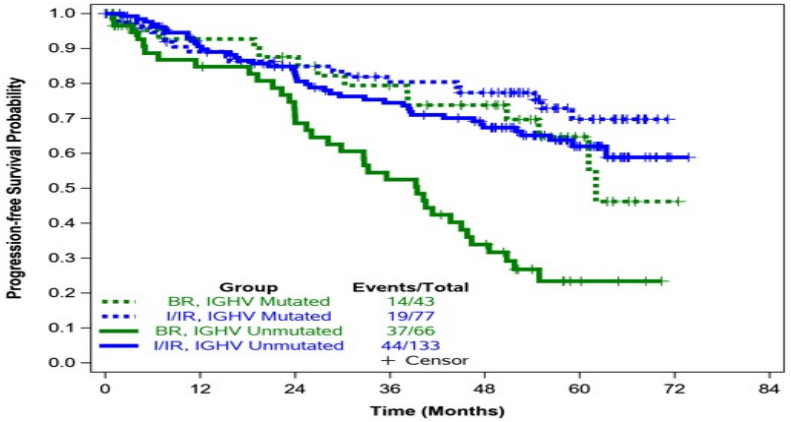
Treatment Effect
I/IR vs BR

No TP53 Abn
Hazard Ratio 0.39
95% CI: 0.27-0.55

TP53 Abn
Hazard Ratio 0.07
95% CI: 0.03-0.18

Interaction P = 0.0006

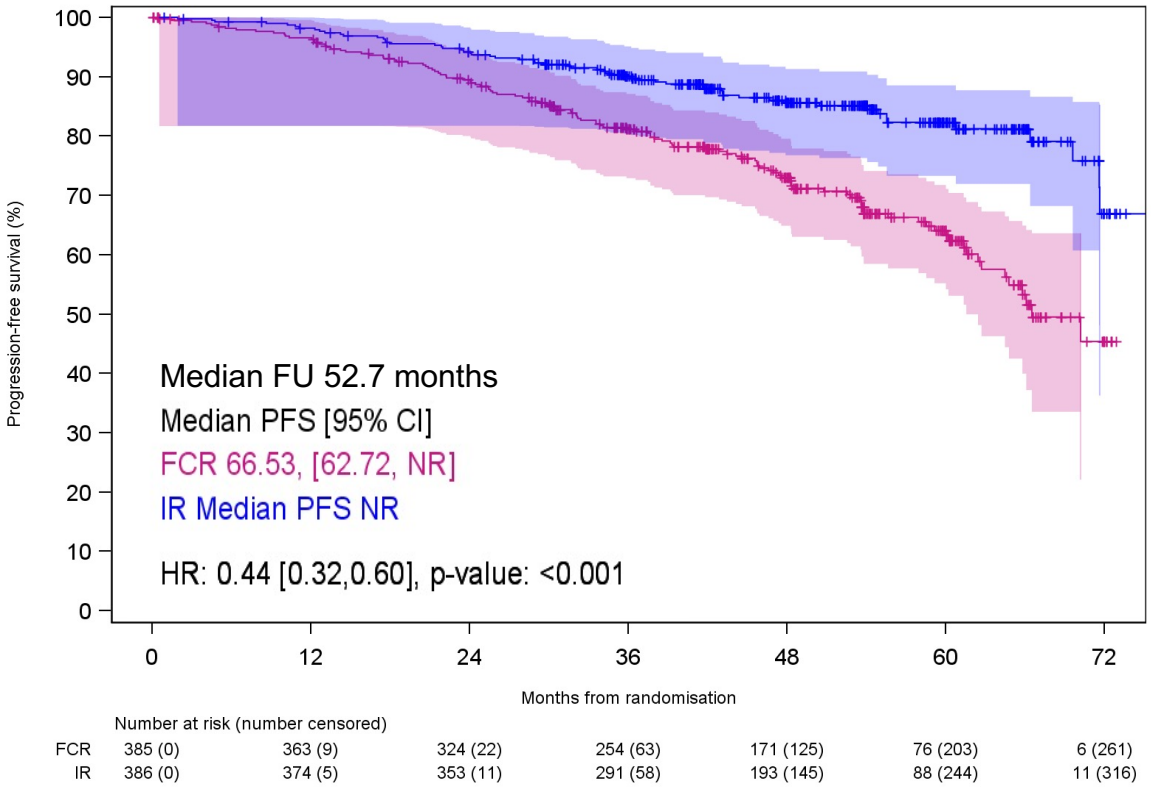
PFS: IGHV status



Woyach et al., ASH 2021; abstract 639

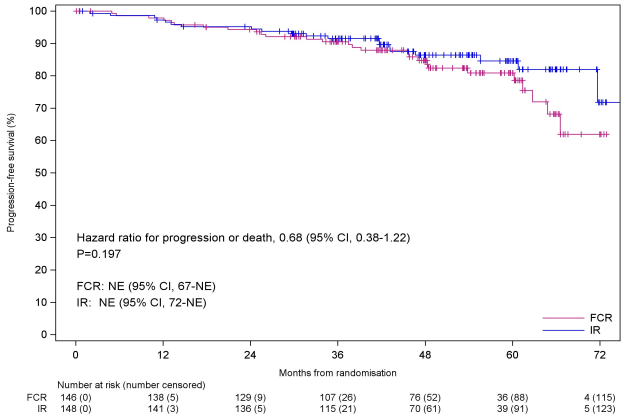
Phase III NCRI FLAIR Trial: Ibrutinib plus rituximab vs FCR

