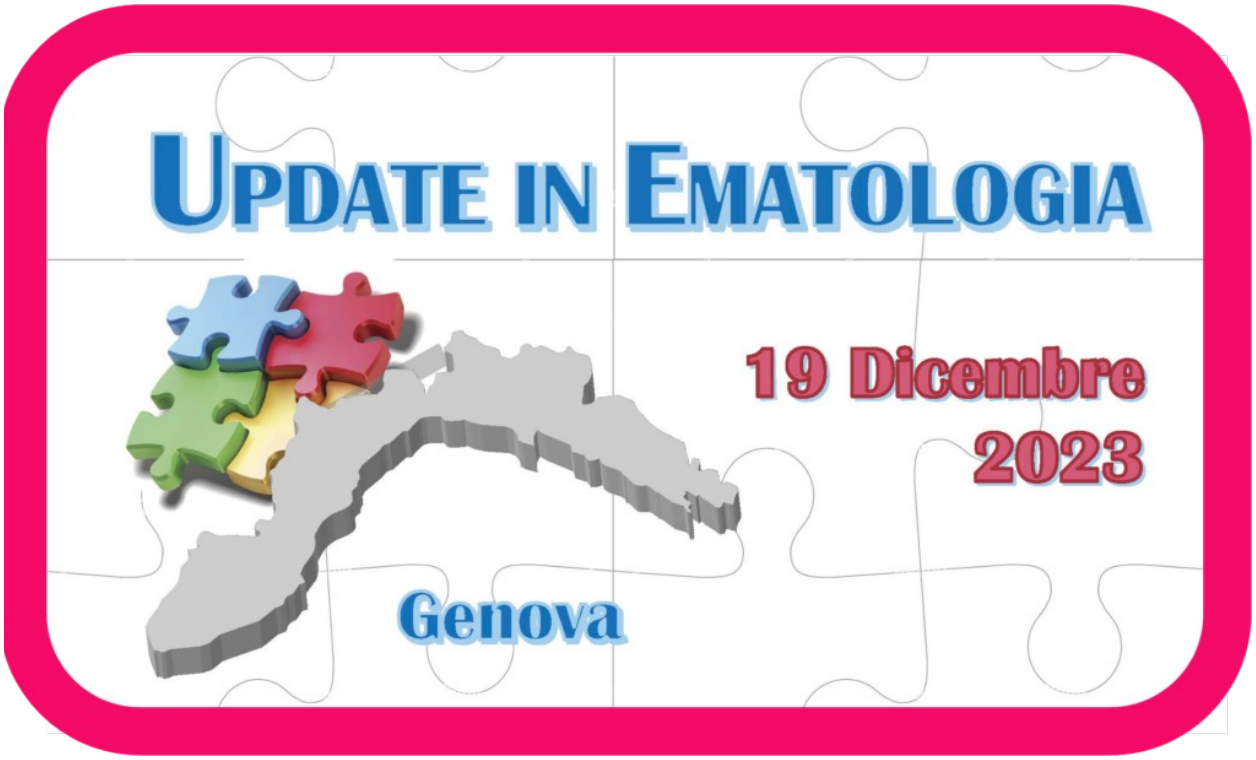


Ibatici Adalberto

La terapia del paziente giovane con Leucemia Linfatica Cronica

haematologica

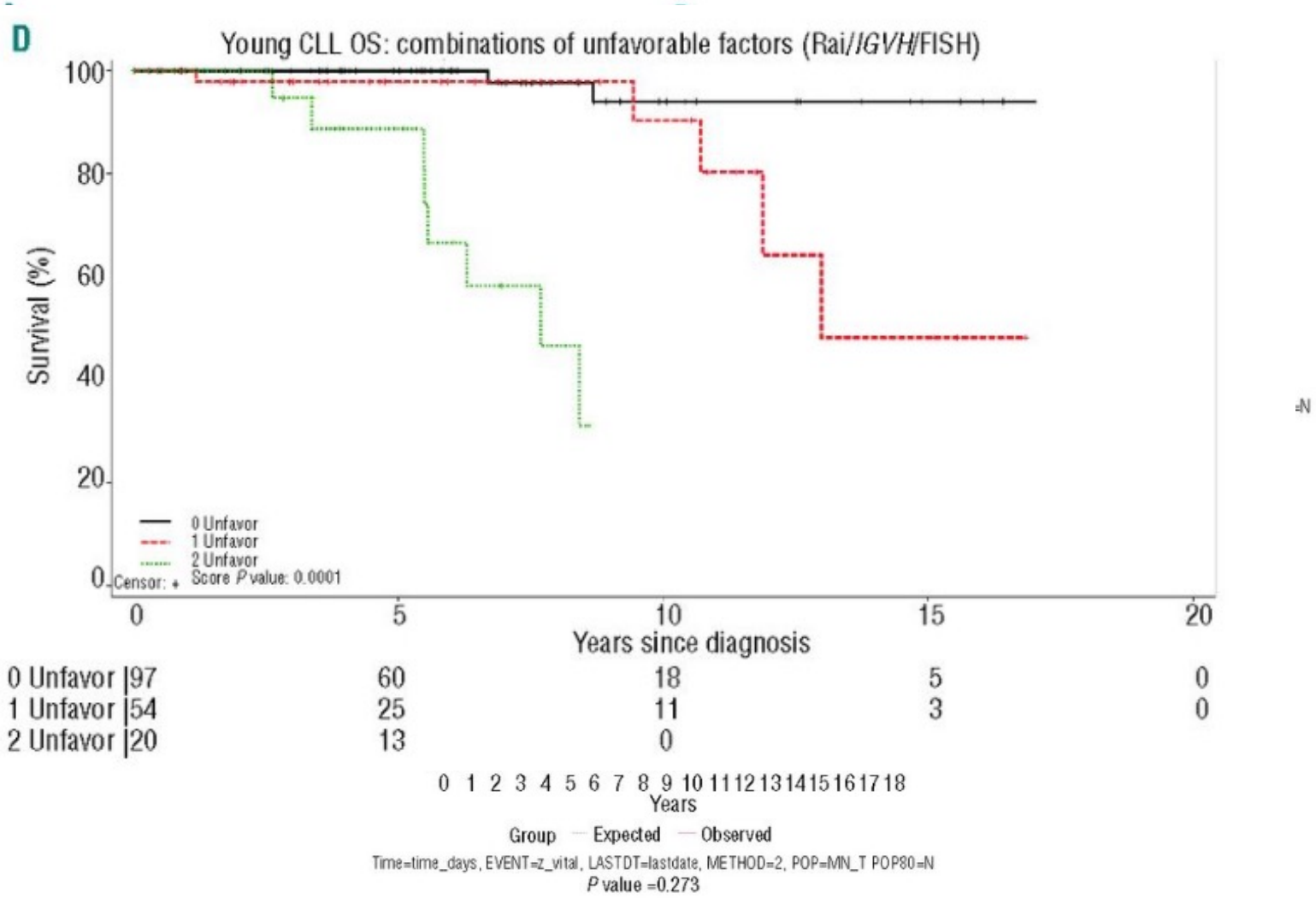
Vol. 99 No. 1 (2014): January, 2014

ARTICLES

Chronic lymphocytic leukemia in young (≤ 55 years) patients: a comprehensive analysis of prognostic factors and outcomes

Sameer A. Parikh, Kari G. Rabe, Neil E. Kay, Timothy G. Call, Wei Ding, Susan M. Schwager, Deborah A. Bowen, Michael Conte, Diane F. Jelinek, Susan L. Slager, Tait D. Shanafelt

Comparison of overall survival with the general population



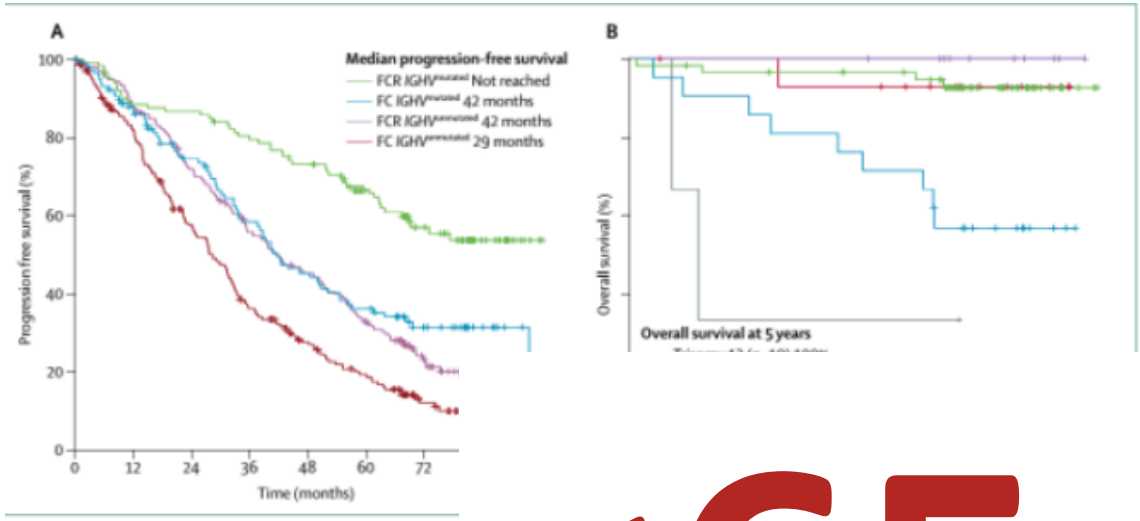
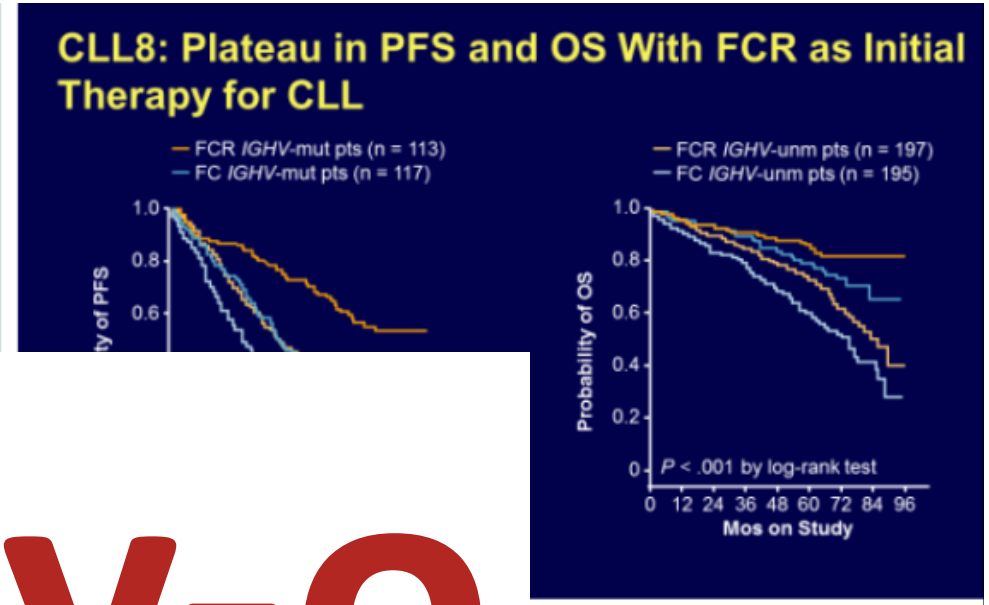


Figure 3: Long-term benefit of fludarabine, cyclophosphamide,
(A) Progression-free survival with FCR according to IGHV status in
5·9 years.[49] (B) Overall survival with FCR for all patients with mutat
observation time of 5·9 years.[49]



<65 y-o

- 69% of patients years.
- More important lian PFS had not been reached, and relapses were rarely observed after 9 years
- Trisomy 12, del(13q), or del(11q) pts with M-IGHV had an OS of > 80% at 8 years
- FCR can achieve durable remissions in a sizeable subgroup of patients physically fit CLL patients without TP53 aberration

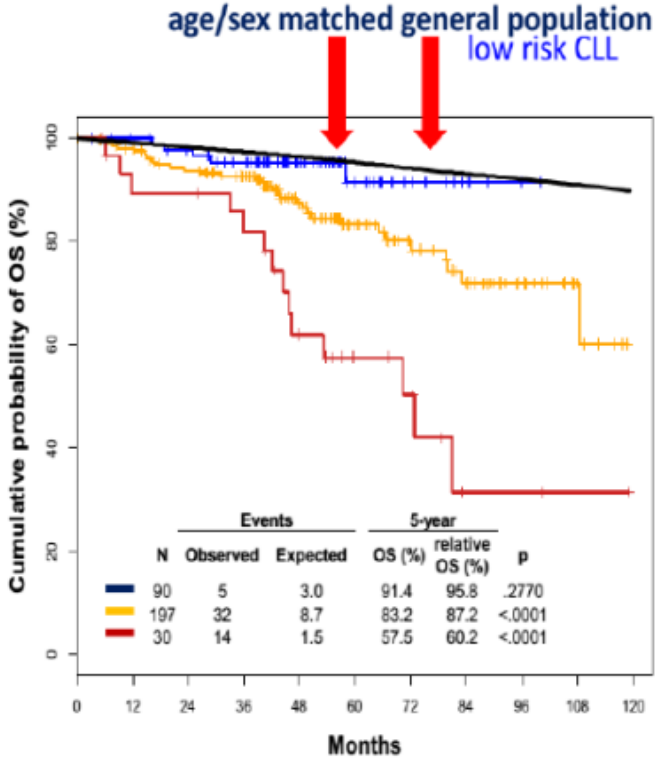
Very low-risk group even cured by chemotherapy/ FCR?

	Events	Total	5-years OS	95% CI
	5	90	91.4	87.1-95.7
	32	197	83.2	80,0-86.4
	14	30	57.5	47.6-67.4

Pairwise comparisons of the OS curves

p			
	-	0.0341	<0.0001
	0.0341	-	0.0004
	<0.0001	0.0004	-

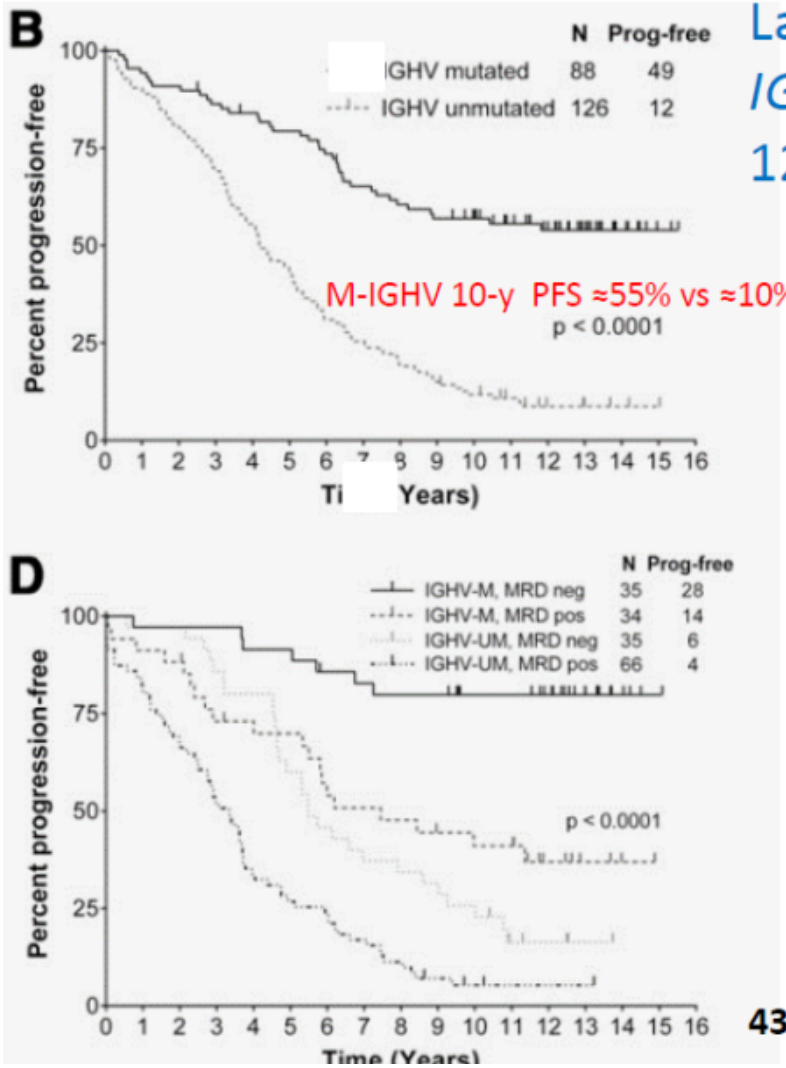
low risk:
mutated IGHV, no 11q-, no 17p-



Pts with M-IGHV and no del(17p) or del(11q) had a life expectancy of 91% at 5y, superimposable to a matched normal general population

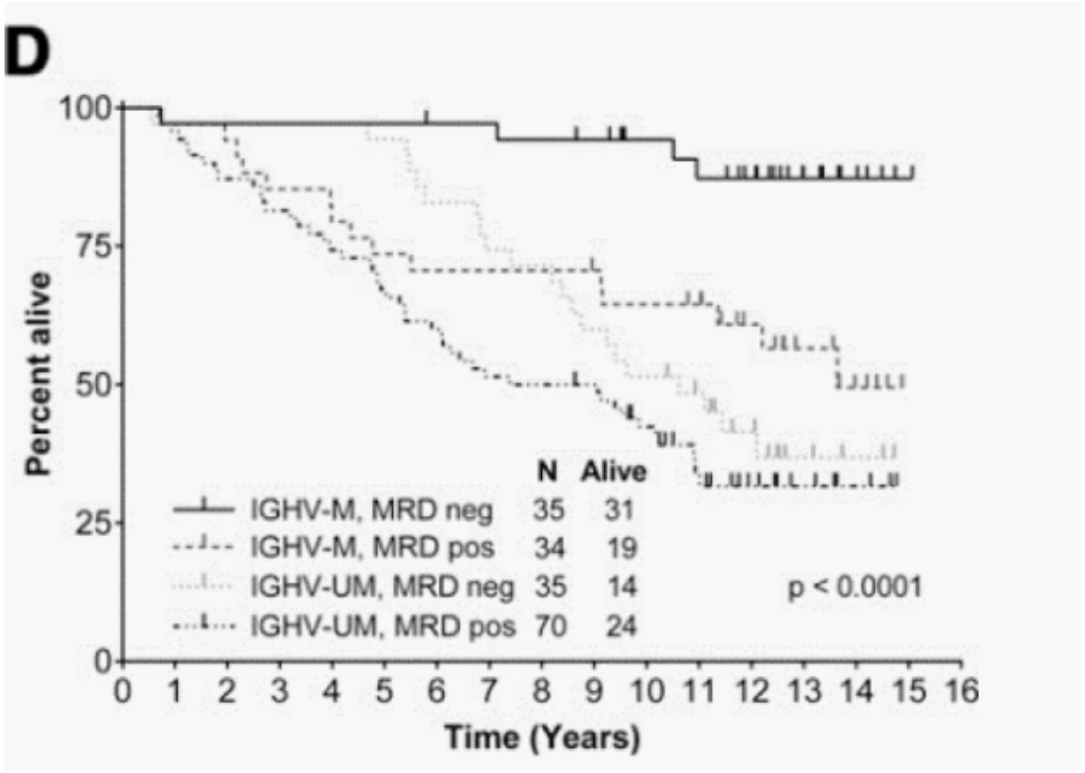
Rossi et al. Blood 2015

FCR300 Phase II Trial: Plateau in PFS With FCR as 1st line therapy



Last relapses occurred at Yr 10, with a plateau in PFS for *IGHV*-mutated pts.