Primary endpoint: PFS



Hillmen et al., ASH 2021; abstract 642

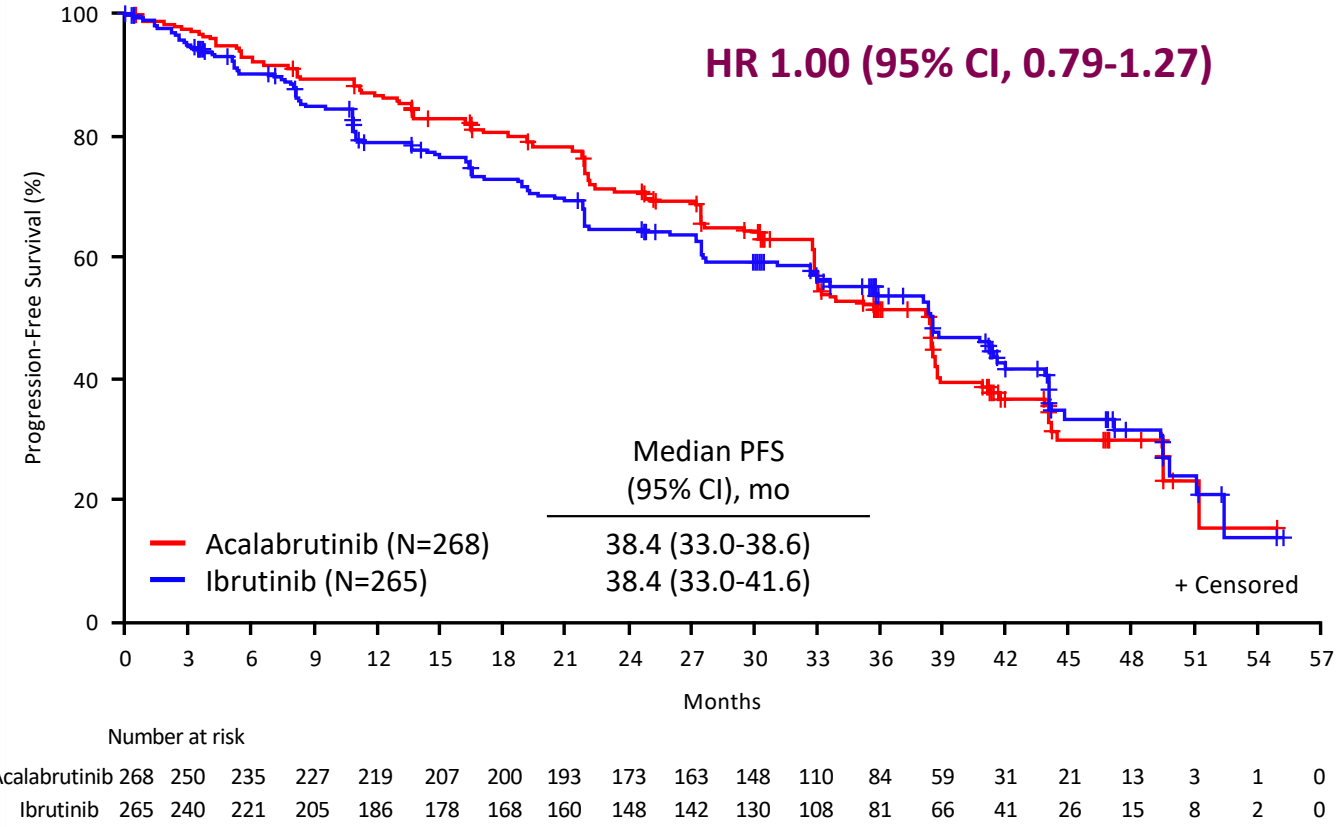
IGHV mutated CLL excl. Subset 2 (n=294)



Cause of death * *, Deaths at any time in FU	**FCR (n=29)**	**IR (n=30)**
CLL	4	3
Non-haematological malignancy	4	7
AML/MDS	3	0
ALL	1	0
Richters transformation	3	1
Infections (non-COVID)	6	4
COVID-19	3	3
Haemorrhage	1	2
Cardiac	2	9
Other	2	1
Total	**29**	**30**

Phase 3 ELEVATE RR study: Acalabrutinib vs Ibrutinib in HR CLL

Primary endpoint: non-inferiority IRC-Assessed PFS



Median follow-up 41 months

	Acalabrutinib (N=268)	Ibrutinib (N=265)
Events, n (%)	143 (53.4)	136 (51.3)
Death	22 (8.2)	28 (10.6)
PD	121 (45.1)	108 (40.8)
Censored, n (%)	125 (46.6)	129 (48.7)
PFS (95% CI), %		
12 months	86.7 (81.8-90.3)	78.8 (73.1-83.4)
24 months	70.9 (64.8-76.1)	64.5 (58.1-70.2)
36 months	51.4 (44.7-57.8)	53.8 (47.0-60.1)

Noninferiority achieved if the upper bound of the 95% CI of HR is less than the prespecified NI margin of 1.429

HR, hazard ratio; IRC, independent review committee; PFS, progression-free survival.

Byrd J et al, Oral presentation ASCO 2021

Phase 3 ELEVATE RR study: Acalabrutinib vs Ibrutinib in HR CLL

Most common AEs

Events, n (%)	Any grade		Grade ≥3	
	Acalabrutinib (n=266)	Ibrutinib (n=263)	Acalabrutinib (n=266)	Ibrutinib (n=263)
Diarrhea[a,b]	92 (34.6)	**121 (46.0)**	3 (1.1)	**13 (4.9)**
Headache[a,b]	**92 (34.6)**	53 (20.2)	**4 (1.5)**	0
Cough[a]	**77 (28.9)**	56 (21.3)	2 (0.8)	1 (0.4)
URTI	71 (26.7)	65 (24.7)	5 (1.9)	1 (0.4)
Neutropenia	56 (21.1)	65 (24.7)	52 (19.5)	60 (22.8)
Pyrexia	62 (23.3)	50 (19.0)	8 (3.0)	2 (0.8)
Arthralgia[a]	42 (15.8)	**60 (22.8)**	0	2 (0.8)
Hypertension[a,b]	23 (8.6)	**60 (22.8)**	11 (4.1)	**23 (8.7)**
Anemia	58 (21.8)	49 (18.6)	31 (11.7)	34 (12.9)
Fatigue[b]	54 (20.3)	44 (16.7)	**9 (3.4)**	0
Nausea	47 (17.7)	49 (18.6)	0	1 (0.4)
Contusion[a]	31 (11.7)	**48 (18.3)**	0	1 (0.4)
Pneumonia	47 (17.7)	43 (16.3)	28 (10.5)	23 (8.7)
Atrial fibrillation[a]	24 (9.0)	**41 (15.6)**	12 (4.5)	9 (3.4)
Thrombocytopenia	40 (15.0)	35 (13.3)	26 (9.8)	18 (6.8)

Higher incidence in **bold red** for terms with statistical differences.
Among most common AEs above, grade 5 were reported in 5 (1.9%) acalabrutinib patients (pyrexia, n=1; pneumonia, n=4) and 4 (1.5%) ibrutinib patients (URTI, n=1; pneumonia, n=3).
[a]Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for any grade events.
[b]Based on Barnard's exact test, two-sided P-value <0.05 without multiplicity adjustment for grade ≥3 events.
Includes AEs reported at ≥15% incidence (any grade) in either arm.
AE, adverse event; URTI, upper respiratory tract infection.

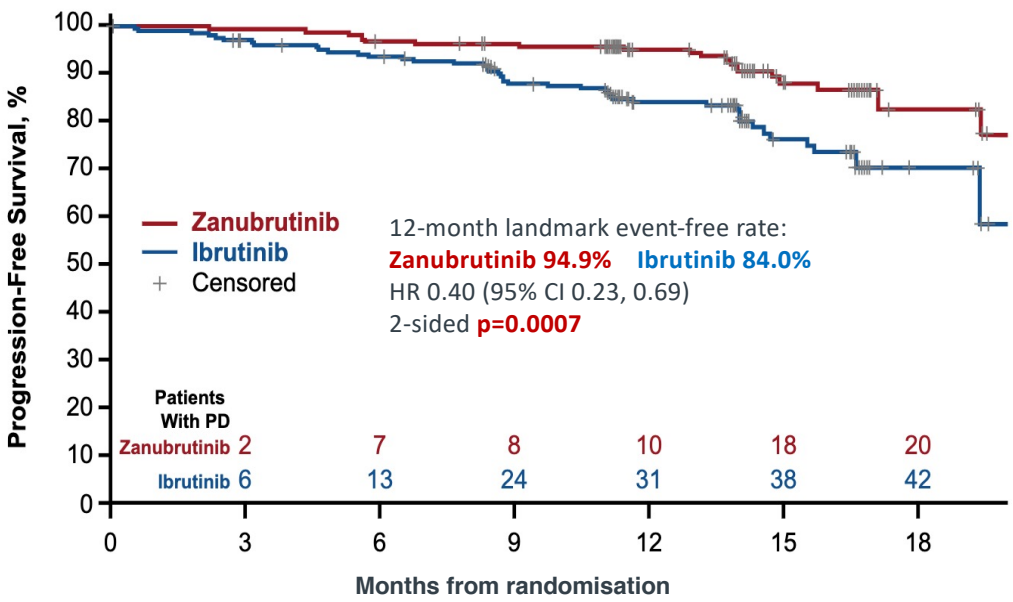
Ghia P et al, Oral presentation JSH 2021

Phase 3 ALPINE study: Ibrutinib vs zanubrutinib in RR CLL

ORR by investigator assessment

	Zanubrutinib (n=207), n (%)	Ibrutinib (n=208), n (%)
Primary endpoint: ORR (PR+CR)	162 (78.3) 95% CI: 72.0, 83.7	130 (62.5) 95% CI: 55.5, 69.1
	Superiority 2-sided *P*=0.0006 compared with pre-specified alpha of 0.0099	
CR/CRi	4 (1.9)	3 (1.4)
nPR	1 (0.5)	0
ORR (PR-L+PR+CR)	183 (88.4)	169 (81.3)
PR-L	21 (10.1)	39 (18.8)
SD	17 (8.2)	28 (13.5)
PD	1 (0.5)	2 (1.0)
Discontinued or new therapy prior to 1st assessment	6 (2.9)	9 (4.3)
	del(17p) (n=24), n (%)	**del(17p) (n=26), n (%)**
ORR (PR+CR)	20 (83.3)	14 (53.8)

PFS by investigator assessment



CR, complete response; CRi, CR with incomplete bone marrow recovery; nPR, nodular partial response; ORR, overall response rate; PD, progressive disease; PFS, progression-free survival; PR, partial response; PR-L, partial response with lymphocytosis; SD, stable disease

Hillmen P, et al. Oral presentation at EHA 2021 (Abstract LB1900)

Phase 3 ALPINE study: Zanubrutinib vs Ibrutinib in RR CLL

AEs of Special Interest

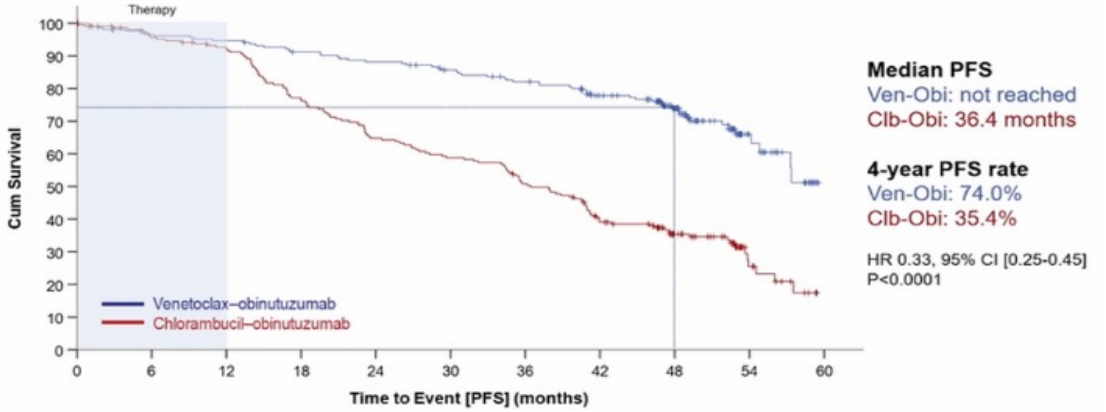
Safety Analysis Population	Zanubrutinib (n=204), n (%)		Ibrutinib (n=207), n (%)	
	Any Grade	Grade ≥3	Any Grade	Grade ≥3
Cardiac disorders[a]	28 (13.7)	5 (2.5)	52 (25.1)	14 (6.8)
Atrial fibrillation and flutter (key 2º endpoint)	**5 (2.5)**	**2 (1.0)**	**21 (10.1)**	**4 (1.9)**
Hemorrhage Major hemorrhage[b]	73 (35.8) 6 (2.9)	6 (2.9) 6 (2.9)	75 (36.2) 8 (3.9)	6 (2.9) 6 (2.9)
Hypertension	34 (16.7)	22 (10.8)	34 (16.4)	22 (10.6)
Infections	122 (59.8)	26 (12.7)	131 (63.3)	37 (17.9)
Neutropenia[c]	58 (28.4)	38 (18.6)	45 (21.7)	31 (15.0)
Thrombocytopenia[c]	19 (9.3)	7 (3.4)	26 (12.6)	7 (3.4)
Secondary primary malignancies Skin cancers	17 (8.3) 7 (3.4)	10 (4.9) 3 (1.5)	13 (6.3) 10 (4.8)	4 (1.9) 2 (1.0)