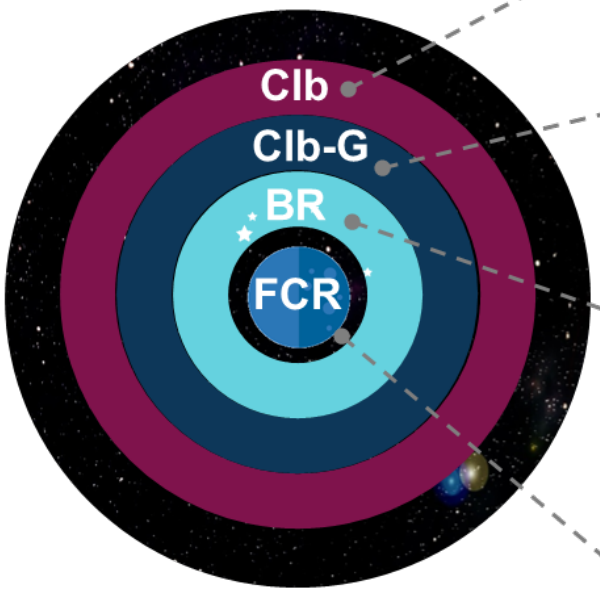
12·8-year PFS was 80% for M-IGHV pts who were MRD-neg



43% of all patients treated with FCR were MRD neg

Thompson et al., Blood 2016

IBRUTINIB vs CHT in TN



RESONATE 2
I > Clb

Age ≥65

- ibrutinib alone
- Chlorambucil alone

iLLUMINATE
IG > G-Clb

Age≥65 or comorbid

- ibrutinib-obinutuzumab
- Chlorambucil-obinutuzumab

ALLIANCE
I and IR > BR

Age ≥65

- ibrutinib
- IR
- BR

ECOG 1912
IR > FCR

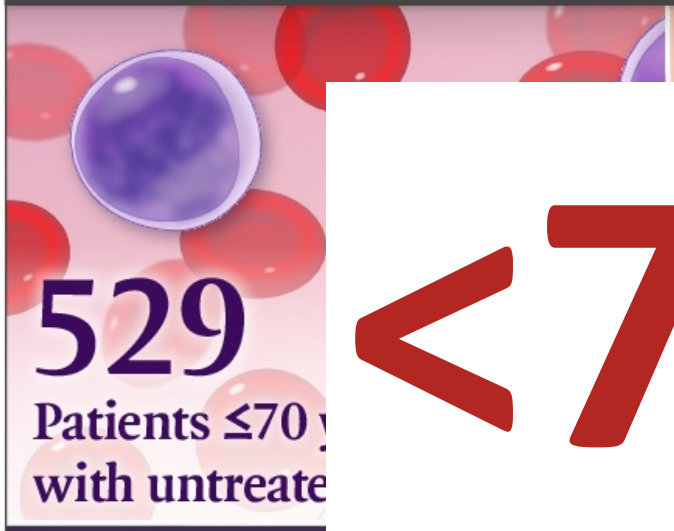
Age ≤70

- ibrutinib - rituximab
- FCR

The NEW ENGLAND JOURNAL of MEDICINE

Ibrutinib–Rituximab or Chemoimmunotherapy for CLL

MULTICENTER, OPEN-LABEL, PHASE 3 RANDOMIZED TRIAL



529
Patients ≤70 y
with untreate

<70 y-o

Ibrutinib–Rituximab

Chemoimmunotherapy
lp
5)

larabine–
le–rituximab

Progression-free survival at 3 yr

89.4%

72.9%

HR for progression or death, 0.35;
95% CI, 0.22 to 0.56; P < 0.001

Grade ≥3 infectious complications more common with chemoimmunotherapy

T.D. Shanafelt et al. 10.1056/NEJMoa1817073

ECOG 1912 trial
A randomized, phase 3 study of IR vs FCR in younger patients with TN CLL

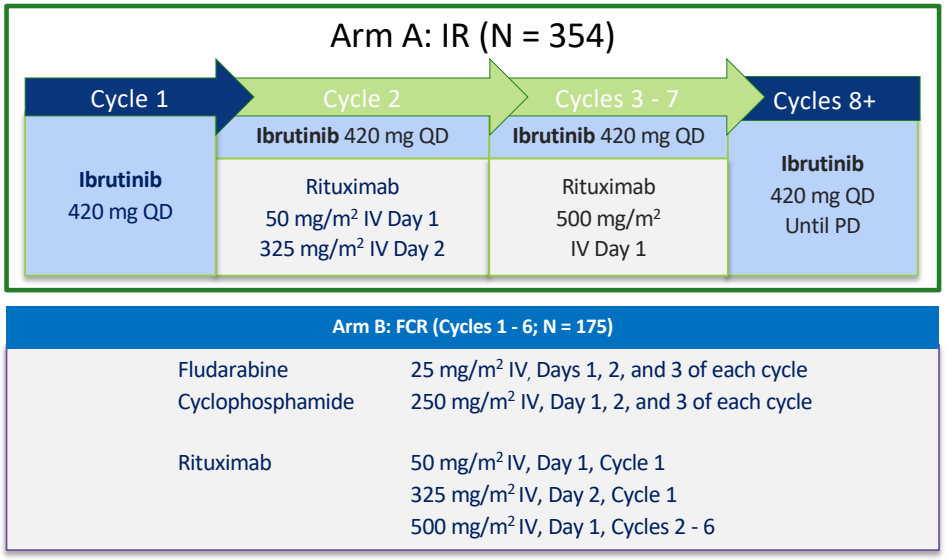
N = 529
Cycle = 28 days

Key eligibility:
Age ≤ 70 years
TN CLL requiring therapy

Patients with del(17)p were excluded

Stratification factors:
Age: < 60 vs. ≥ 60 y
PS 0,1 vs 2
Stage: 3/4 vs. 1/2
Baseline cytogenetic abnormalities on FISH: deletion 11q23 vs. other

RANDOMIZE 2:1



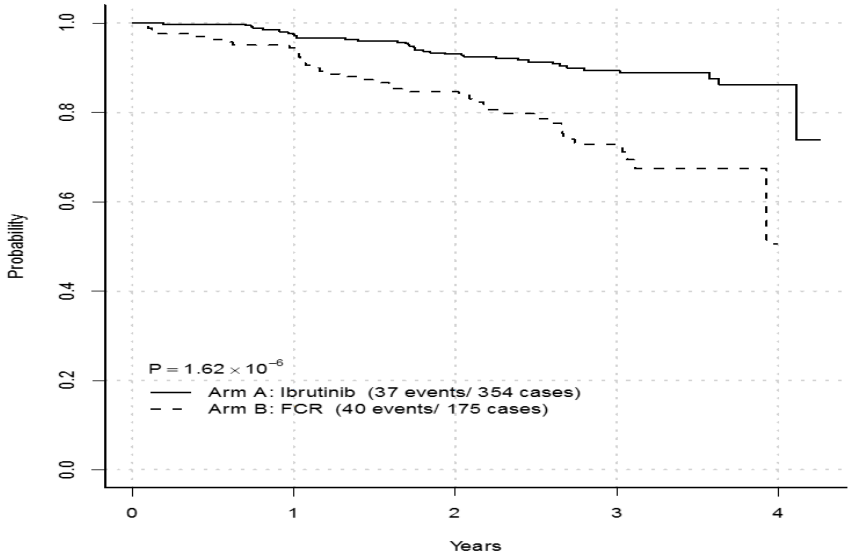
Primary endpoint: PFS • Secondary endpoint: OS

Abbreviations: FCR, fludarabine, cyclophosphamide, rituximab; IR, ibrutinib + rituximab; IV, intravenous; mg, milligram; m^2, meters squared; OS, overall survival; PD, disease progression; PFS, progression free survival; QD, daily; TN, treatment-naïve.

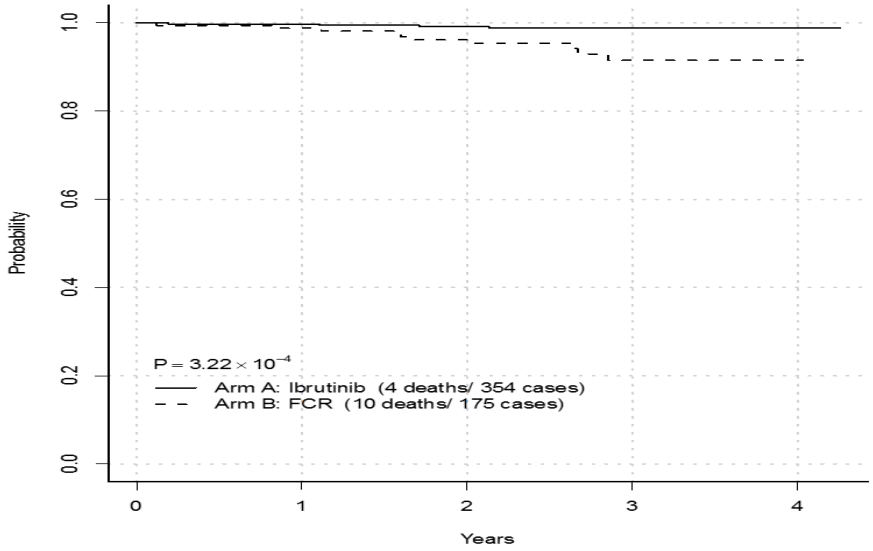
Shanafelt TD et al LBA#4 ASH 2018.

ECOG1912: Progression-free survival median follow-up: 33.4 mos

PFS (all randomized)



OS (all randomized pts)

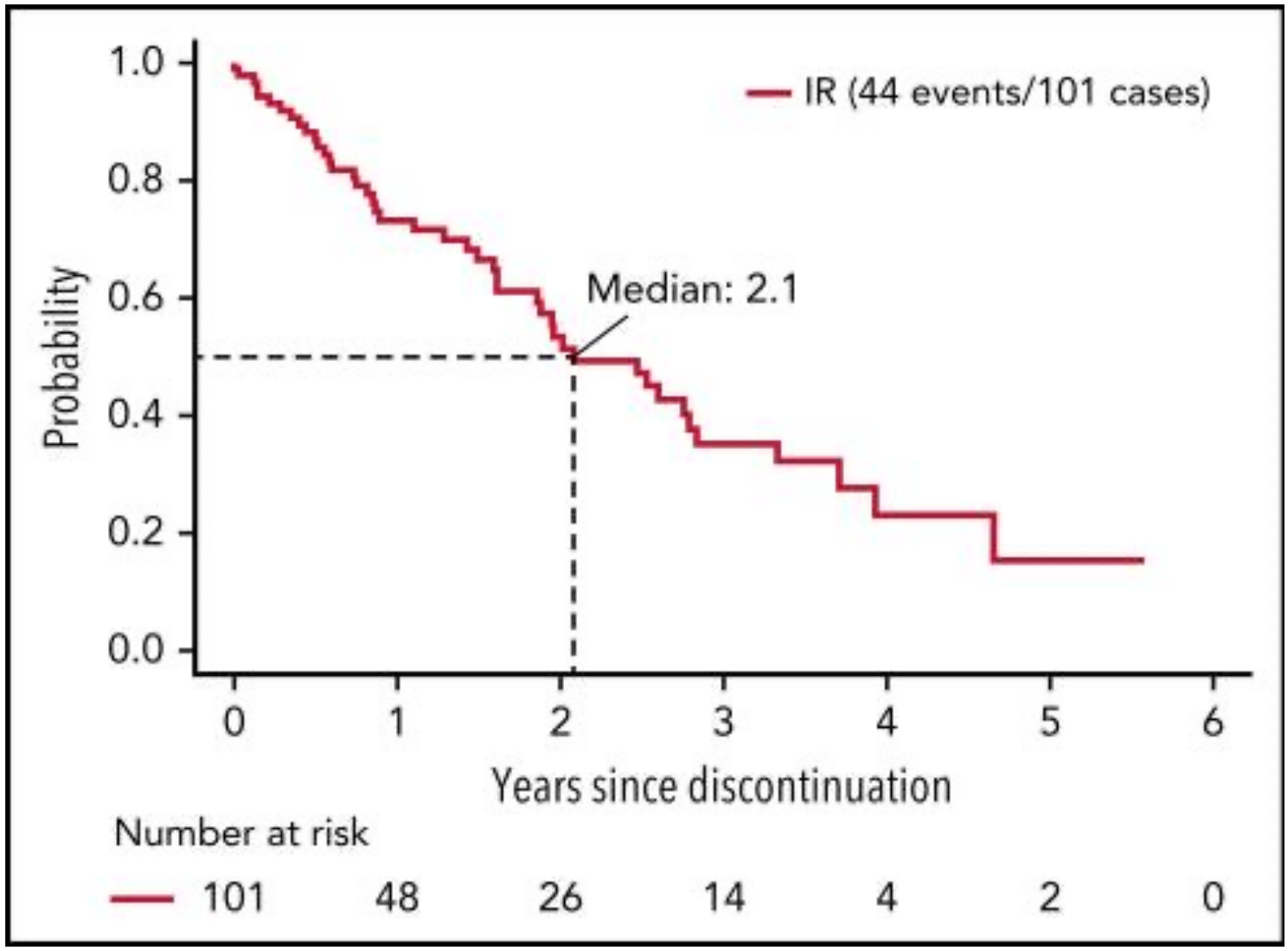


	HR	95% CI	p-value
PFS	0.352	0.223-0.558	P<0.0001
OS	0.168	0.053-0.538	P=0.0003

IR was superior to FCR independent of:

- **Age**
- **Sex**
- **Performance status**
- **Disease stage**
- **Del(11)q**
- **IR was superior to FCR for uIGHV**

Shanafelt TD et al LBA#4 ASH 2018.