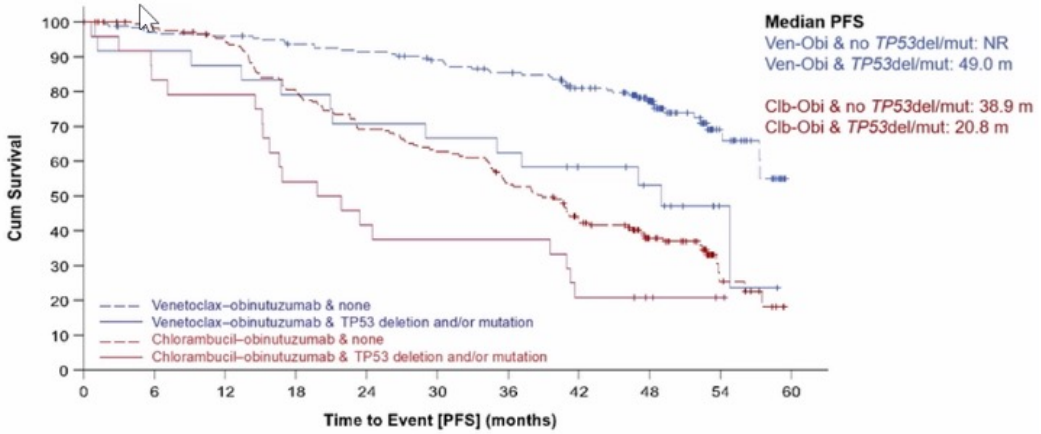
AE, adverse events. All events are of any grade unless otherwise specified.
[a] Cardiac disorders leading to treatment discontinuation: zanubrutinib 0 patients and ibrutinib 7 (3.4%) patients.
[b] Includes hemorrhages that were serious or grade ≥3 or CNS hemorrhages of all grades.
[c] Pooled terms including neutropenia, neutrophil count decreased, and febrile neutropenia; thrombocytopenia and platelet count decreased.

ALPINE study. Hillmen et al. LB1900 EHA 2021

Phase 3 CLL14 study: First-line venetoclax + obinutuzimab

4 year follow-up: PFS and TP53 status



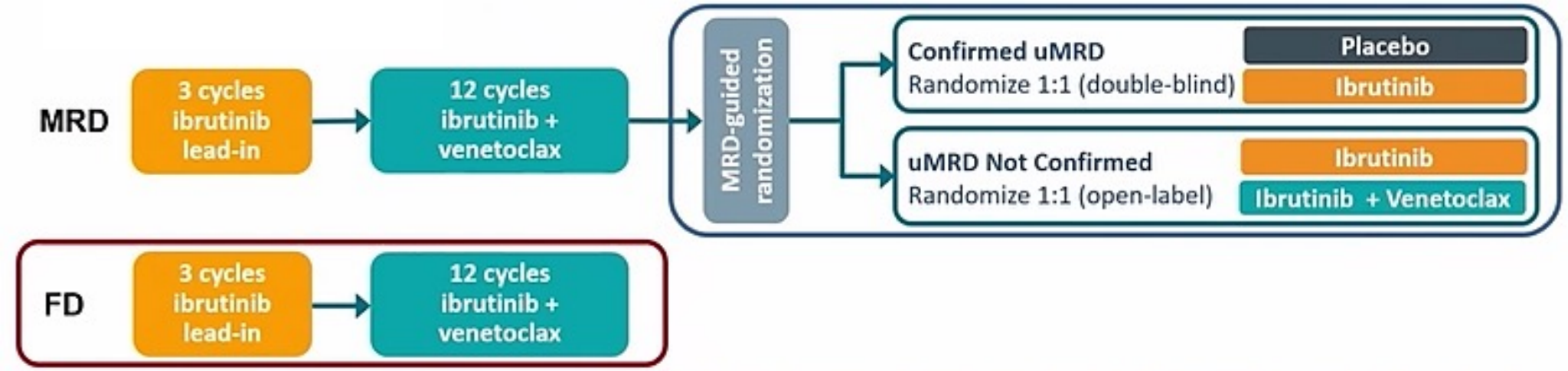


Median observation time = 52.4 months

Al-Sawaf et al., EHA 2021; S146 (oral presentation)

Phase 2 CAPTIVATE: First-line ibrutinib + venetoclax

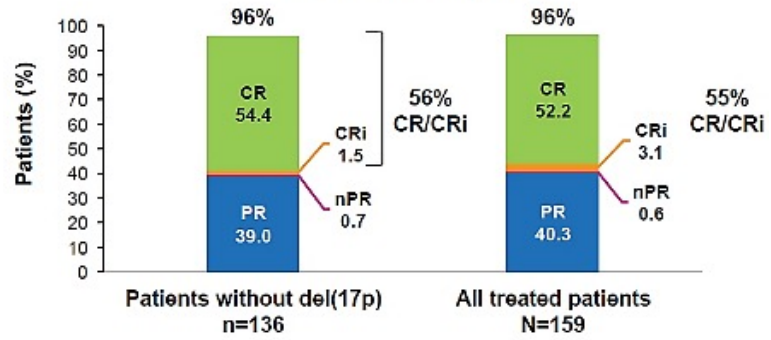
CAPTIVATE is an international, multicenter phase 2 study evaluating 3 cycles of ibrutinib followed by 12 cycles of combined ibrutinib + venetoclax that comprises two cohorts: MRD and fixed-duration (FD)



Ghia et al., J Clin Oncol 2021;39(suppl15):abstract 7501;
Allan et al., EHA 2021; S147; Wierda et al., iwCLL 2021; abstract 1084132

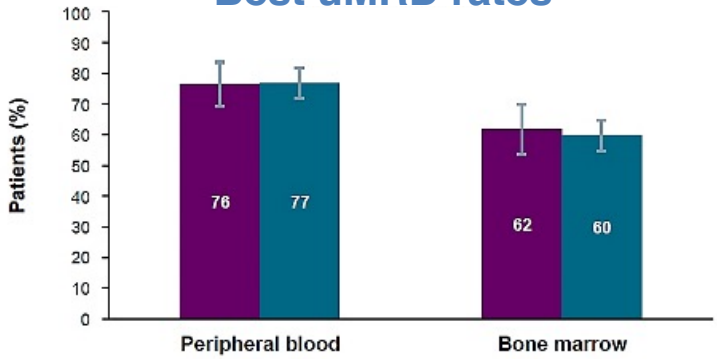
Phase 2 CAPTIVATE trial: primary analysis of the FD cohort

Best overall response

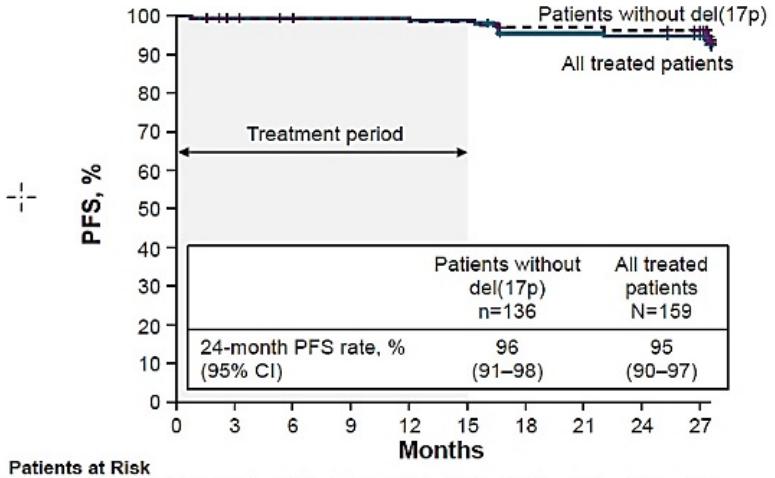


DOCR ≥12 cycles n/N (%)	66/76 (87)	78/88 (89)`

Best uMRD rates



PFS



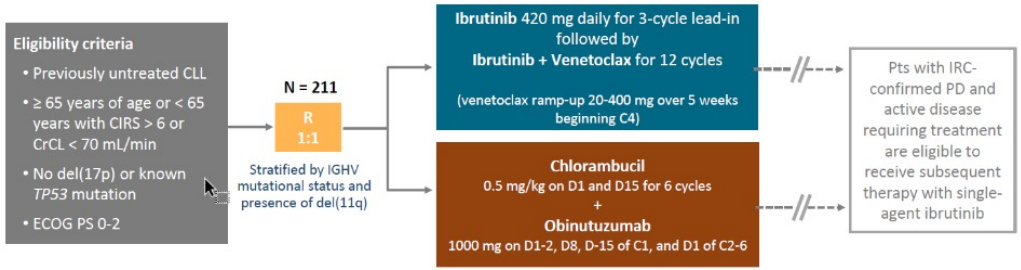
Patients at Risk										
All treated patients	159	155	153	152	152	151	144	144	143	141
Patients without del(17p)	136	132	130	129	129	128	125	125	124	122

Estimated 24-month PFS rates

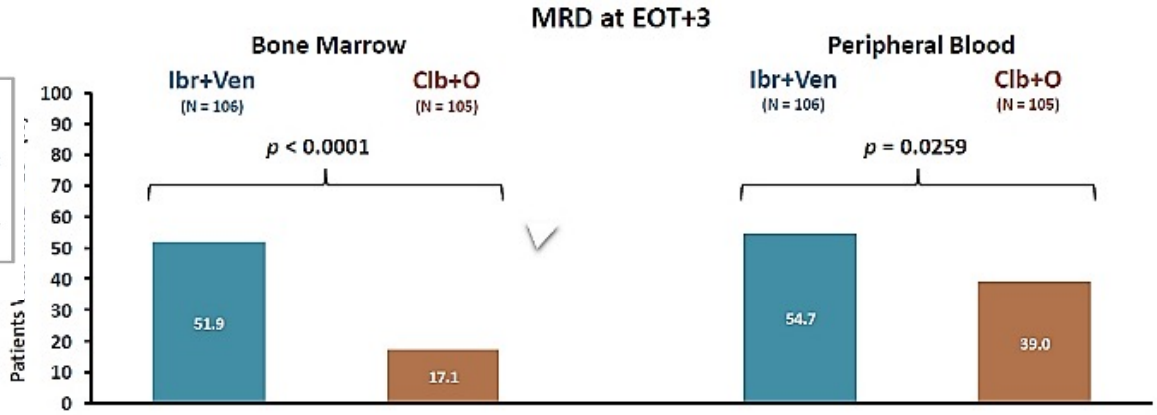
- Unmutated IGHV: 93% (95% CI 85, 97)
- Mutated IGHV: 97% (95% CI 88, 99)