updated results

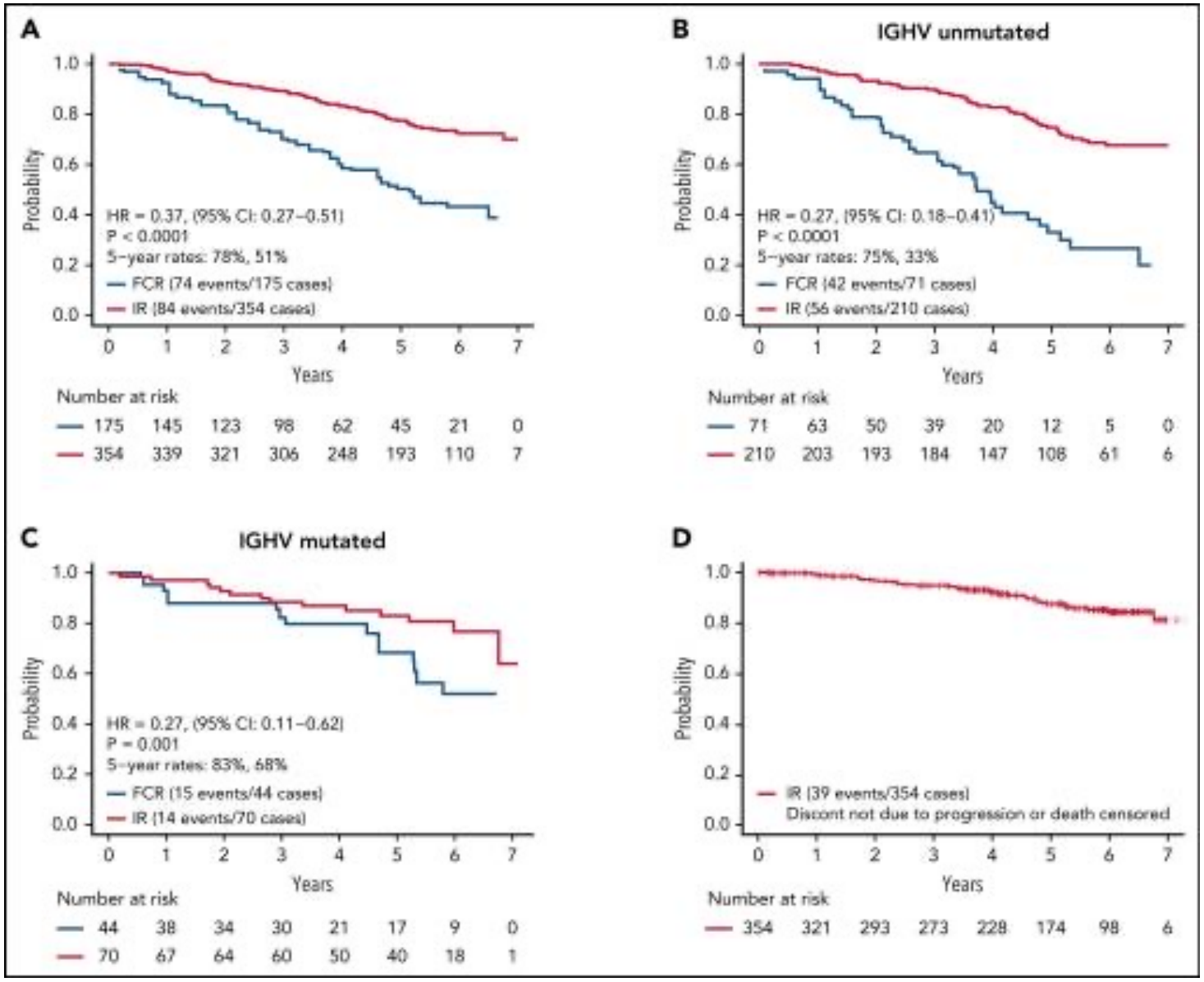
E1912 trial

Median time to PD

= 25 mos

For a reason other than progression or death

Shanafelt Blood 2022



updated results

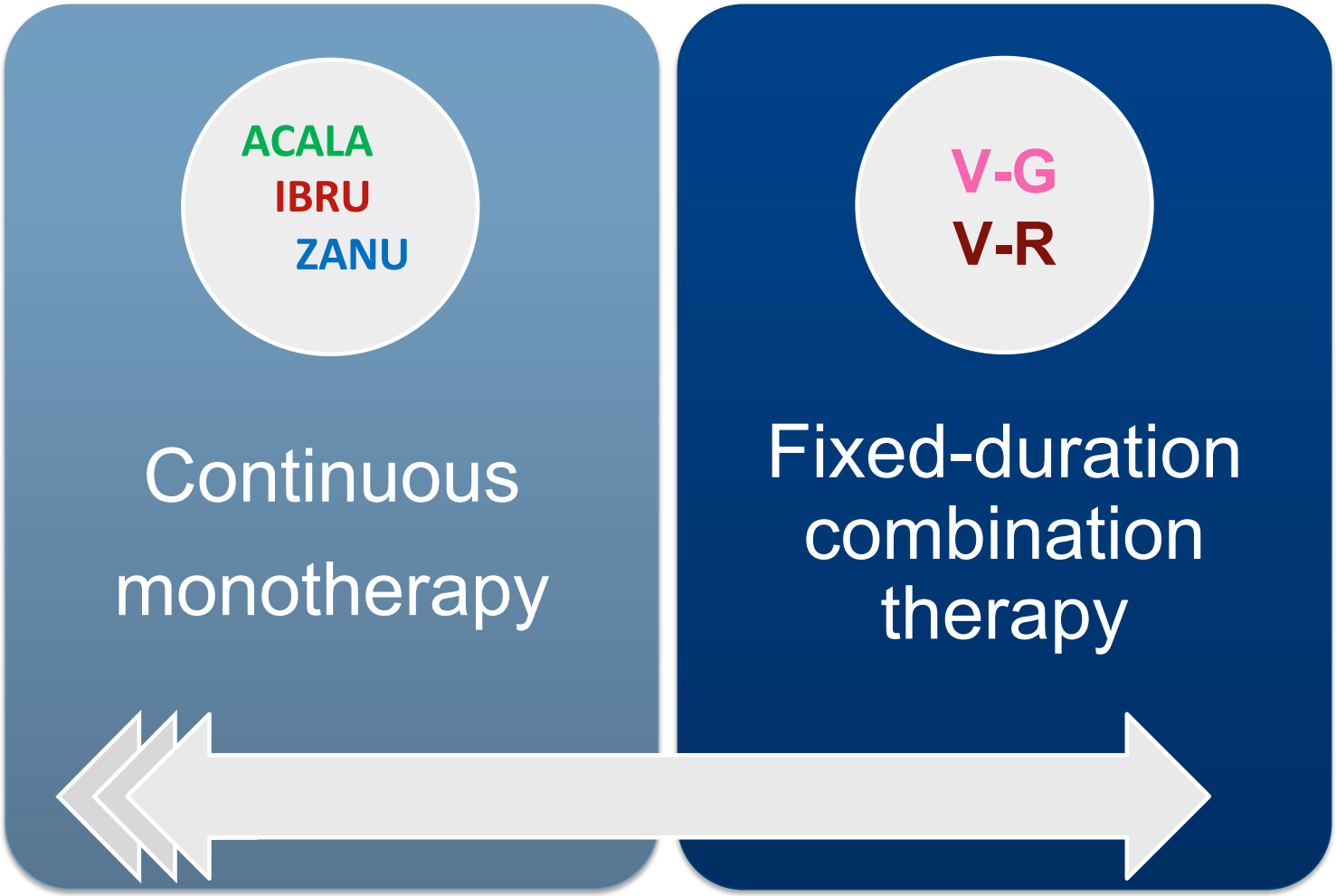
E1912 trial

5-yrs PFS 78% vs 51%

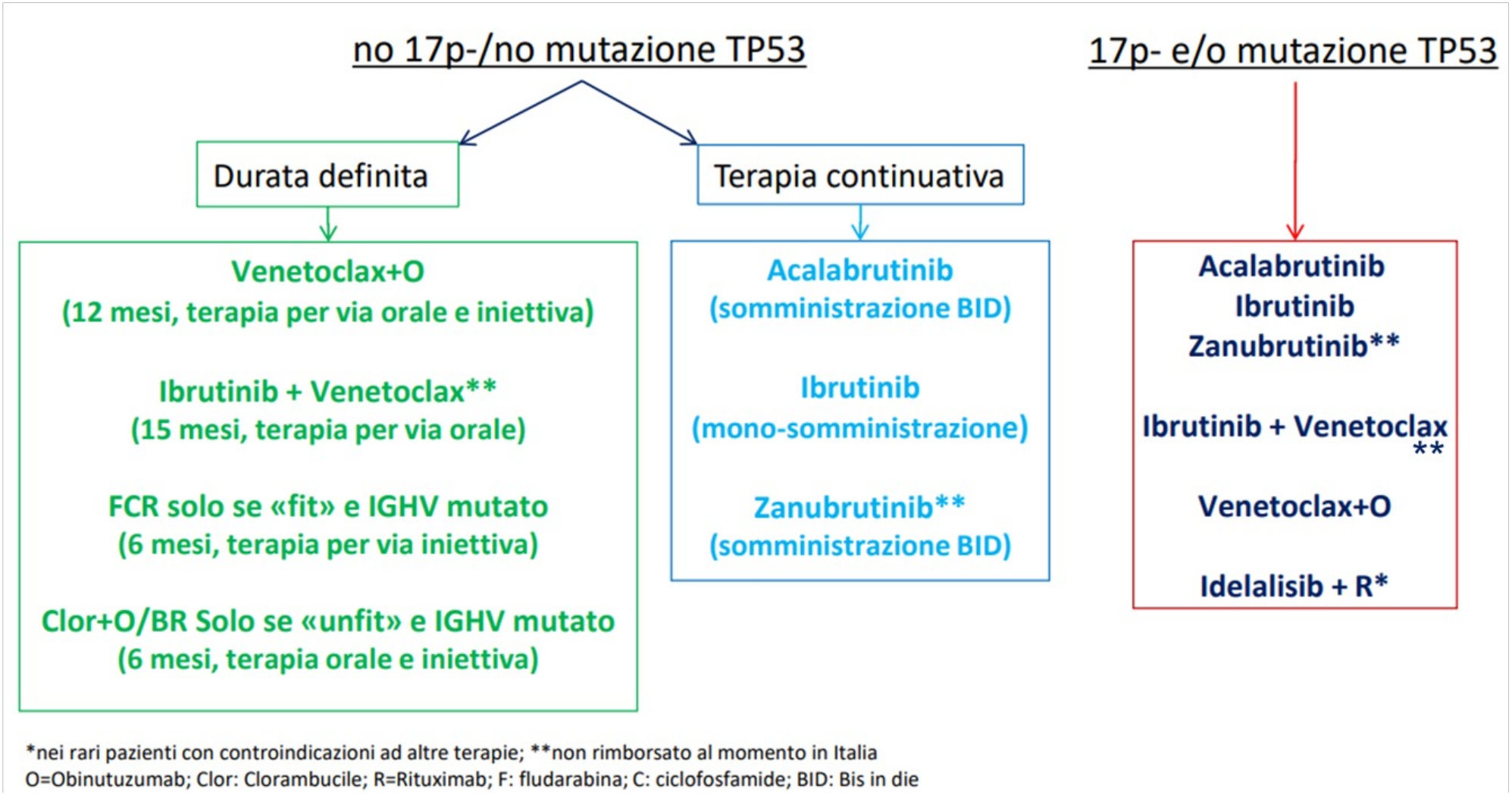
5-yrs PFS 75% vs 33%

5-yrs PFS 83% vs 68%

Shanafelt Blood 2022


ACALA
IBRU
ZANU
Continuous monotherapy
V-G
V-R
Fixed-duration combination therapy

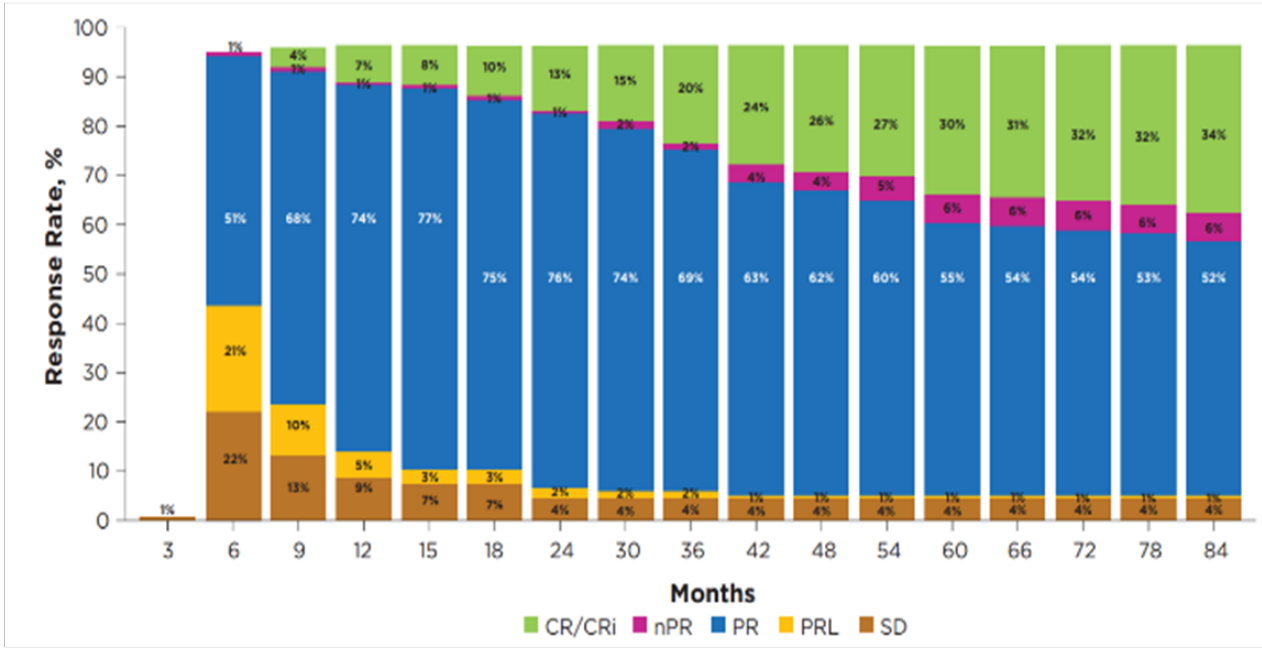
Principali opzioni approvate da EMA per la terapia di prima linea nella LLC nel 2023



*nei rari pazienti con controindicazioni ad altre terapie; **non rimborsato al momento in Italia
O=Obinutuzumab; Clor: Clorambucile; R=Rituximab; F: fludarabina; C: ciclofosfamide; BID: Bis in die

RESONATE-2: Investigator-Assessed Overall Response Rate With Ibrutinib

CONTINUED DEEPENING OF RESPONSES AND SUSTAINED EFFICACY IN HIGH-RISK CLL



PFS 67% (mIGHV) and 62% (uIGHV) at 6.5 yrs

- At up to 8 years of follow-up, the CR/CRi rate increased over time to 34% (ORR 92%)
- ORR and CR rates were similar, irrespective of del(11q) or IGHV mutation status

P. Barr et al., BLOOD ADVANCES 2022

ELEVATE-TN study design

TN CLL (N=535)

Key inclusion criteria

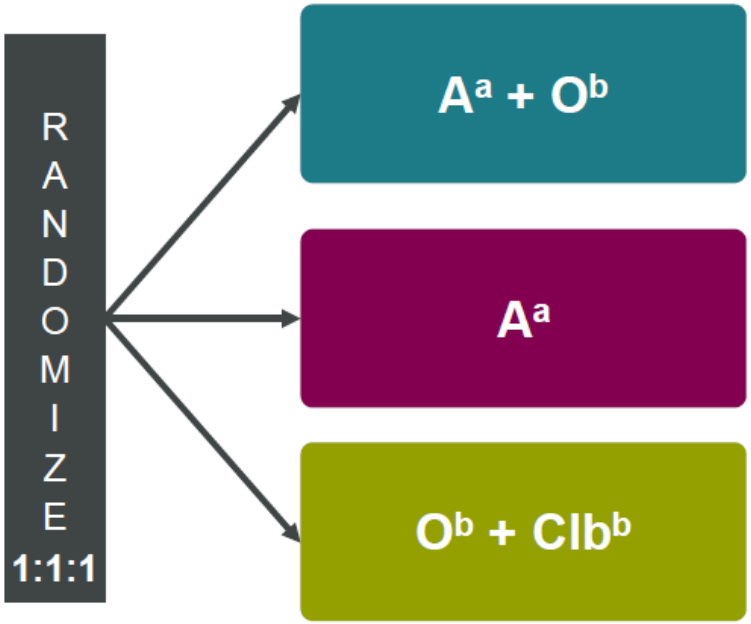
- Age ≥65 years, or >18 to <65 years with:
  - Creatinine clearance 30–69 mL/min (by Cockcroft-Gault equation)
  - CIRS-G score >6
- TN CLL requiring treatment per iwCLL 2008 criteria[6]
- ECOG PS ≤2

Key exclusion criteria

- Significant cardiovascular disease

Stratification

- del(17p), yes vs no
- ECOG PS 0–1 vs 2
- Geographic region



Primary endpoint

- PFS (IRC-assessed): A+O vs O+Clb

Secondary/other endpoints

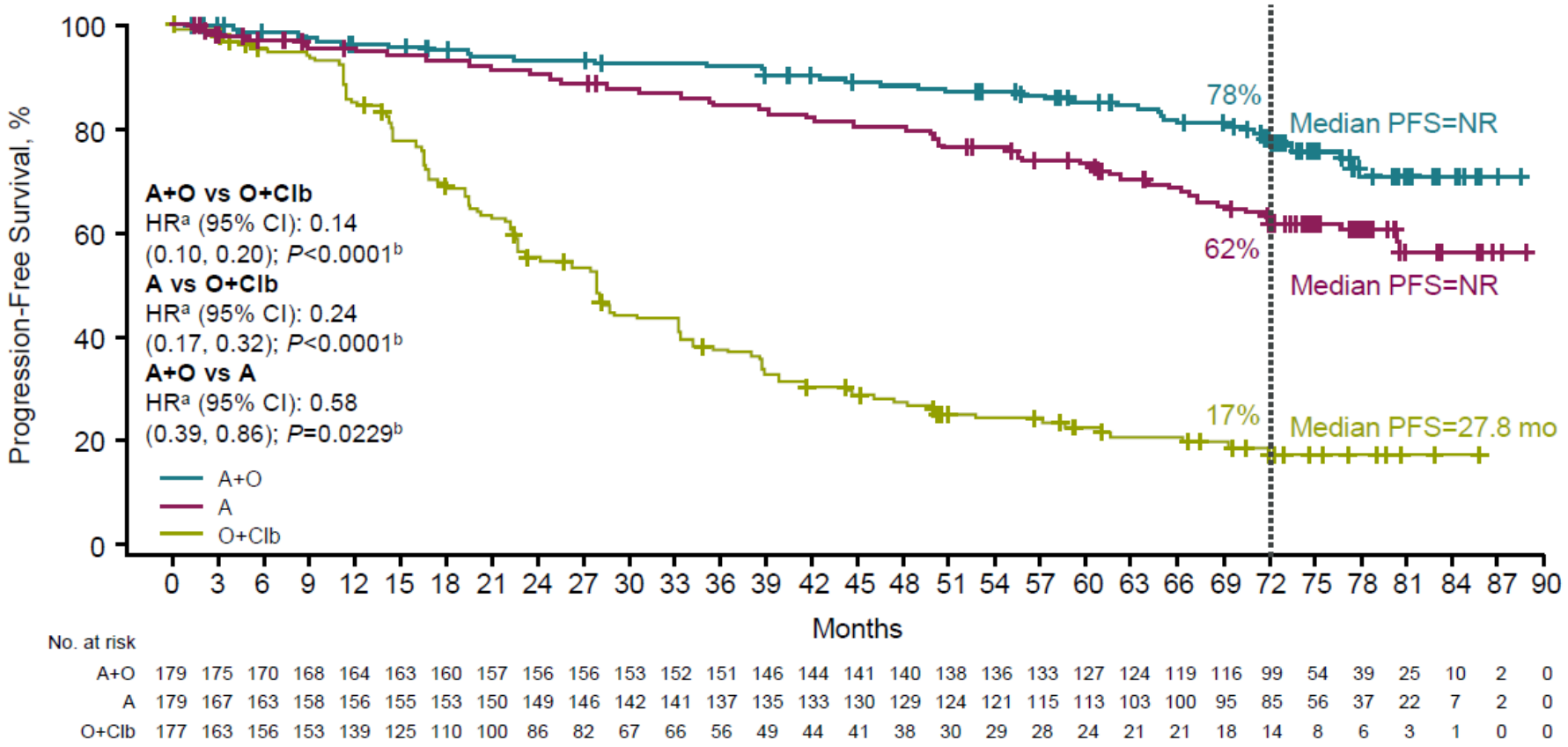
- PFS (IRC-assessed): A vs O+Clb
- PFS (INV-assessed)
- ORR (IRC- and INV-assessed)
- TTNT
- OS
- uMRD
- Safety

***Crossover** from O+Clb to A was allowed after IRC-confirmed progression*

Note: After interim analysis, PFS assessments were by investigator only.[3]
All analyses are ad-hoc and *P*-values are descriptive.

NCT02475681. Data cutoff: March 3, 2023. Patients were enrolled between September 2015 and February 2017.
[a]Continued until disease progression or unacceptable toxicity at 100 mg PO BID.
[b]Treatments were fixed duration and administered for 6 cycles.

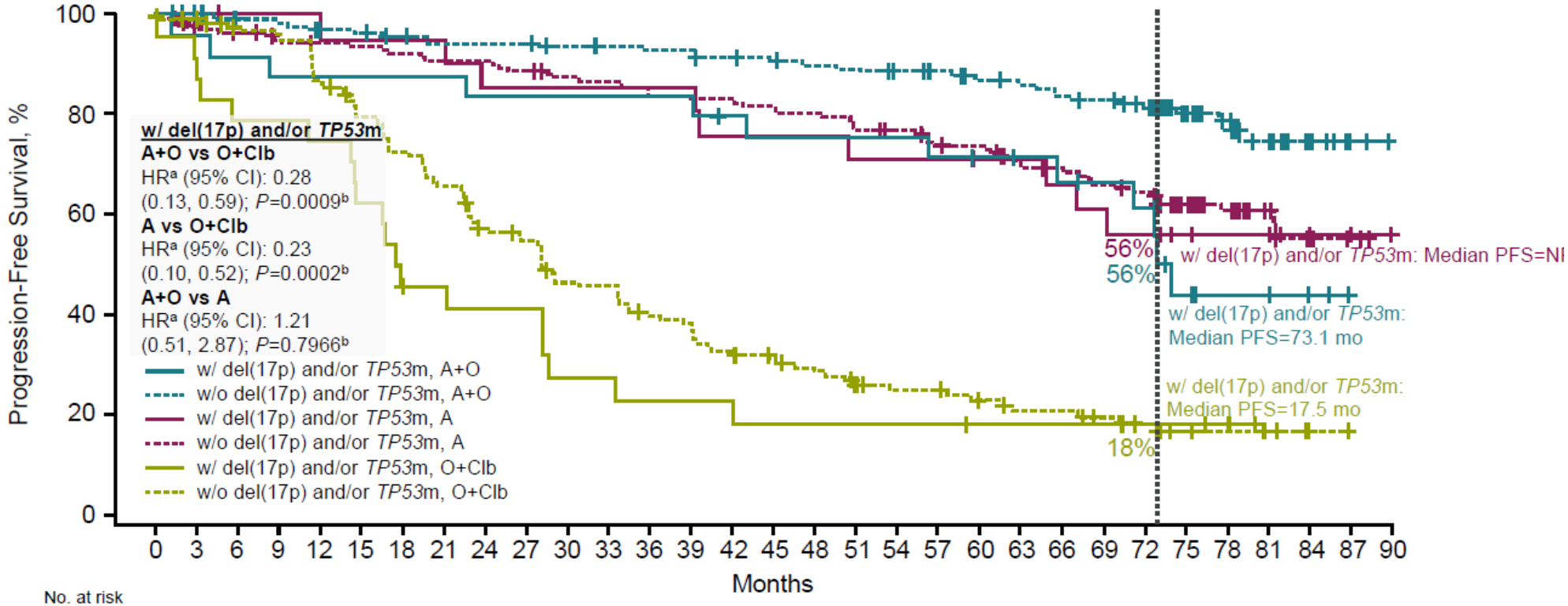
Median PFS was significantly higher for A-containing arms vs O+Clb



- Median PFS was significantly higher for A+O vs A

[a]Hazard ratio based on stratified Cox proportional-hazards model.
[b]*P*-value based on stratified log-rank test.

Median PFS was significantly higher for A-containing arms vs O+Clb in patients with del(17p) and/or *TP53*m

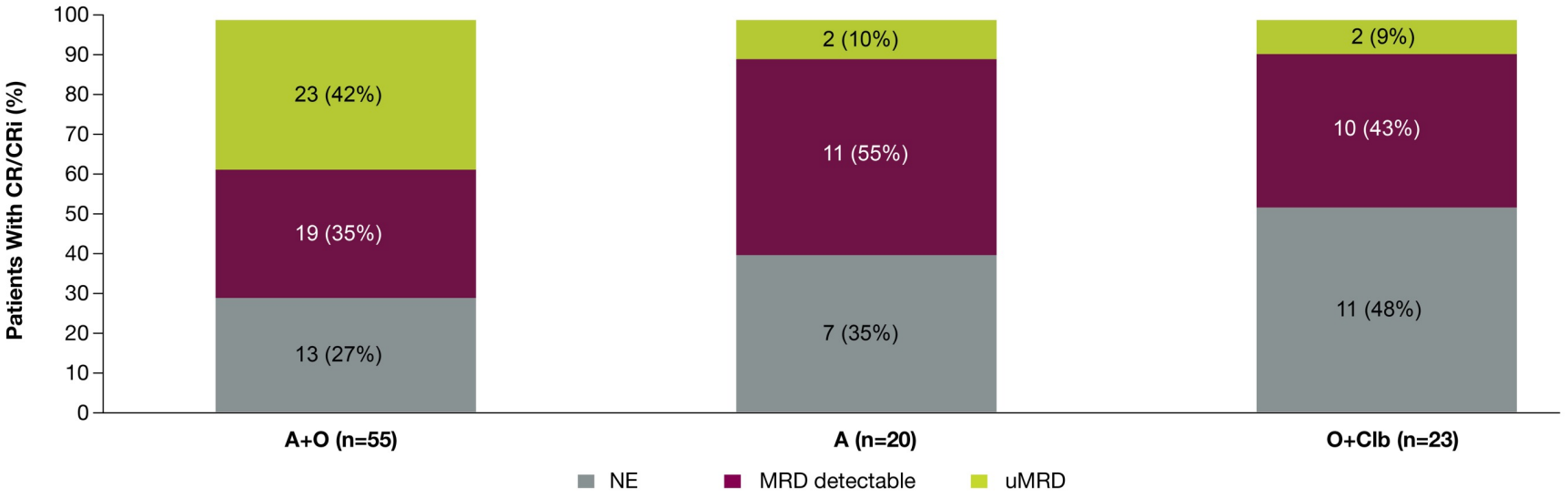


No. at risk																															
w/ del(17p) and/or *TP53m*, A+O	25	24	23	22	22	22	22	22	21	21	21	21	21	20	19	18	18	18	18	17	16	15	14	13	10	5	5	3	2	0
w/o del(17p) and/or *TP53m*, A+O	154	151	147	146	142	141	138	135	135	135	132	131	130	126	125	123	122	120	118	116	111	109	105	103	89	49	34	22	8	2
w/ del(17p) and/or *TP53m*, A	23	22	21	21	20	20	20	19	18	18	18	18	18	17	16	16	16	15	15	15	14	14	13	11	11	7	7	4	2	1
w/o del(17p) and/or *TP53m*, A	156	145	142	137	136	135	133	131	131	128	124	123	119	118	117	114	113	109	106	100	99	89	87	84	74	49	30	18	5	1
w/ del(17p) and/or *TP53m*, O+Clb	25	21	19	19	18	15	10	9	9	9	6	6	5	5	4	4	4	4	4	4	3	3	3	3	3	3	1	0		
w/o del(17p) and/or *TP53m*, O+Clb	152	142	137	134	121	110	100	91	77	73	61	60	51	44	40	37	34	26	25	24	21	18	18	15	11	5	5	3	1	0

[a]Hazard ratio based on unstratified Cox proportional-hazards model.
[b]*P*-value based on unstratified log-rank test.