Ghia P, et al. Oral presentation at ASCO 2021 (Abstract 7501)

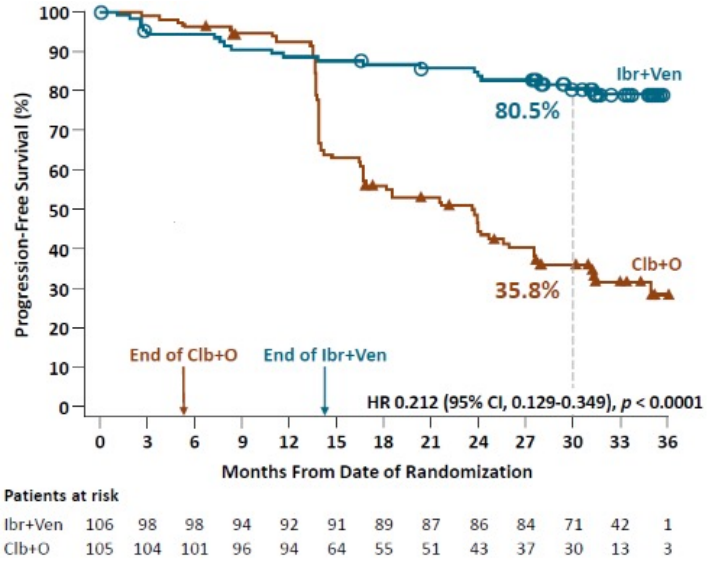
GLOW: MRD outcomes



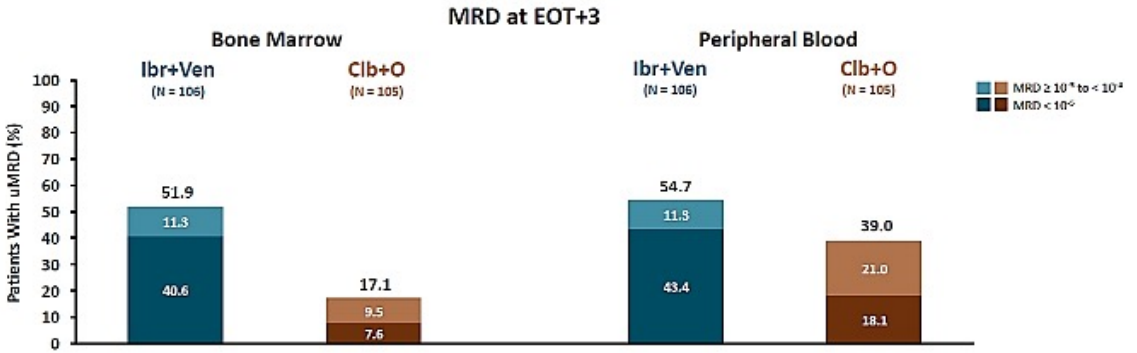
uMRD rate <10^{-4} was significantly higher in both compartments with Ibr+Ven



Superior PFS with I+V vs Clb+O was maintained with a median 34.1 months of follow-up



uMRD rate <10^{-5} was higher with ibr+Ven vs Clb+O in both compartments

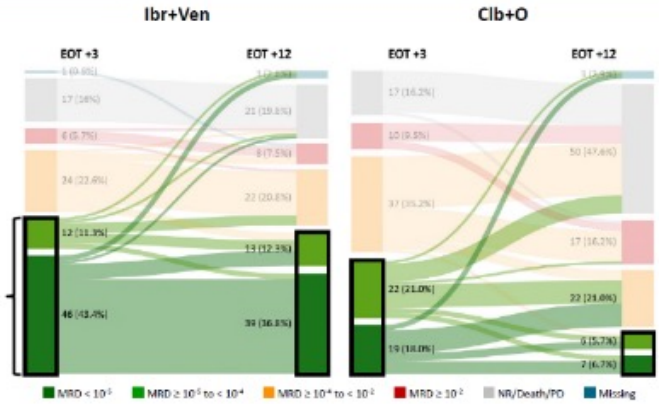


Munir et al., ASH 2021; abstract 70

Phase 3 GLOW study: MRD outcomes

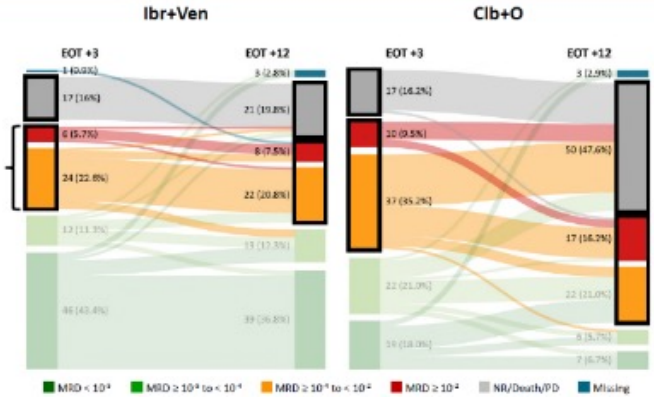
uMRD in PB Was Better Sustained With Ibr+Ven From EOT+3 to EOT+12

- **84.5%** (49/58) of patients had sustained uMRD < 10^{-4} and **80.4%** (37/46) had sustained uMRD < 10^{-5} with Ibr+Ven[a]
  - 29.3% (12/41) and 26.3% (5/19) with Clb+O
- uMRD < 10^{-4} rate decreased 6% with Ibr+Ven vs 27% with Clb+O

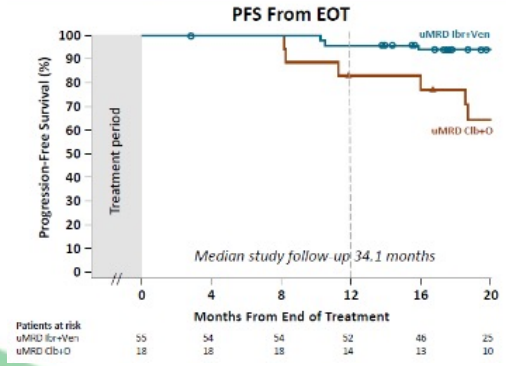


With Ibr+Ven, Detectable MRD Was Less Likely to Worsen or Lead to Progression by EOT+12 vs Clb+O