MRD[a] Status in Patients With CR/CRi

- Among patients with CR/CRi, higher uMRD rates were sustained at the last 2 timepoints in a higher proportion of patients receiving A+O vs O+Clb (42% vs 9%)



Peripheral blood testing to assess MRD occurred for patients with bone marrow-confirmed CR. Peripheral blood MRD status based on last two timepoints (most recent assessments available by the data cutoff) in patients with CR/CRi.

[a]MRD was defined as the proportion of subjects with <1 CLL cell in 10^4 leukocytes.

A = acalabrutinib; Clb = chlorambucil; CR = complete response; CRi = CR with incomplete marrow recovery; MRD = minimal residual disease; uMRD = undetectable minimal residual disease; NE = not estimable; O = Obinutuzumab; OS = overall survival; vs = versus.

Sharman JP et al. Poster Presented at: ASCO; June 3-7, 2022; Chicago, Illinois.

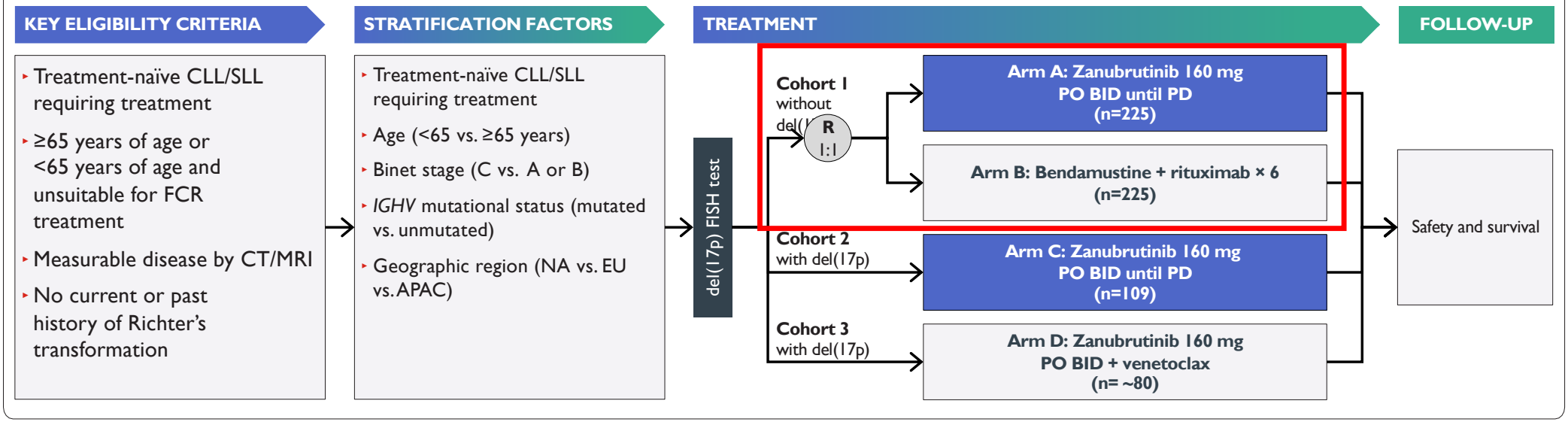
Trial Design

SEQUOIA – Arms A & B

PHASE 3

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1
Key Secondary Endpoints: Cohort 1: ORR, DOR, safety; Cohort 2: ORR, PFS, DOR; Cohort 3: ORR, PFS, DOR, rate of undetectable MRD at $<10^{-4}$ sensitivity, safety



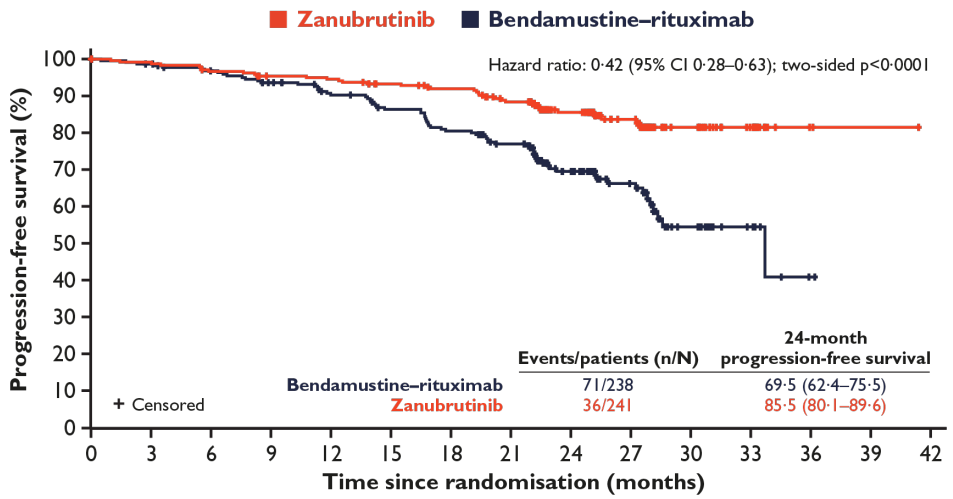
The study listed above relates to an investigational product that has not yet been approved by any regulatory agency as a safe and effective treatment of any disease.

*Previously untreated patients.
1L=first line, APAC=Asia/Pacific, BID=twice daily, CLL=chronic lymphocytic leukemia, CT=computed tomography, DOR=duration of response, EU=European Union, FCR=fludarabine, cyclophosphamide, and rituximab (chemotherapy regimen), FISH=fluorescence in situ hybridization, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, MRD=minimal residual disease, MRI=magnetic resonance imaging, NA=North America, ORR=overall response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PO=per oral, R=randomized, SLL=small lymphocytic lymphomae.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03336333. Accessed January 2021. 2. Tam et al. Lancet Oncology. 2022. 22;S1460-2045. 3. Brown JR et al. ASH 2020. Abstract 1306. 4. Tedeschi et al. ASH 2021 Abstract 67

PFS by IRC Assessment for Patients Without del17(p)

SEQUOIA – Arms A & B



Number at risk (number censored)

Bendamustine–rituximab	238 (0)	218 (17)	210 (21)	200 (24)	187 (30)	176 (33)	164 (33)	150 (40)	89 (89)	54 (121)	20 (148)	8 (160)	1 (166)	0 (167)		
Zanubrutinib	241 (0)	237 (2)	230 (3)	224 (6)	222 (6)	214 (11)	208 (14)	195 (19)	123 (86)	79 (128)	31 (174)	17 (188)	2 (203)	1 (205)	0 (205)	

- At the pre-specified interim analysis, the primary endpoint of SEQUOIA was met
  - The difference in PFS between Arms A and B met prespecified criteria for superiority
  - Median PFS was not reached in either Arm (Arm 95% CI NE to NE; Arm B 28.1 months to NE; HR 0.42, 95% CI 0.28 to 0.63; two-sided p<0.0001)
- With a median follow-up of 26.2 months (IQR 23.7-29.6):
  - 36 (15%) patients in Arm A had progressed or died per IRC
  - 71 (30%) patients in Arm B had progressed or died per IRC
- Estimated 24-month PFS was 85.5% (95% CI 80.1-89.6) in Arm A and 69.5% (62.4-75.5) in Arm B

Figure adapted from Tam et al. Lancet Oncology. 2022. 22;S1460-2045
Data cutoff: May 7, 2021
CI=confidence interval, HR=hazard ratio, NE=not evaluable, IQR=interquartile range, IRC=independent review committee, PFS=progression-free survival.
Tam et al. Lancet Oncology. 2022. 22;S1460-2045

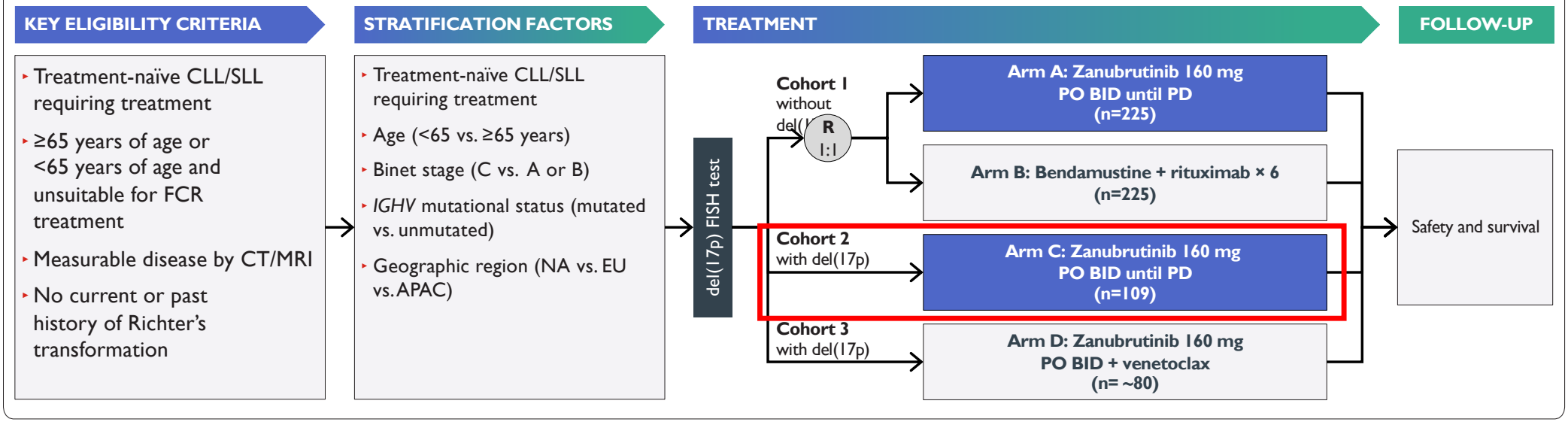
Trial Design

SEQUOIA – Arm C

PHASE 3

Study Identifier: BGB-3111-304, NCT03336333

Primary Endpoint: PFS by IRC in Cohort 1
Key Secondary Endpoints: Cohort 1: ORR, DOR, safety; Cohort 2: ORR, PFS, DOR; Cohort 3: ORR, PFS, DOR, rate of undetectable MRD at $<10^{-4}$ sensitivity, safety



The study listed above relates to an investigational product that has not yet been approved by any regulatory agency as a safe and effective treatment of any disease.

*Previously untreated patients.
1L=first line, APAC=Asia/Pacific, BID=twice daily, CLL=chronic lymphocytic leukemia, CT=computed tomography, DOR=duration of response, EU=European Union, FCR=fludarabine, cyclophosphamide, and rituximab (chemotherapy regimen), FISH=fluorescence in situ hybridization, IGHV=immunoglobulin heavy-chain variable region gene, IRC=independent review committee, MRD=minimal residual disease, MRI=magnetic resonance imaging, NA=North America, ORR=overall response rate, OS=overall survival, PD=progressive disease, PFS=progression-free survival, PO=per oral, R=randomized, SLL=small lymphocytic lymphomae.

1. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03336333. Accessed January 2021. 2. Tam et al. Lancet Oncology. 2022. 22;S1460-2045. 3. Brown JR et al. ASH 2020. Abstract 1306. 4. Tedeschi et al. ASH 2021 Abstract 67

PFS and OS by IRC Assessment for Patients With del(17p)

SEQUOIA – Arm C

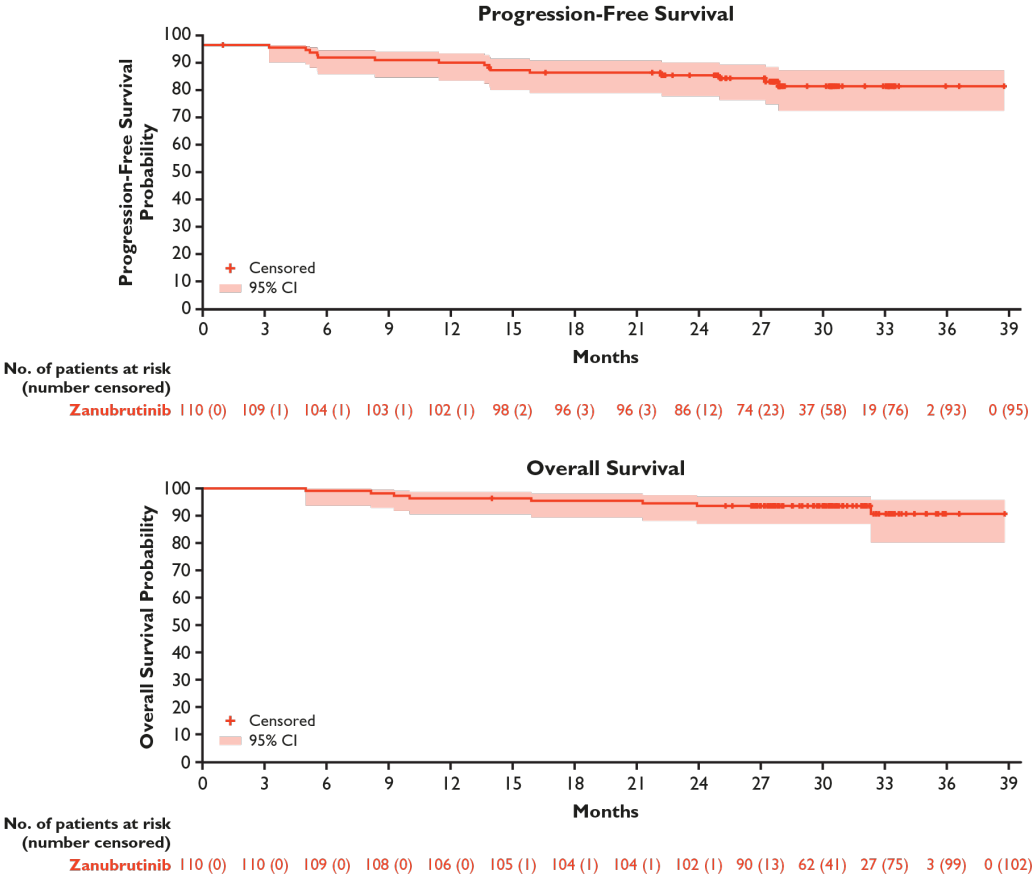
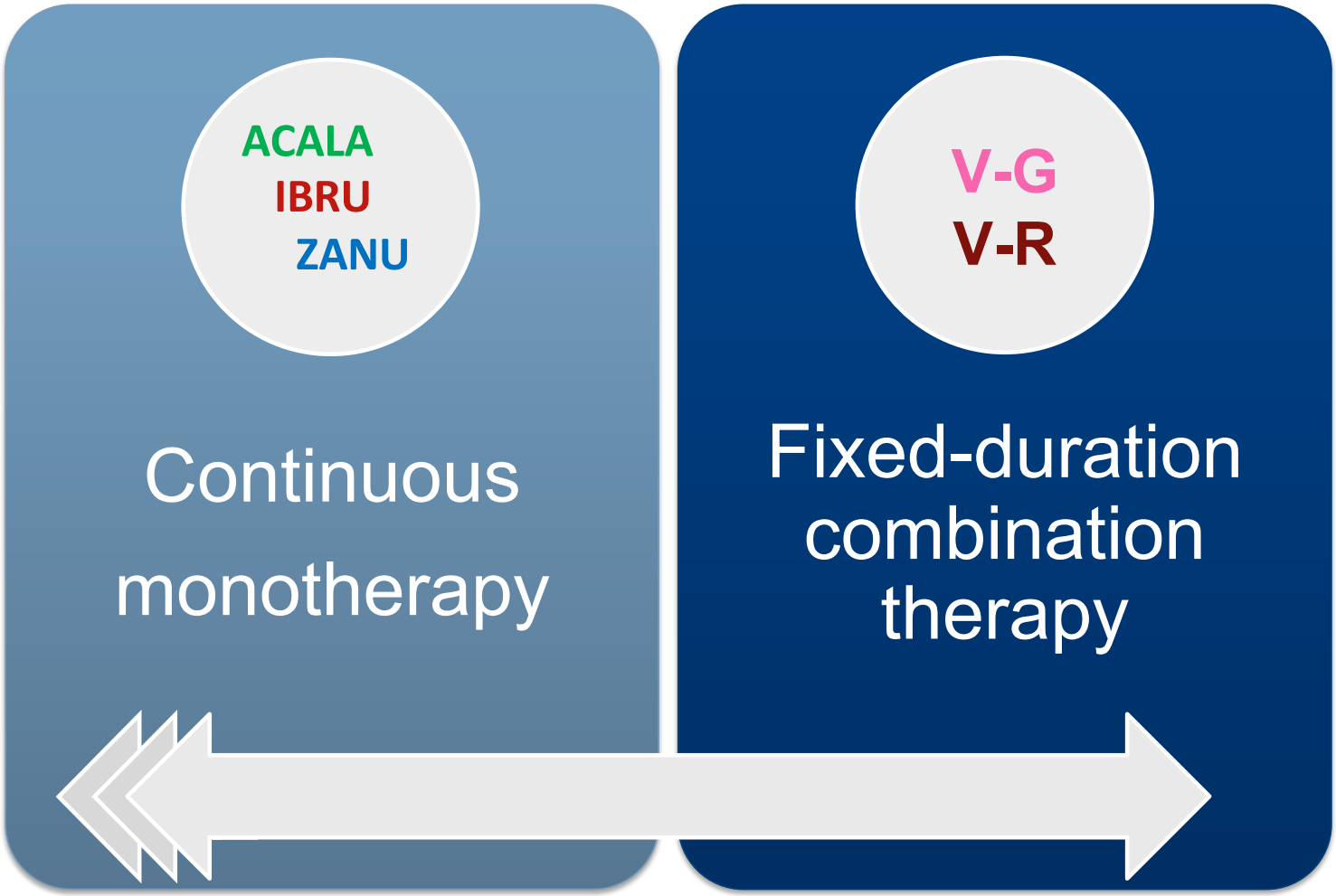


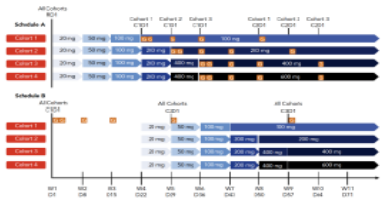
Figure adapted from Tam et al. Lancet Oncology. 2022. 22;S1460-2045
Data cutoff: May 7, 2021
CI=confidence interval, HR=hazard ratio, IQR=interquartile range, OS=overall survival, PFS=progression-free survival.
Tam et al. Lancet Oncology. 2022. 22;S1460-2045