- Patients with detectable MRD ≥ 10^{-4} in the Ibr+Ven arm were less likely to:
  - Convert to PD vs those in the Clb+O arm
  - Have worsening of detectable MRD levels

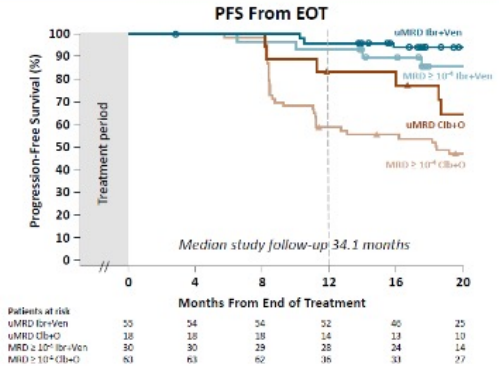


PFS According to Bone Marrow MRD Status at EOT+3



- In patients with **uMRD < 10^{-4}** in BM, PFS rate was better sustained post-treatment with Ibr+Ven vs Clb+O

With Ibr+Ven, PFS Rate Was Sustained in the First Year Post-treatment Irrespective of MRD Status in BM at EOT+3

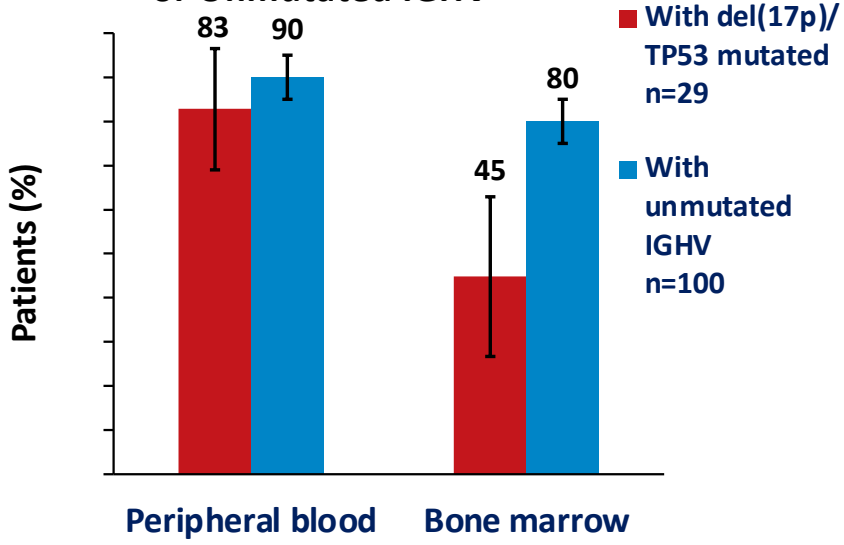


- PFS rate during the first year post-treatment was sustained > 90% with Ibr+Ven, independent of BM MRD status

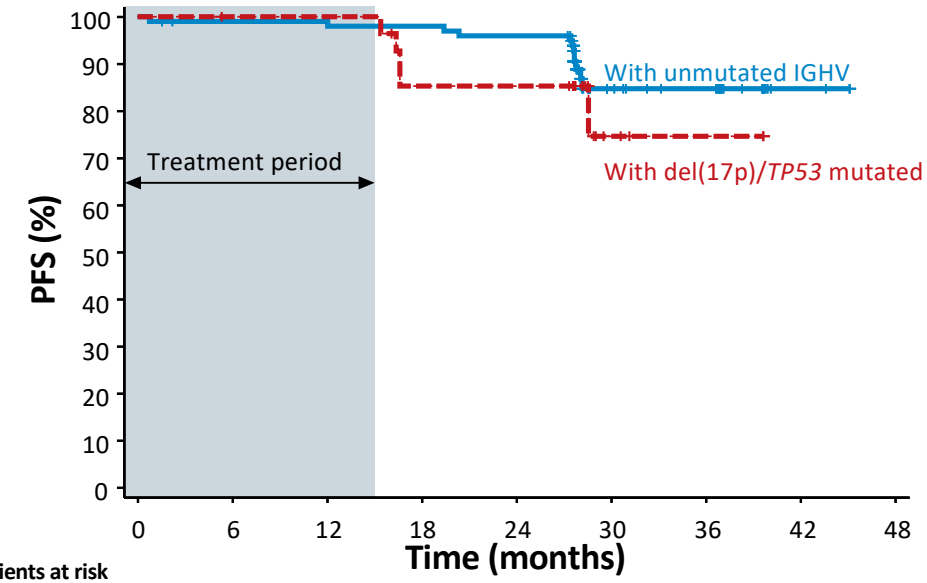
Munir et al., ASH 2021; abstract 70

Phase 2 CAPTIVATE study: Efficacy in CLL With high-risk features

Best uMRD Rates With del(17p)/*TP53* Mutated or Unmutated IGHV[a]



PFS With del(17p)/*TP53* Mutated or Unmutated IGHV[b]



Patients at risk									
With unmutated IGHV	100	97	97	96	94	32	27	3	0
With del(17p)/*TP53* mutated	29	28	28	23	23	4	2	0	

- Analysis of uMRD rates showed lower bone marrow uMRD rates in patients with del(17p)/*TP53* mutated
- analysis of PFS by individual high-risk features showed a decrease in PFS among the small subset of patients with del(17p)/*TP53* mutated

[b]*Unmutated IGHV without del(17p)TP53 mutation.*

Allan et al. AACR 2022, PCYC-1142;