- At a median follow-up of 30.5 months (IQR 27.6–33.1)
  - 15 (14%) of 110 patients in Arm C had progressed or died per IRC
  - One patient had died without progression
- Median PFS by IRC was not reached (95% CI NE–NE).
- At 24 months, estimated PFS by IRC was 88.9% (95% CI 81.3–93.6)
- Similar 24-month PFS was observed by investigators (87.0%, 95% CI 79.0–92.1)
- Estimated 24-month overall survival for Arm C was 93.6% (95% CI 87.1–96.9)


ACALA
IBRU
ZANU
Continuous monotherapy
V-G
V-R
Fixed-duration combination therapy

Key data sets on Ven-Obi

GP28331



1L/rrCLL

6x Obi-Ven or Ven-Obi
6x Ven

N=87

2-y-PFS 91/85%

Flinn et al, Blood 2019

(B)AG

1L/rrCLL

(2x Benda)
6x Ven-Obi

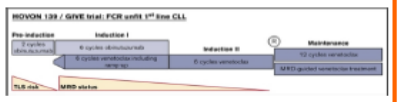
MRD-guided up to 18 Ven-Obi

N=66

15m-PFS 100/92%

Cramer et al, Lancet Oncol 2018

HOVON 139



1L

6x Ven-Obi
6x Ven

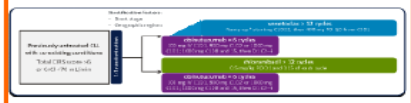
followed by
12x Ven
or
MRD-guided 12x Ven

N=70

3-y-PFS 95%

Kersting et al, Lancet Oncol, 2022

CLL14



1L

6x Ven-Obi
6x Ven

N= 216

3-y-PFS 82%

Fischer et al, NEJM 2019
Al-Sawaf et al, Lancet Oncol, 2020

CLL13

1L

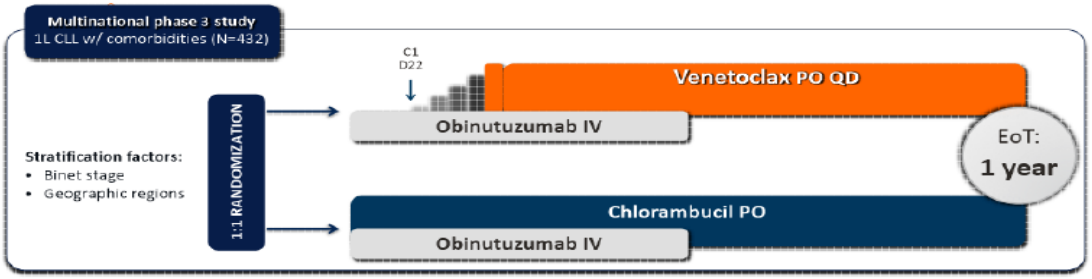
6x Ven-Obi
6x Ven

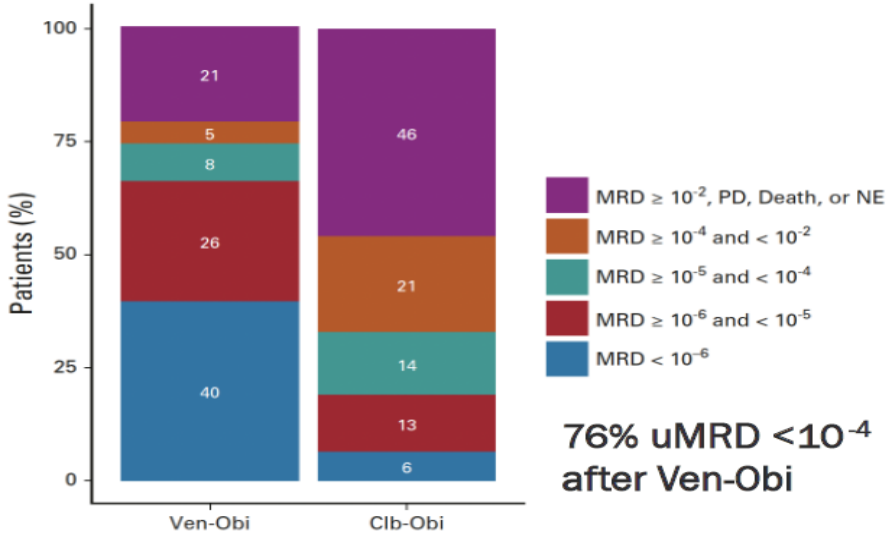
N= 229

3-y-PFS 88%

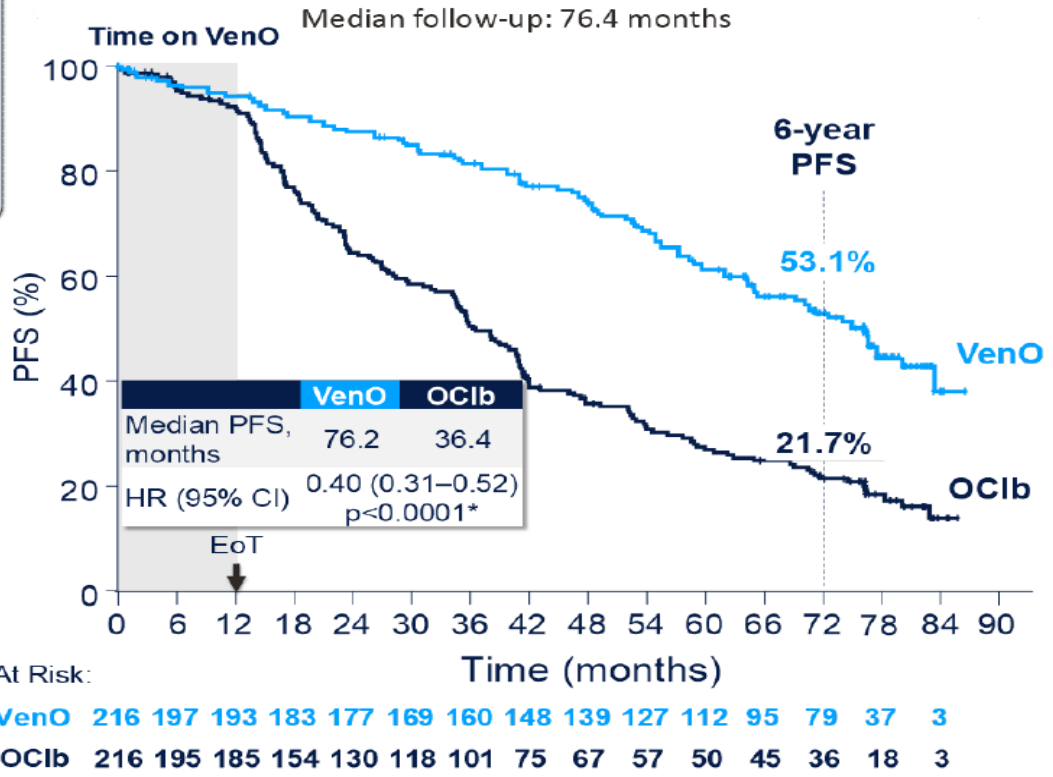
Eichhorst et al, NEJM 2023

CLL14 – Ven-Obi in unfit patients



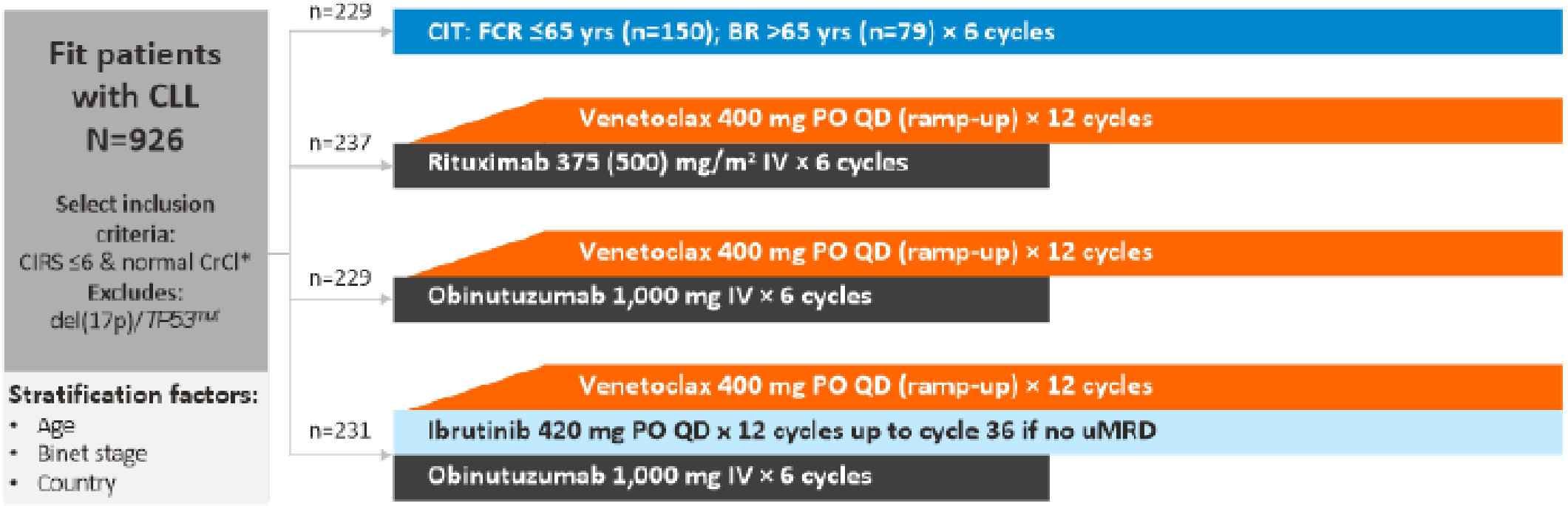


76% uMRD <10^{-4} after Ven-Obi



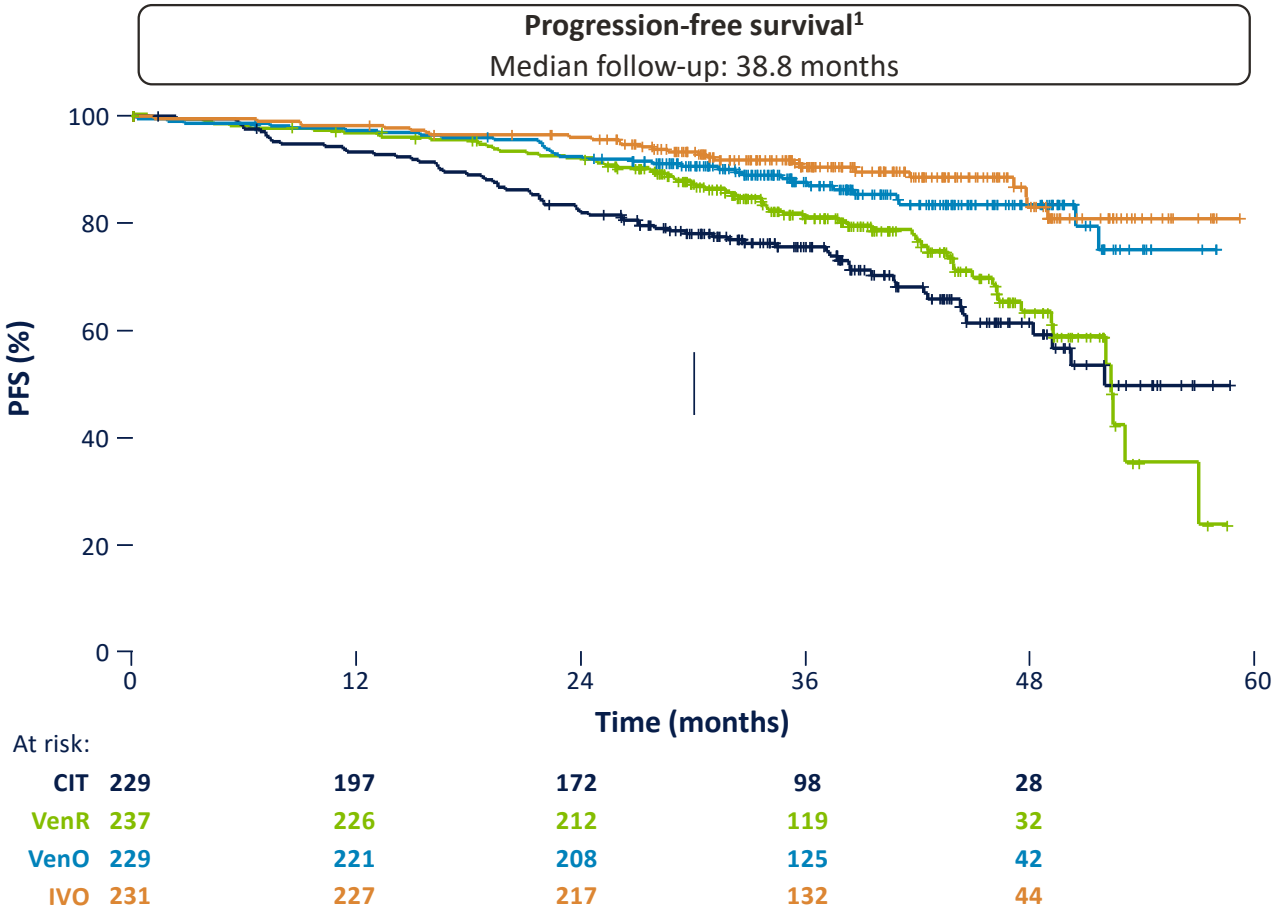
Al-Sawaf et al, EHA 2023

CLL13 – Ven-Obi in fit patients



New/Updated

PFS across all treatment arms



	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI)† p value[1]	–	0.79 (0.53–1.18) p=0.18	0.42 (0.26–0.68) p<0.001	0.32* (0.19–0.54) p<0.001
3-year PFS , %[1]	75.5	80.8	87.7	90.5
Median PFS, months[2]	52.0	52.3	NR	NR

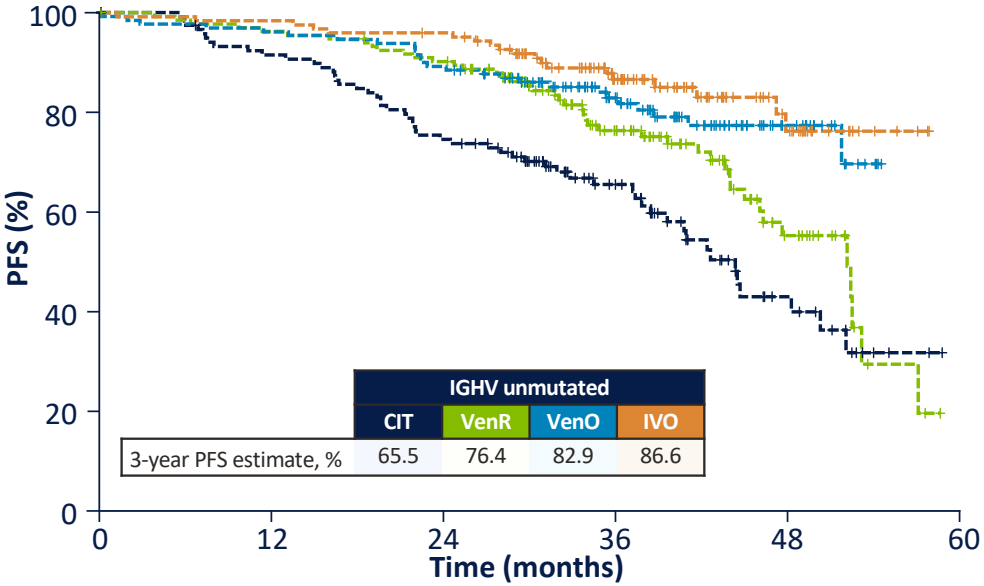
* Co-primary endpoint: IVO vs CIT; † 97.5% CI reported as per Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.
CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; NR, not reached; O, obinutuzumab; R, rituximab; Ven, venetoclax.

1. Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754;
2. Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

New/Updated

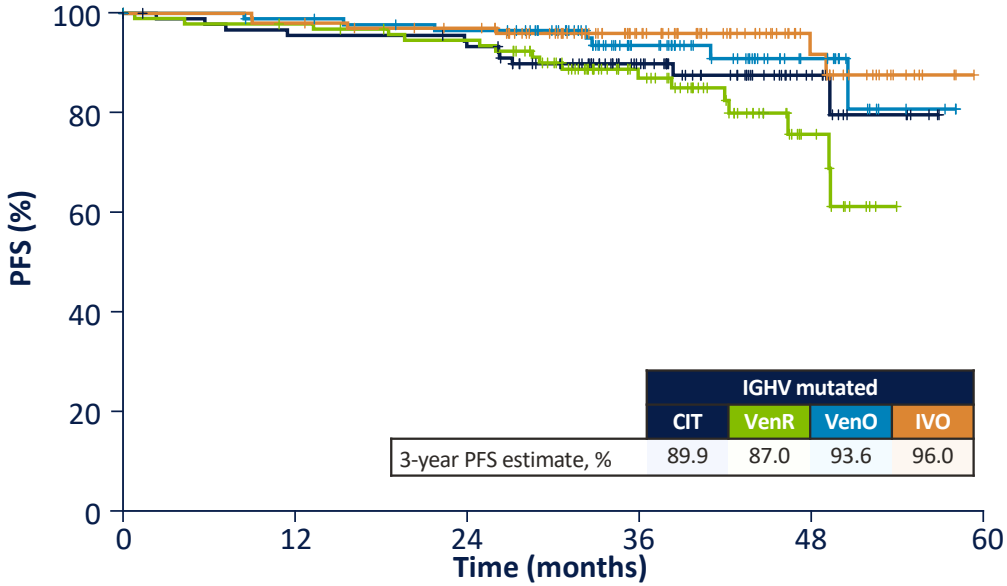
PFS by IGHV mutational status

PFS: IGHV unmutated
Median follow-up: 38.8 months



At risk:					
CIT	131	108	88	48	14
VenR	134	128	119	67	20
VenO	130	125	116	71	21
IVO	123	121	117	70	22

PFS: IGHV mutated
Median follow-up: 38.8 months



At risk:					
CIT	95	86	83	50	14
VenR	95	91	86	49	12
VenO	89	86	82	48	17
IVO	101	99	94	59	22

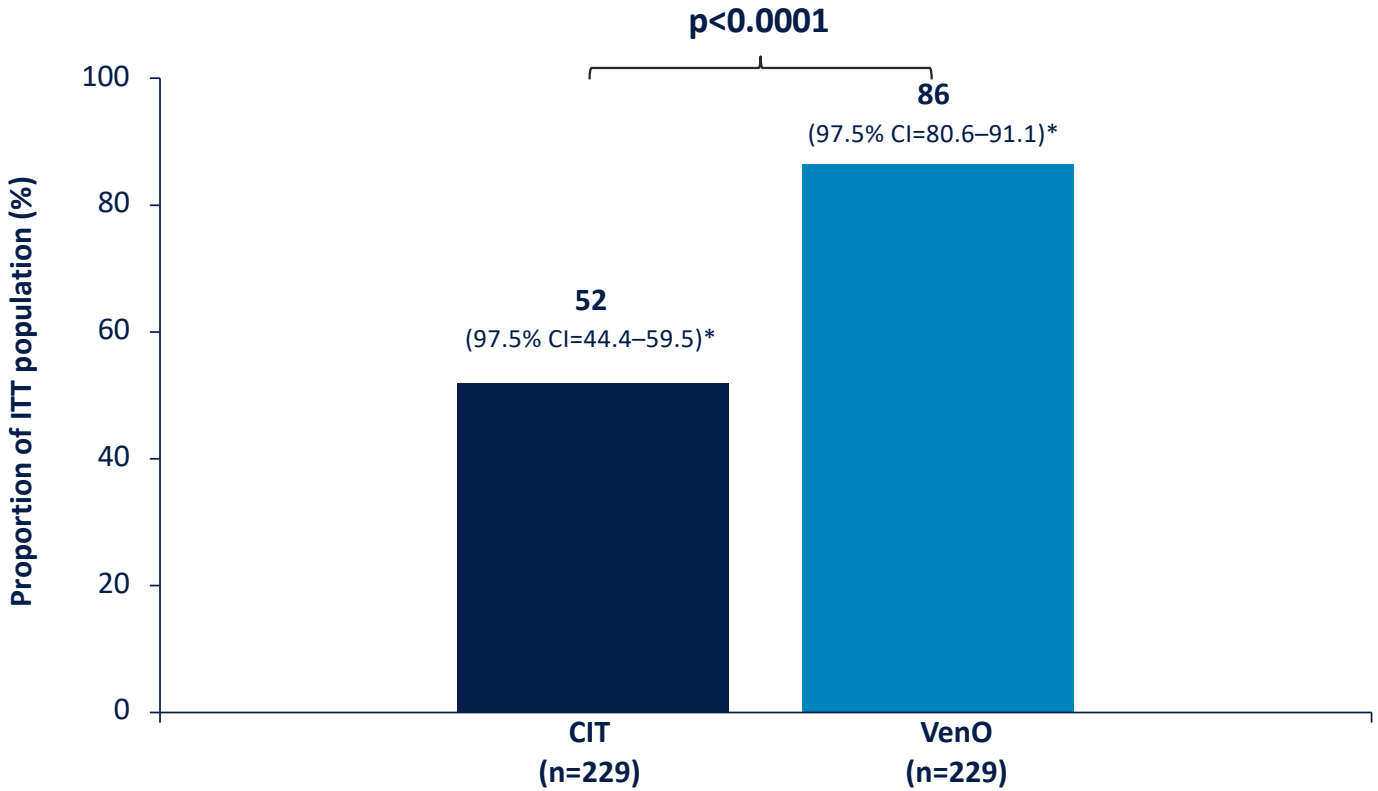
CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; Ven, venetoclax.

Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.

New/Updated

uMRD rates for VenO and CIT in PB at month 15

Co-primary endpoint: uMRD ($<10^{-4}$) rates in PB in ITT population by FCM at month 15



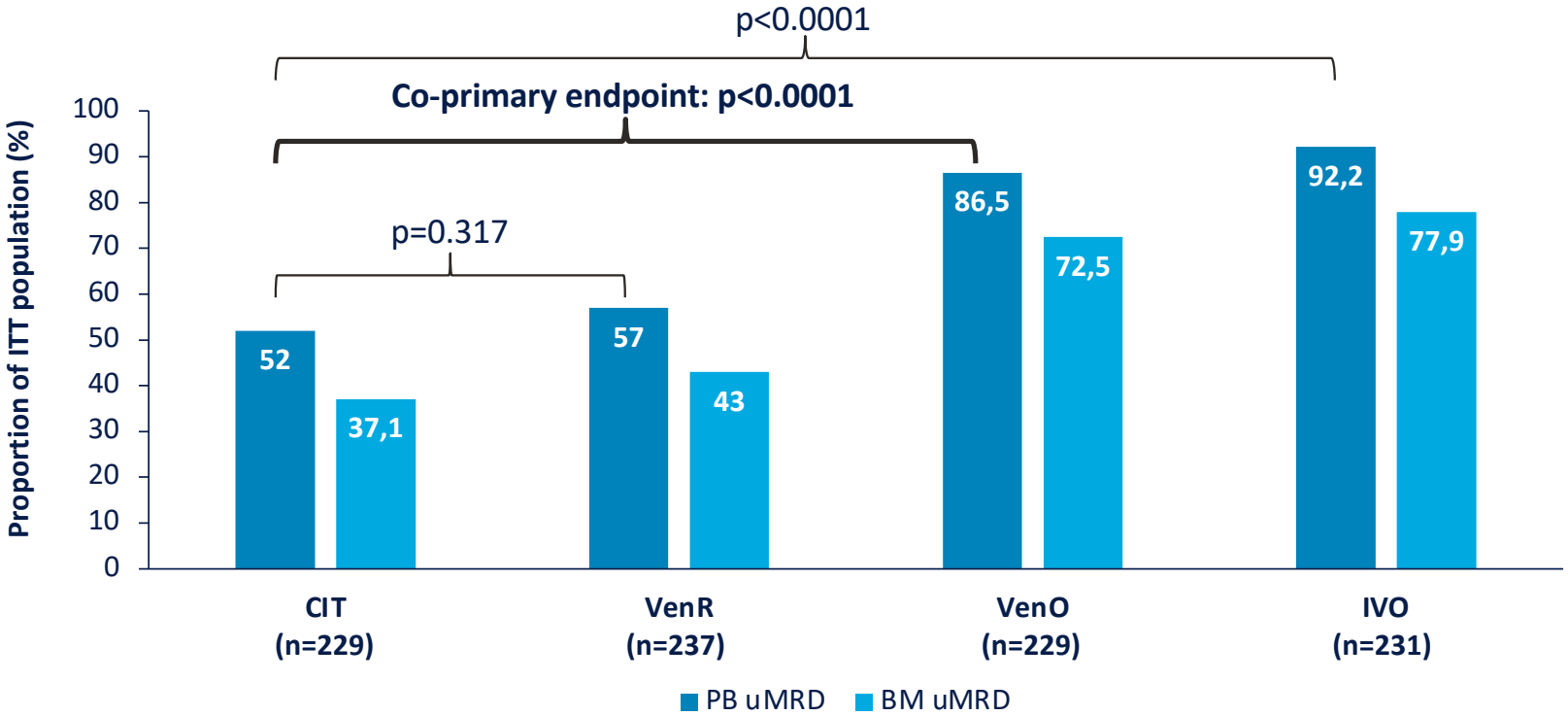
* 97.5% CI reported as per Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.
CIT, chemoimmunotherapy; FCM, flow cytometry; ITT, intent-to-treat; O, obinutuzumab; PB, peripheral blood; Ven, venetoclax.

Eichhorst B, *et al. N Engl J Med* 2023; 388:1739–1754.

New/Updated

uMRD rates in PB and BM across all arms

uMRD ($<10^{-4}$) rates in the ITT population by FCM*
Month 15 in PB (all arms) and final restaging in BM: Month 9 (CIT); month 15 (VenR, VenO, and IVO)



* ITT analysis (BM): 181 patients (71 CIT, 45 VenR, 30 VenO, and 35 IVO) with missing BM samples were counted as MRD positive; ITT analysis (PB): 63 patients (34 CIT, 15 VenR, 10 VenO, and 4 IVO) with missing PB samples (4.8%) were counted as MRD positive.
BM, bone marrow; CIT, chemoimmunotherapy; FCM, flow cytometry; ITT, intent-to-treat; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; PB, peripheral blood; R, rituximab; Ven, venetoclax.

Eichhorst B, *et al.* ASH 2021. Abstract 71 (Oral);
Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.

New/Updated

Most common Grade ≥3 TEAEs and AEs of interest

Grade ≥3 TEAEs (≥5%) and AEs of interest independent from incidence

The most common Grade ≥3 TEAEs reported overall were neutropenia (42.8%), infections (15.8%), thrombocytopenia (9.4%), TLS (7.3%), and febrile neutropenia (6.5%)

CTC Grade ≥3 AEs (≥5%) and AEs of interest	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)	Total (N=912)
Anemia*	16 (7.4)	9 (3.8)	11 (4.8)	9 (3.9)	45 (4.9)
Neutropenia*	98 (45.4)	94 (39.7)	103 (45.2)	95 (41.1)	390 (42.8)
Thrombocytopenia*	18 (8.3)	8 (3.4)	34 (14.9)	26 (11.3)	86 (9.4)
Febrile neutropenia*	24 (11.1)	10 (4.2)	7 (3.1)	18 (7.8)	59 (6.5)
Infections†	40 (18.5)	25 (10.5)	30 (13.2)	49 (21.2)	144 (15.8)
TLS*,‡	9 (4.2)	24 (10.1)	19 (8.3)	15 (6.5)	67 (7.3)
Atrial fibrillation*	1 (0.5)	1 (0.4)	0 (0.0)	6 (2.6)	8 (0.9)
Infusion-related reaction*	12 (5.6)	19 (8.0)	26 (11.4)	10 (4.3)	67 (7.3)
Hypertension*	3 (1.4)	5 (2.1)	4 (1.8)	13 (5.6)	25 (2.7)
Pneumonia*	12 (5.6)	4 (1.7)	12 (5.3)	15 (6.5)	43 (4.7)

No major differences observed in hematologic AEs among all four arms.
Grade ≥3 infections were more common with IVO and CIT vs VenO or VenR

Median follow-up: 38.8 months; * Adverse events reported as single term; † Adverse event reported as high-level term; ‡ Including clinical and laboratory **TLS according to Cairo–Bishop as per protocol; no fatal TLS occurred**. CIT, chemoimmunotherapy; CTC, Common Terminology Criteria; IRR, infusion-related reactions; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; TEAE, treatment-emergent adverse event; TLS, tumor lysis syndrome; Ven, venetoclax.

Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754.

New/Updated

SPMs and Richter transformation

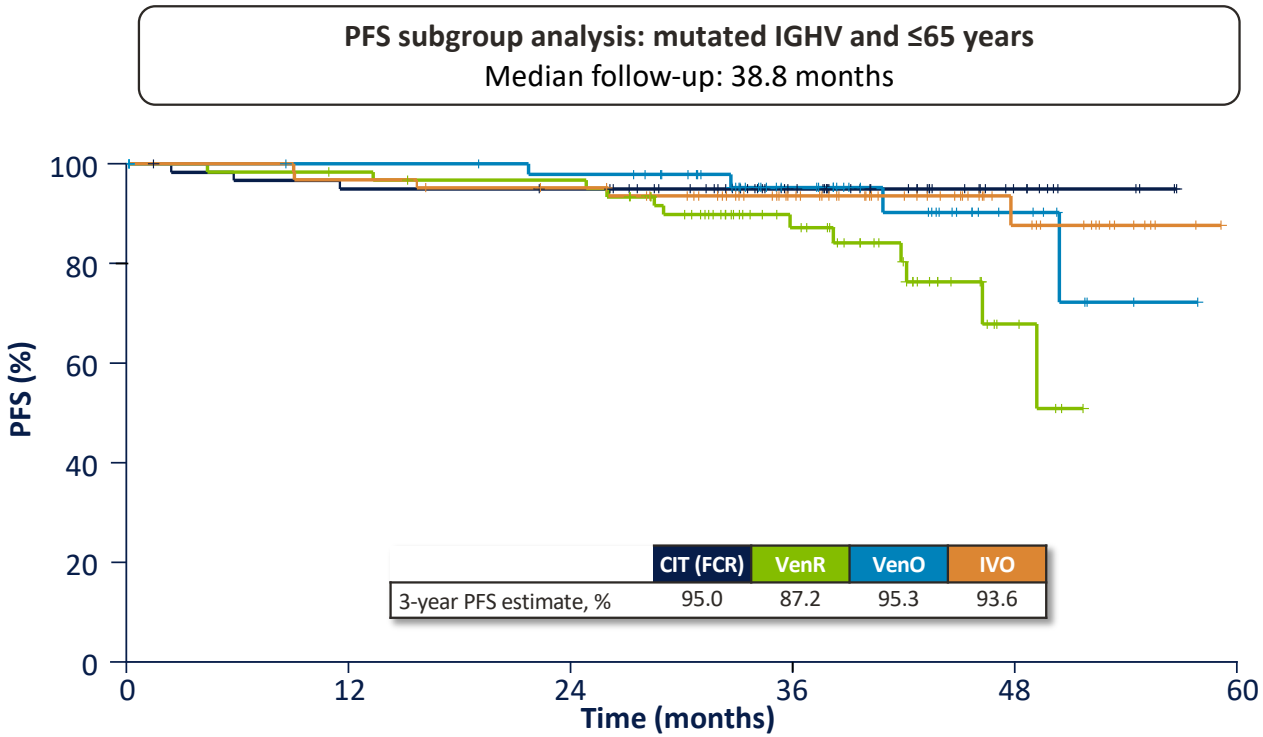
AE	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)
Second primary malignancies,* n	**49**	**24**	**27**	**29**
Solid tumors	18	9	13	15
Hematologic malignancies	4	1	0	4
Non-melanoma skin cancer	27	14	14	10
Basal cell carcinoma	16	13	7	6
Squamous cell carcinoma	11	1	7	4
Richter transformation	**6**	**4**	**6**	**2**

Secondary neoplasia occurred more frequently with CIT vs venetoclax-based regimens

Median follow-up: 38.8 months.
* Second primary malignancies counted as events, not as patients affected.
CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; SPM, second primary malignancy; Ven, venetoclax.

Eichhorst B, *et al. N Engl J Med* 2023; **388:**1739–1754 (incl. suppl).

PFS by IGHV status: Subgroup with mutated IGHV and ≤65 years

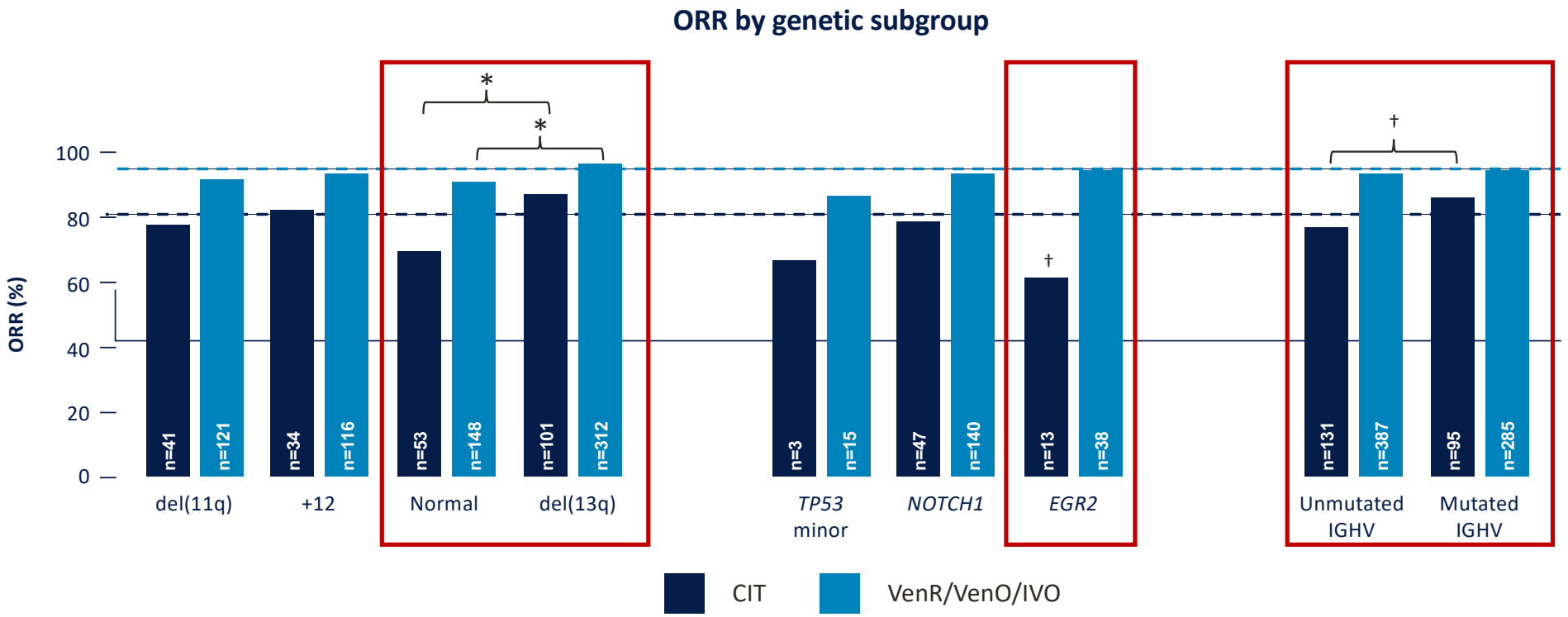


At risk:					
CIT (FCR)	65	57	56	34	10
VenR	62	60	58	33	5
VenO	50	48	46	27	8
IVO	63	61	58	40	15

CIT, chemoimmunotherapy; FCR, fludarabine + cyclophosphamide + rituximab; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; Ven, venetoclax.

Eichhorst B, *et al.* EHA 2022. Abstract LB2365 (Oral).

Response and genetic subgroups: Full trial population

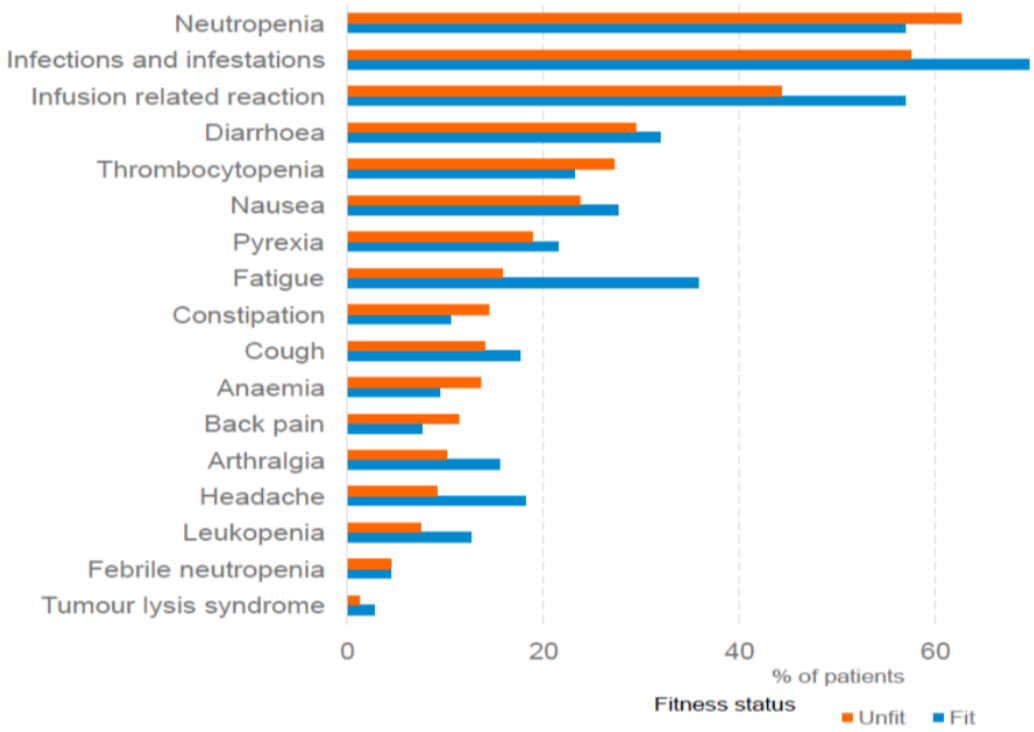


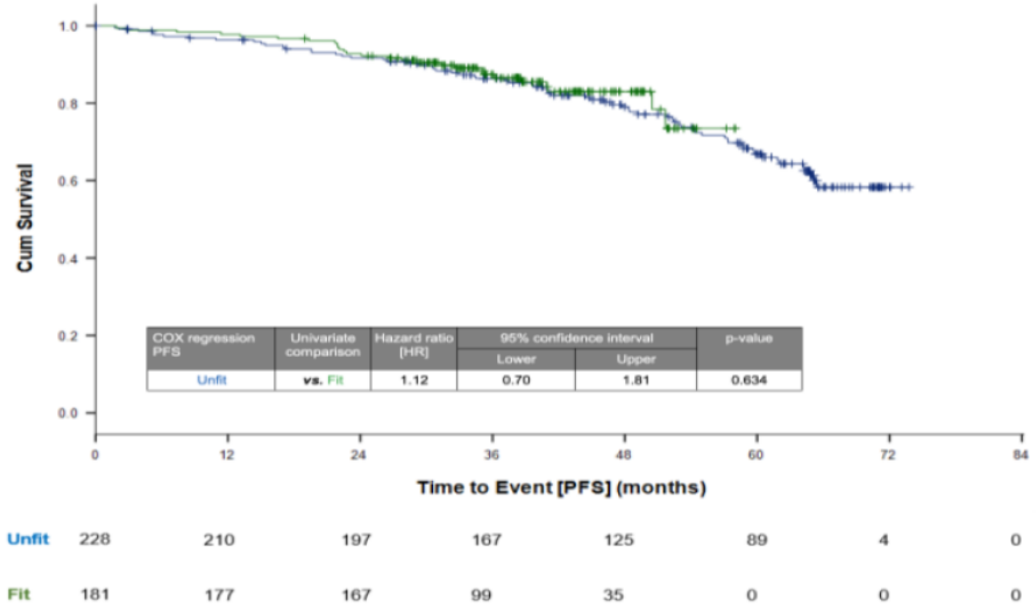
Patients with del(13q) had the best ORR in CIT arm and venetoclax arms. ORR was consistent across all other gene mutations for venetoclax arms, whereas for CIT, patients with unmutated IGHV or mutated *EGR2* had a non-significant trend for lower ORR with CIT

* $p<0.05$; † $p=0.08$.
CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; Ven, venetoclax.