Phase 2 CAPTIVATE – Fixed-duration cohort

Safety analysis

Majority of AEs with IV were low grade

AEs, n (%)	All treated patients N=159	
Most frequent AEs (≥30%)	**Grade 1/2**	**Any grade**
Diarrhea	94 (59)	99 (62)
Nausea	66 (42)	68 (43)
Neutropenia	14 (9)	66 (42)
Arthralgia	51 (32)	53 (33)
Grade 3/4 AEs (≥5%)	98 (62)	
Neutropenia	52 (33)	
Infections[a]	13 (8)	
Hypertension	9 (6)	
Neutrophil count decreased	8 (5)	
AEs of clinical interest (any grade)		
Atrial fibrillation	7 (4)	
Major hemorrhage[a]	3 (2)	
Any serious AE	36 (23)	
Fatal AEs	1 (1)[b]	

Discontinuations and dose reductions were rare

AEs, n (%)	All treated patients N=159
AEs leading to discontinuation	8 (5)
Ibrutinib only	5 (3)
Venetoclax only	0
Both ibrutinib and venetoclax	3 (2)[a]
AEs leading to dose reduction	33 (21)
Ibrutinib only	9 (6)
Venetoclax only	18 (11)
Both ibrutinib and venetoclax	6 (4)

- **88% of patients with AEs leading to dose reduction had resolution of AEs at the time of analysis**
- **8 patients who progressed after fixed duration treatment were retreated with single-agent ibrutinib**
  - **6/8 responded with PR, with 2 patients pending response evaluation**

Ghia et al. ASCO 2021, CAPTIVATE-FD

Phase 3 GLOW study: Safety and TLS risk reduction

Grade 3 or higher AEs in ≥5% of patients

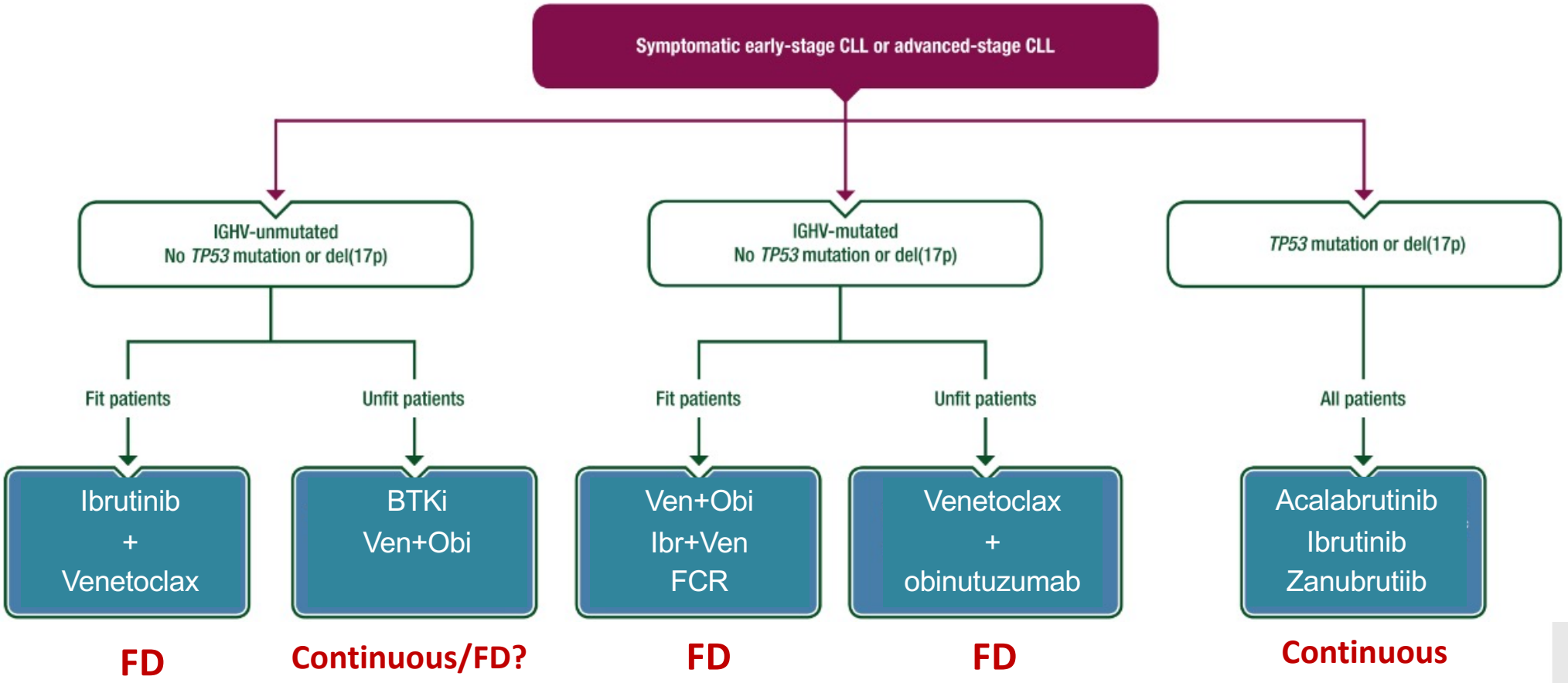
	I+V (N = 106)	Clb+O (N = 105)
Median exposure, mos (range)	13.8 (0.7-19.5)	5.1 (1.8-7.9)
Any, %	75.5	69.5
Neutropenia[a]	34.9	49.5
Infections[b]	17.0	11.4
Thrombocytopenia	5.7	20.0
Diarrhea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7

[a]Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O
[b]Includes multiple preferred terms

- After 3 cycles of ibrutinib lead-in, <2% of patients remained at risk for TLS based on high-tumor burden
- 2 (1.9%) patients with I+V arm discontinued ibrutinib due to atrial fibrillation
- SAEs in ≥5% of patients for I+V vs Clb+O: infections (12.3% vs 8.6%) and atrial fibrillation (6.6% vs 0%)
- Rate of secondary malignancies at the time of analysis: 8.5% for I+V vs 10.5% for Clb+O

Kater et al., EHA 2021; LB1902 (oral presentation)

A possible future for frontline therapy



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ERIC european research initiative on CLL

TRANSCAN-2

Associazione Italiana per la Ricerca sul Cancro

Con la ricerca, contro il cancro.