Tausch E, *et al.* ASH 2022. Abstract 345 (Oral).

Does fitness matter with Ven-Obi?





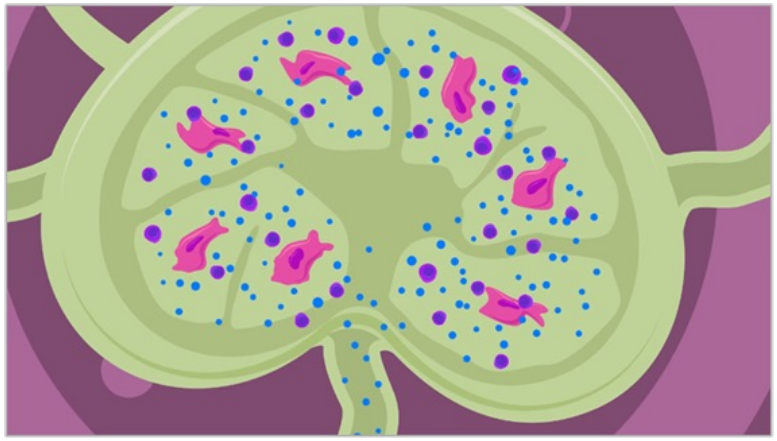
COX regression PFS	Univariate comparison	Hazard ratio [HR]	95% confidence interval		p-value
			Lower	Upper	
Unfit	vs. Fit	1.12	0.70	1.81	0.634

No substantial impact of fitness on toxicity and efficacy of Ven-Obi.

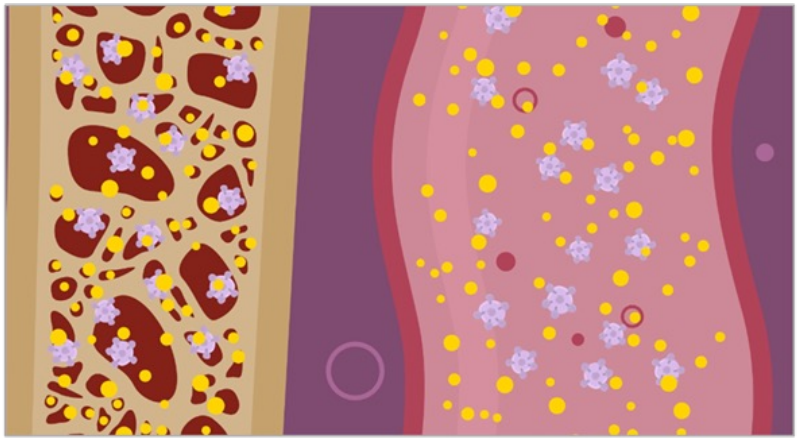
Unpublished data

DISTINCT I+V MoAs WORK TOGETHER TO CLEAR CLL CELLS[1,2]

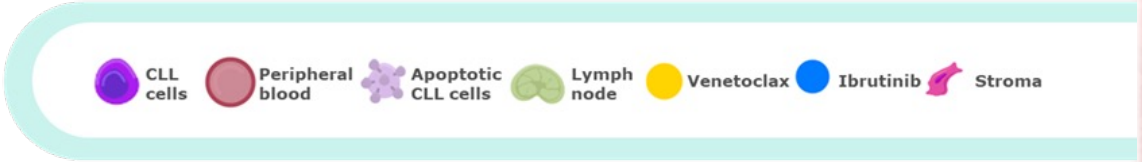
Synergistic combination of ibrutinib and venetoclax with a **distinct and complementary mechanism of action**[1,2]

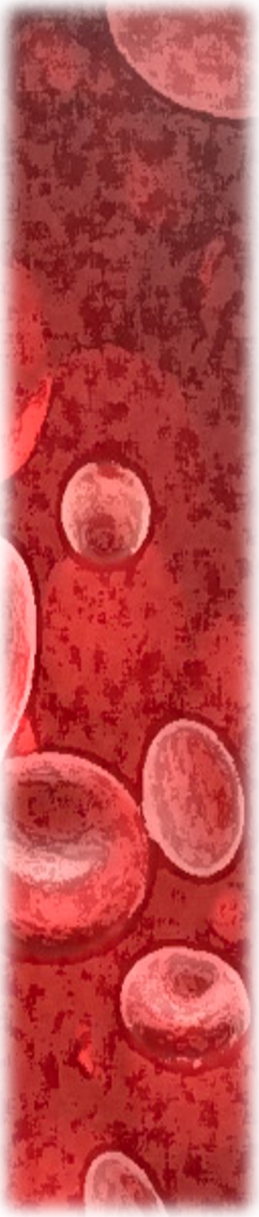


- Ibrutinib is more active in lymph nodes than in blood, where it helps to inhibit proliferation of malignant CLL cells by inciting them to return to peripheral blood[1,2]



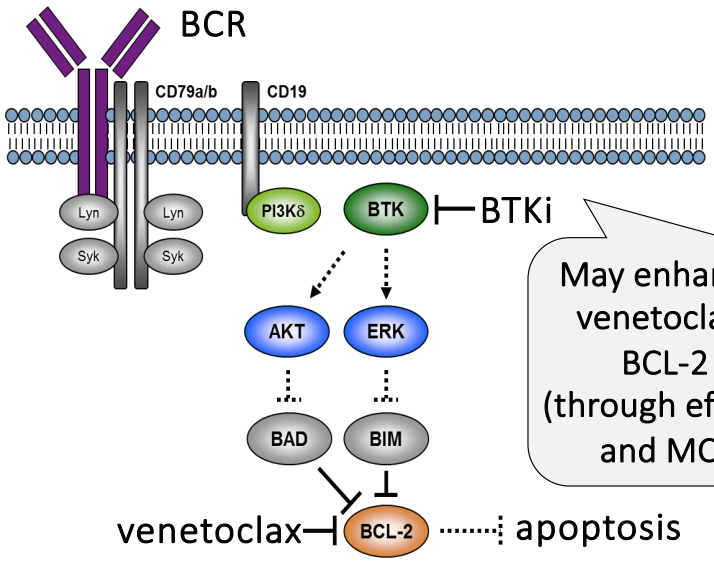
- Conversely, venetoclax is more active in blood and marrow, where it can deepen measurable cellular responses[3]





1. Lu P, et al. Blood Cancer J. 2021;11(2):39.
2. Balakrishnan K, et al. Eur Med J. 2017;2(1):24–30.
3. Kater AP, et al. Blood Adv. 2021;5(23):5410–14.

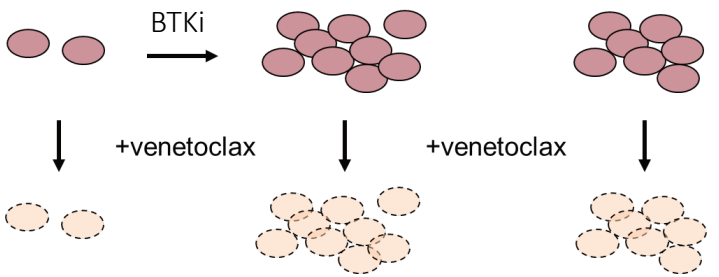
Combined BTK and BCL-2 Inhibition



May enhance sensitivity to venetoclax by increasing BCL-2 dependency (through effects on BAD/BIM and MCL-1/BCL-X_L)[1–4]

BTK inhibition mobilizes CLL cells into the blood[3–7]

Venetoclax depletes CLL from the circulation, lymph nodes, and BM[3,6,8]



BTK inhibition sensitizes CLL cells to venetoclax by interrupting TLR9-induced CD40 upregulation and protein translation[9]

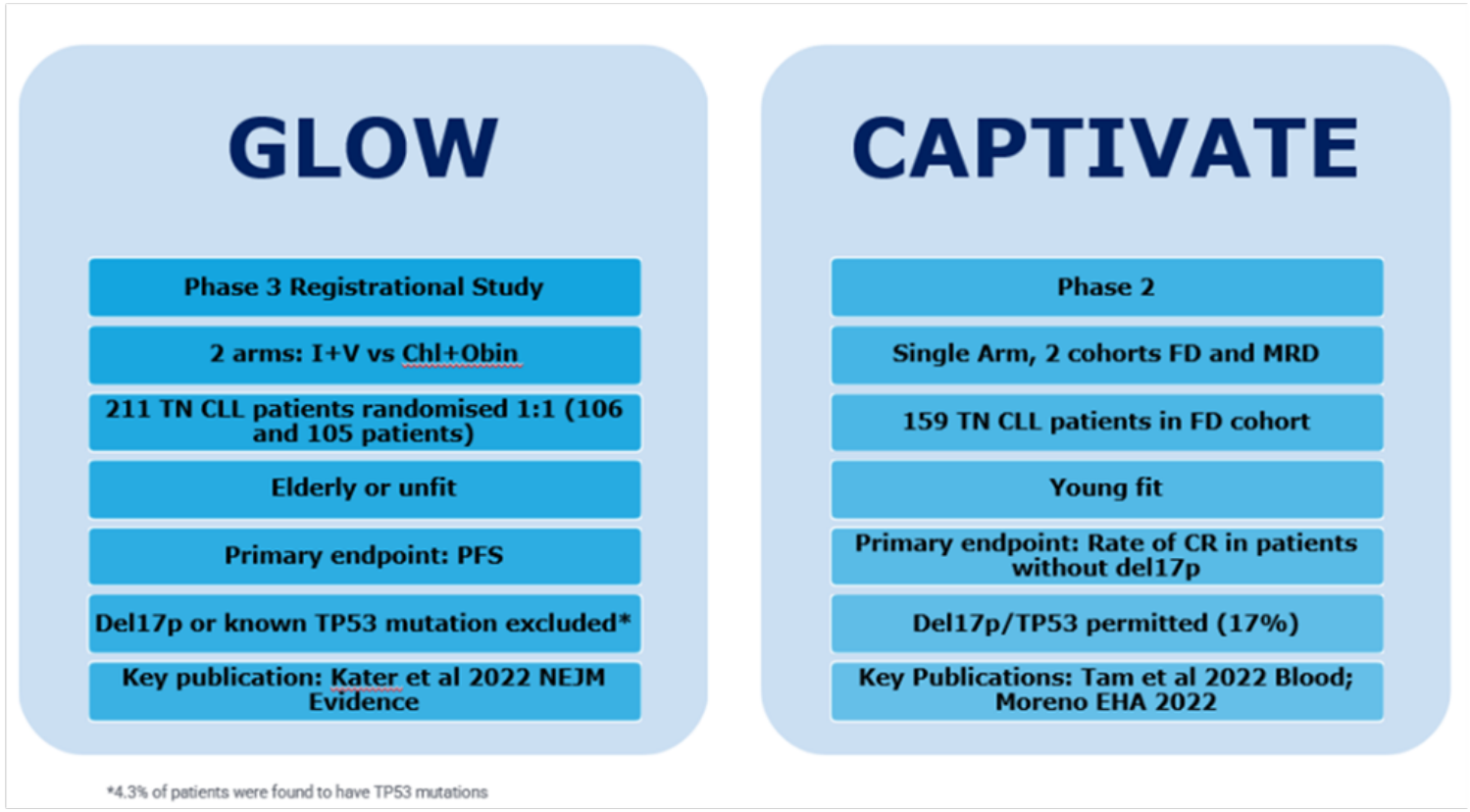
Venetoclax and BTKis have synergistic and complementary antitumor activity in CLL.
Safety profiles are not overlapping

Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib.
Non è ancora rimborsato in Italia.

BCL-2, B-cell lymphoma 2; BCR, B-cell receptor; BM, bone marrow; BTK, Bruton's tyrosine kinase; BTKi, Bruton's tyrosine kinase inhibitor; CD40, cluster of differentiation 40; TLR9, Toll-like receptor 9.

1. Valentin R, *et al. Blood* 2018; **132:**1248–1264; 2. Deng J, *et al. Leukemia* 2017; **31:**2075–2084;
3. Cervantes-Gomez F, *et al. Clin Cancer Res* 2015; **21:**3705–3715; 4. Patel VK, *et al. Leukemia* 2018; **32:**920–930;
5. Leverson JD, *et al. Cancer Discov* 2017; **7:**1376–1393; 6. Wang YLL, *et al.* ASH 2019. Abstract 475 (Oral);
7. Herman SEM, *et al. Clin Cancer Res* 2017; **23:**2831–2841; 8. Roberts AW, *et al. N Engl J Med* 2016; **374:**311–322;
9. Kielbassa K, *et al.* EHA 2023. Abstract S140 (Oral).

KEY COMBINATION STUDIES



Kater et al 2022 NEJM Evidence; Tam et al 2022 Blood; Moreno et al EHA 2022 Poster

Summary of Studies with Reported Results for Venetoclax + Ibrutinib

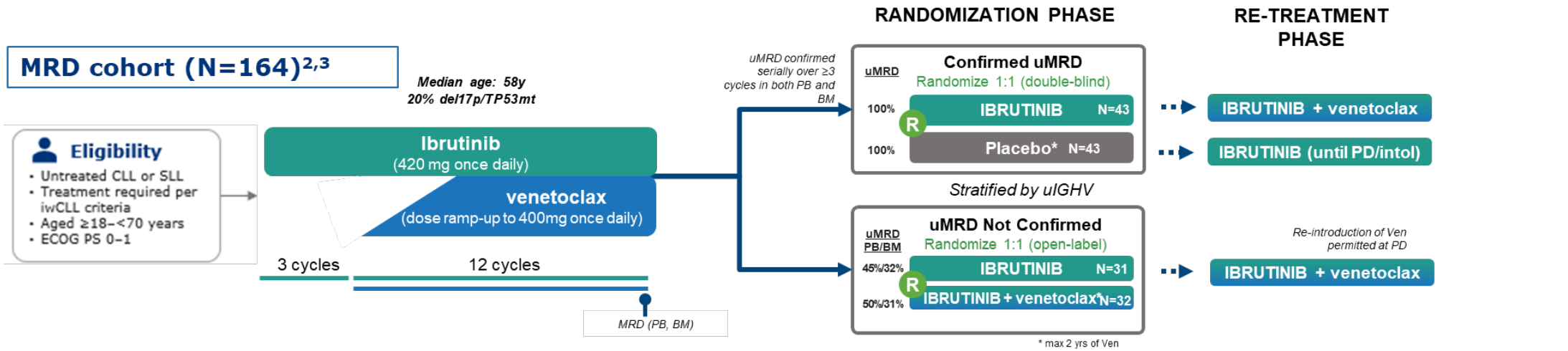
Trial	Population	Experimental Arm	Primary Endpoint	Latest Update
CAPTIVATE[1–4] (MRD cohort)	Phase 2 trial in 1L patients with CLL aged <70 years	Venetoclax, C4–15 + Ibrutinib, C1–15 → Randomized to treatment per MRD status	1-year DFS	AACR 2023 (MRD cohort)
CAPTIVATE[5–7] (FD cohort)	Phase 2 trial in 1L patients with CLL aged ≤70 years	Venetoclax, C4–15 + Ibrutinib, C1–15	CR/CRi	EHA 2023 (FD cohort)
GLOW[8–10]	Phase 3 trial in 1L patients with CLL aged ≥65 years or <65 years with CIRS >6 or CrCl <70 mL/min	Venetoclax, C4–15 + Ibrutinib, C1–15 → PD → Ibrutinib	IRC-assessed PFS	EHA 2023

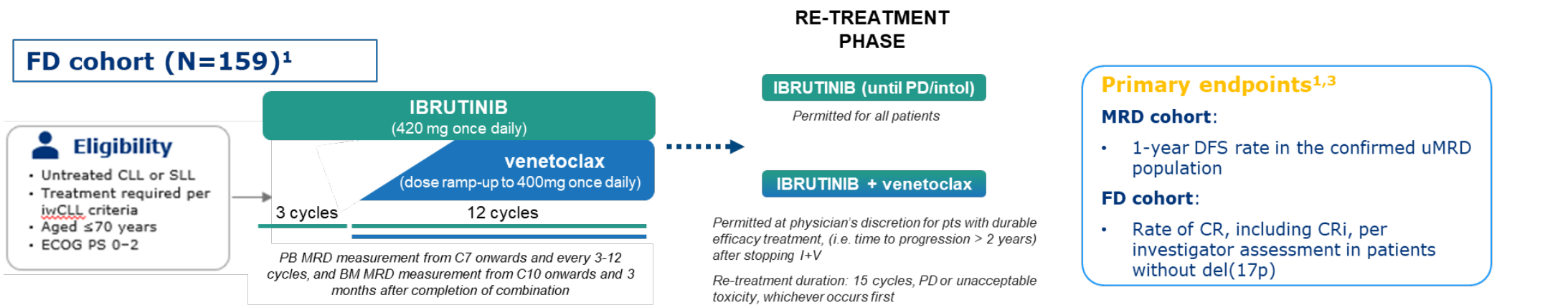
Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib. Non è ancora rimborsato in Italia.

See slide notes for footnotes and abbreviations.

See slide notes for references.

TRIAL DESIGN – Phase II CAPTIVATE





Primary endpoints[1,3]

MRD cohort:

- 1-year DFS rate in the confirmed uMRD population

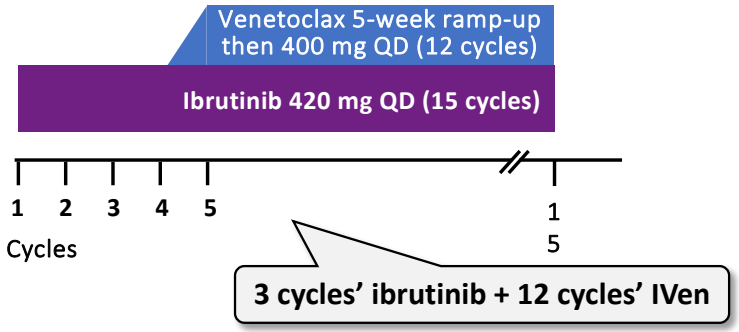
FD cohort:

- Rate of CR, including CRi, per investigator assessment in patients without del(17p)

CAPTIVATE FD Cohort: Ven + Ibr in Previously Untreated CLL

CAPTIVATE: Phase 2 Trial in Previously Untreated CLL (Aged ≤70 Years)[1,2]

FD Cohort



Primary endpoint:
CR rate
for patients without del(17p)

Key secondary endpoints:
- uMRD rates, PFS, OS
- Duration of response, ORR
- Safety, including TLS risk reduction after 3 cycles of ibrutinib

After completion of the FD regimen, patients who subsequently had confirmed PD by iwCLL criteria could be retreated with single-agent ibrutinib until PD or unacceptable toxicity. For patients who had PD 2 years after completion of the FD regimen, retreatment with the FD ibrutinib plus venetoclax regimen could be considered. * Without del(17p) per Dohner hierarchy; † Defined as ≥3 abnormalities by conventional CpG-stimulated cytogenetics. ALC, absolute lymphocyte count; ANC, absolute neutrophil count; CpG, 5'—C—phosphate—G—3';
FD, fixed duration; IVen, ibrutinib + venetoclax; TLS, tumor lysis syndrome.

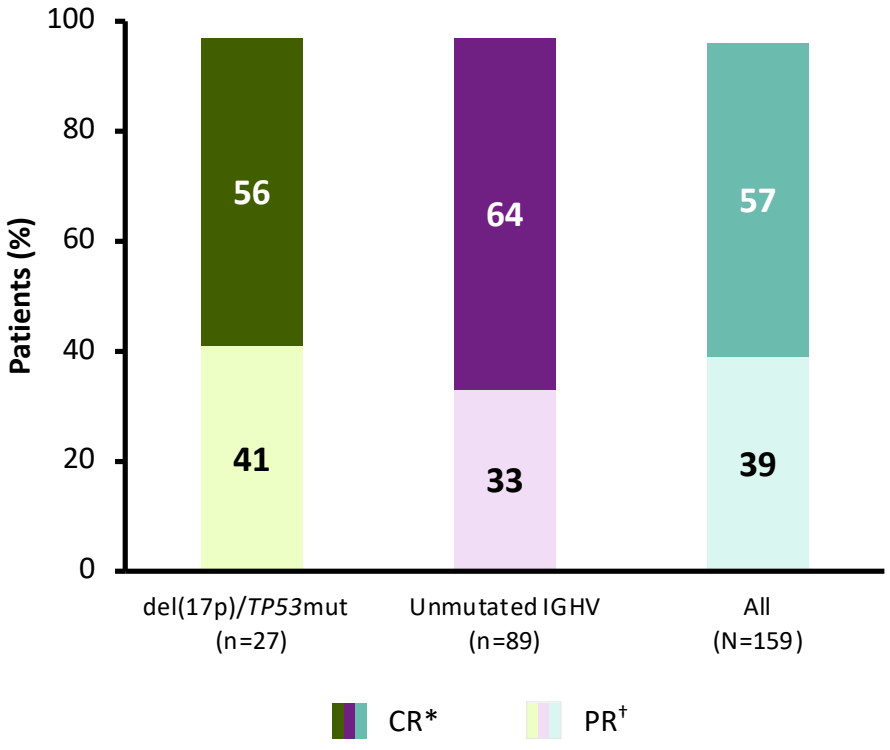
Baseline Characteristics – FD Cohort	IVen (N=159)
Median age, years (range)	60 (33–71)
Male sex, n (%)	106 (67)
Rai Stage III/IV disease, n (%)	44 (28)
Any cytopenia at baseline, n (%)	54 (34)
ANC ≤1.5×10^9/L	13 (8)
Hemoglobin ≤11 g/dL	37 (23)
Platelets ≤100×10^9/L	21 (13)
Lymph node diameter ≥5 cm, n (%)	48 (30)
Median ALC, ×10^9/L (range)	70 (1–503)
ALC ≥25×10^9/L, n (%)	120 (75)
High-risk features, n (%)	
Unmutated IGHV	89 (56)
del(17p)/*TP53* mutation	27 (17)
del(17p)	20 (13)
del(11q)*	28 (18)
Complex karyotype†	31 (19)

Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib.
Non è ancora rimborsato in Italia.

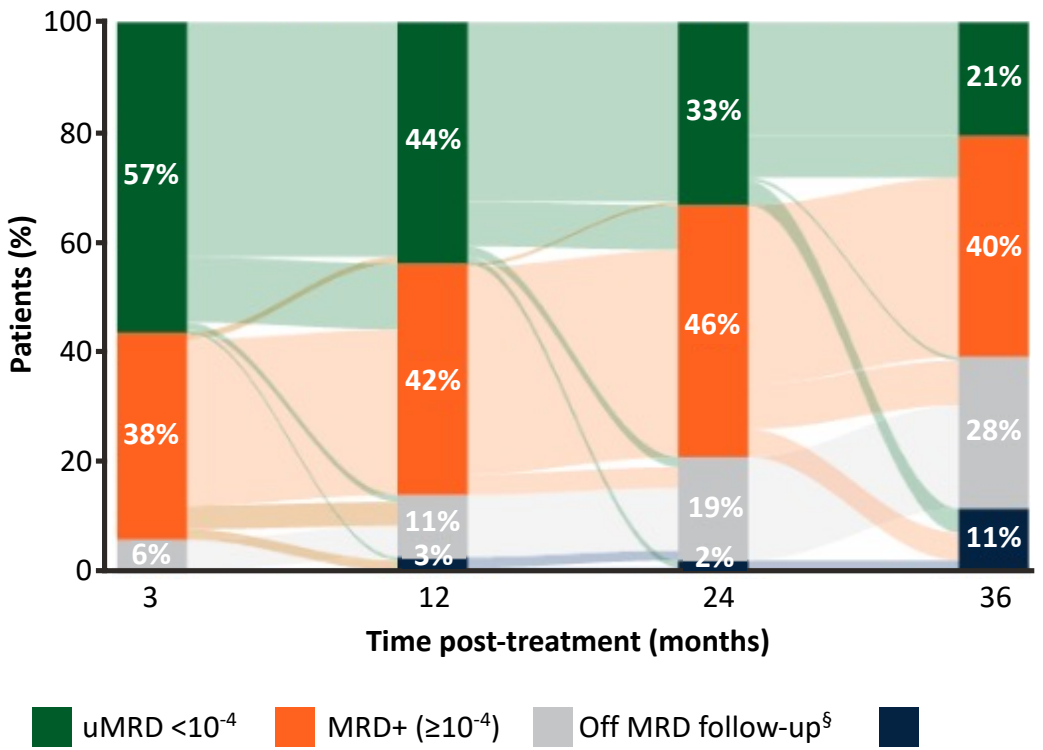
1. Tam CS, *et al. Blood* 2022; **139**:3278–3289;
2. Moreno C, *et al.* EHA 2022. Abstract P669 (Poster).

CAPTIVATE FD Cohort: Response rates

Best Overall Response[1]
(Median time on study: 38.7 months)



Rates of uMRD in PB by Flow Cytometry[2,‡]
(Median time on study: 49.8 Months)



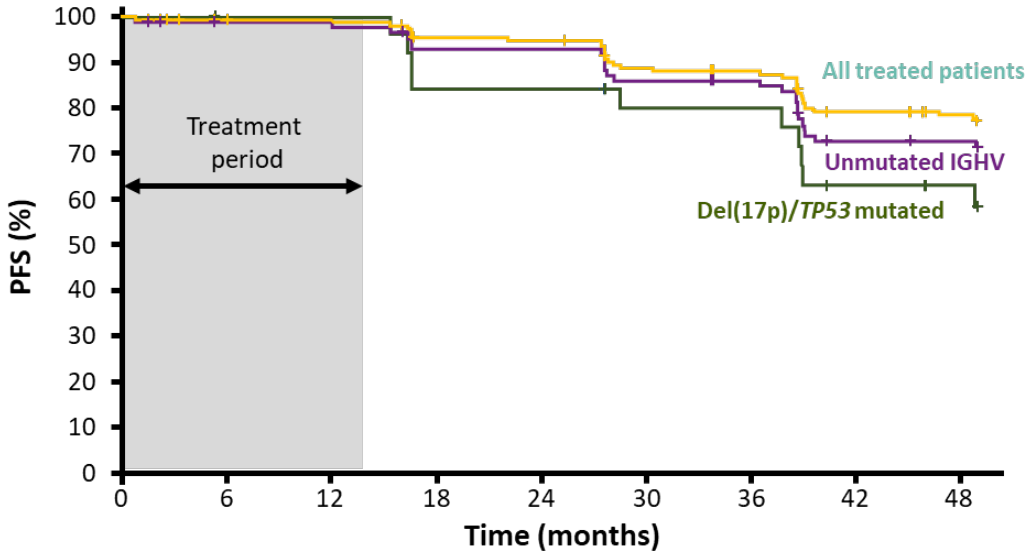
Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib. Non è ancora rimborsato in Italia.

* Included patients achieving CRi; † Included patients achieving nPR; ‡ uMRD <10^{-4}; § Off MRD follow-up included patients who met any one of the criteria: PD, initiation of subsequent therapy, death, or withdrawal from study. FD, fixed duration; PB, peripheral blood.

1. Moreno C, *et al.* EHA 2022. Abstract P669 (Poster);
2. Tedeschi A, *et al.* EHA 2023. Abstract P617 (Poster).

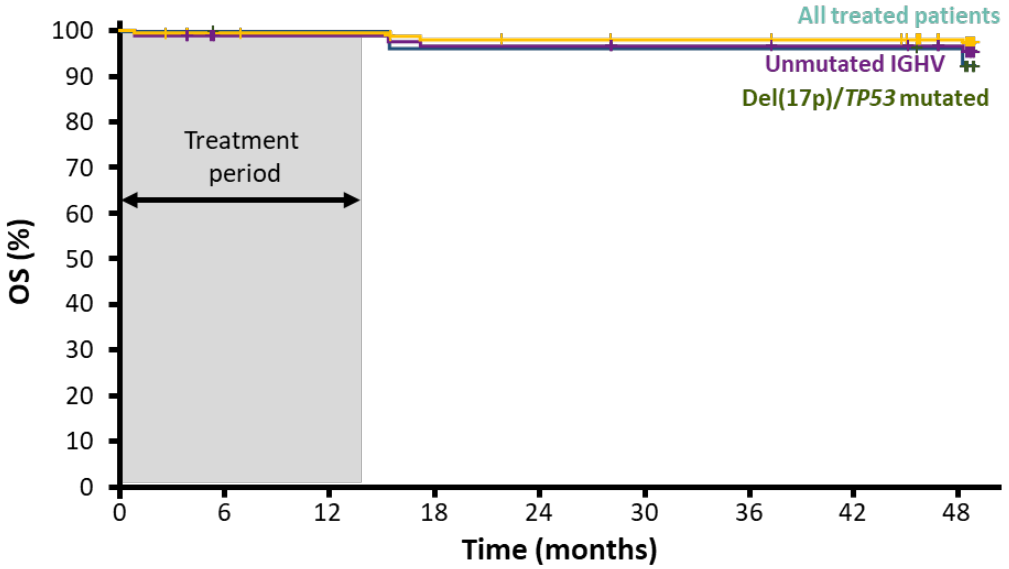
CAPTIVATE FD Cohort: PFS and OS

Investigator-Assessed PFS
(Median follow-up: 49.8 months)



	FD cohort		
	del(17p)/*TP53* (n=27)	Unmutated IGHV (n=89)	All (N=159)
48-month PFS rate, % (95% CI)	63 (41–79)	73 (62–81)	79 (71–84)

OS
(Median follow-up: 49.8 months)



	FD cohort		
	del(17p)/*TP53* (n=27)	Unmutated IGHV (n=89)	All (N=159)
48-month OS rate, % (95% CI)	96 (76–99)	97 (90–99)	98 (94–99)

Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib. Non è ancora rimborsato in Italia.

FD, fixed duration.

Barr PM, *et al.* ASCO 2023. Abstract 7535 (Poster); Tedeschi A, *et al.* EHA 2023. Abstract P617 (Poster).

CAPTIVATE FD Cohort: Safety

AE summary, n (%)[1]	All patients (N=159)
Most common AEs (any grade, ≥30%)	
Diarrhea	99 (62)
Nausea	68 (43)
Neutropenia	66 (42)
Arthralgia	53 (33)
Most common Grade 3/4 AEs (≥5%)	
Neutropenia	52 (33)
Hypertension	9 (6)
Neutrophil count decreased	8 (5)
AEs of clinical interest (any grade)	
Atrial fibrillation	7 (4)
Major hemorrhage*	3 (2)
Any SAE	36 (23)
Fatal AEs	1 (1)†

AE summary, n (%)[1]	All patients (N=159)
AEs leading to discontinuation	**10 (6)**
Ibrutinib only	5 (3)
Venetoclax only	1 (1)‡
AEs leading to dose reduction	**39 (25)**
Ibrutinib only	9 (6)
Venetoclax only	18 (11)

- No TLS events were observed during venetoclax onboarding in combination with ibrutinib[1]
- At the 3-year follow-up, most frequently occurring TEAEs were Grade 1/2 (with the exception of neutropenia)[2]
  - Incidence of neutropenia was similar compared with primary analysis
  - Most TEAEs occurred within 4 months after start of treatment and resolved quickly
  - No new serious AEs or secondary malignancies occurred after the primary analysis
- In the 4-year follow-up, the safety profile remained consistent[3]
  - 1 serious AE of prostate cancer occurred during additional year of follow-up
  - Data on serious AEs and SPMs continue to be collected

Questo regime terapeutico è stato approvato da EMA ed è inserito all'interno dell'RCP di Ibrutinib.
Non è ancora rimborsato in Italia.

* Major hemorrhage was identified using the Standardized MedDRA Query for Hemorrhage, excluding laboratory terms; † Sudden death in 1 patient during ibrutinib lead-in; ‡ Patient discontinued venetoclax because of AE after discontinuing ibrutinib as a result of investigator decision. FD, fixed duration; TEAE, treatment-emergent adverse event.

1. Tam CS, *et al. Blood* 2022; **139**:3278–3289;
2. Moreno C, *et al.* EHA 2022. Abstract P669 (Poster);
3. Tedeschi A, *et al.* EHA 2023. Abstract P617 (Poster).

RETREATMENT WITH IBRUTINIB FOLLOWING I+V IS AN OPTION, WITH PATIENTS ACHIEVING A RESPONSE

CAPTIVATE: Summary of retreated patient characteristics[1]

Patient	Baseline high-risk feature*				Response to FD I+V*		Response to retreatment with ibrutinib
	Del(17p)	*TP53* mutated	u*IGHV*	Complex karyotype	PFS (months)	Best response	
1	No	No	Yes	Unknown	38.5	CR	CR
2	No	No	Yes	No	20.3	PR	PR
3	No	No	Yes	No	19.4	PR	PR
4	No	No	Yes	No	44.2	CR	PR
5	No	No	Yes	Yes	38.6	PR	PR
6	No	No	Yes	No	27.4	PR	PR
7	No	No	Yes	Yes	38.6	PR	PR
8	No	No	Yes	Yes	27.6	CR	PR
9	Yes	No	No	No	28.5	CRi	PR
10	Yes	No	Yes	Yes	16.6	PR	PR
11	No	No	Yes	No	36.5	CR	PR
12	No	No	No	No	27.4	PR	PR
13	No	No	No	Yes	22.0	PR	PR
14	No	No	No	Yes	30.4	PR	PR
15	No	No	Yes	Yes	38.6	CR	PR-L
16	No	No	Yes	No	39.6	PR	SD
17	Yes	Yes	Yes	Yes	48.8	PR	PD

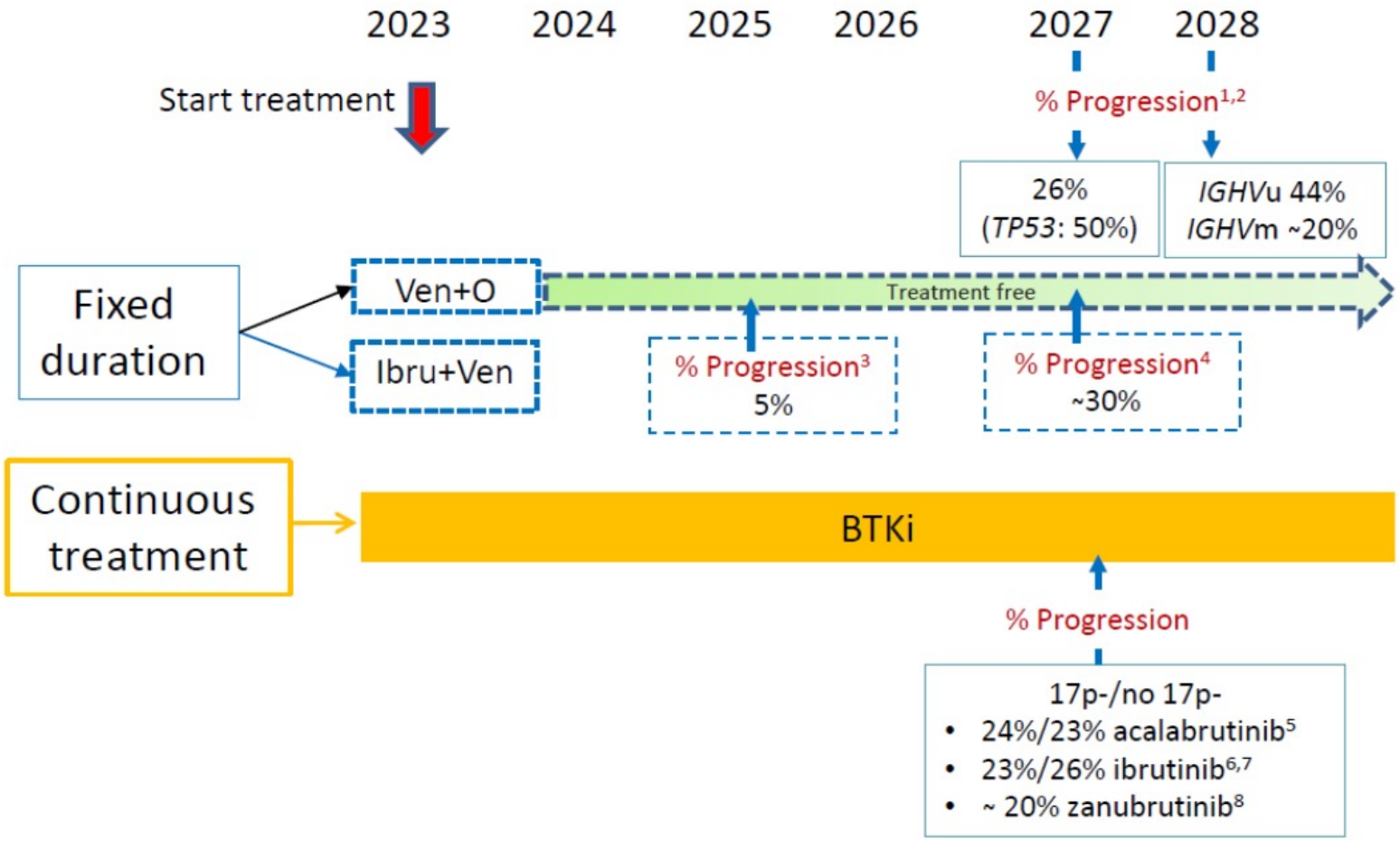
CAPTIVATE[1]

- After progression on I+V, **19 patients have been retreated** with single-agent ibrutinib, with the retreatment duration ranging from **11.1 months (0–38.6)[1]**
- Of the patients retreated with ibrutinib, **17/19 patients were evaluable for response**, with **13 achieving PR, 1 achieving PR-L, 1 with SD and 1 with PD[1]**

GLOW

- **More than 90%** of patients in the I+V arm **did not require subsequent treatment** at 3.5 years of follow-up[2]
- Four patients receiving I+V required subsequent treatment vs. 27 patients receiving Clb+O[3]
  - Patients who **required 2L treatment** after Clb+O received treatment with **subsequent ibrutinib-based therapies[3†]**

Expected outcome at 4 yr in CLL treated with 1st line target therapy



[1]Al-Sawaf O. JCO 2021; [2]Al-Sawaf O. Nat Comm 2023; [3]Tam Blood 2022; [4]Niemann C. ASH 2022; [5]Sharman JP. Leukemia. 2022; [6]Woyach J ASH 2021; [7]Moreno C. Haematologica, 2022; [8]Munir T #639; EHA2023

Poster 1809

Initiating First-Line Ibrutinib in Patients With Chronic Lymphocytic Leukemia (CLL) Improves Overall Survival Outcomes to Rates Approximating an Age-Matched Population ≥ 65 Years

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OBJECTIVE

- The objectives of this study are 1) To compare pooled OS of previously untreated patients with CLL who received ibrutinib to that of the available age-matched general population and 2) To compare the pooled characteristics and OS results with ibrutinib vs CT/CIT across three phase 3 studies.

KEY TAKEAWAYS

- OS benefit has been proven across age and fitness with 1L ibrutinib.
- Dose modification for 1L Ibr-treated pts with CLL was effective in resolving AEs for the majority of patients, allowing them to remain on treatment.
- This study demonstrates that ibrutinib prolonged survival of previously untreated patients with CLL to the extent that it may be comparable to an age-matched general population, whereas CT/CIT did not.

INTRODUCTION

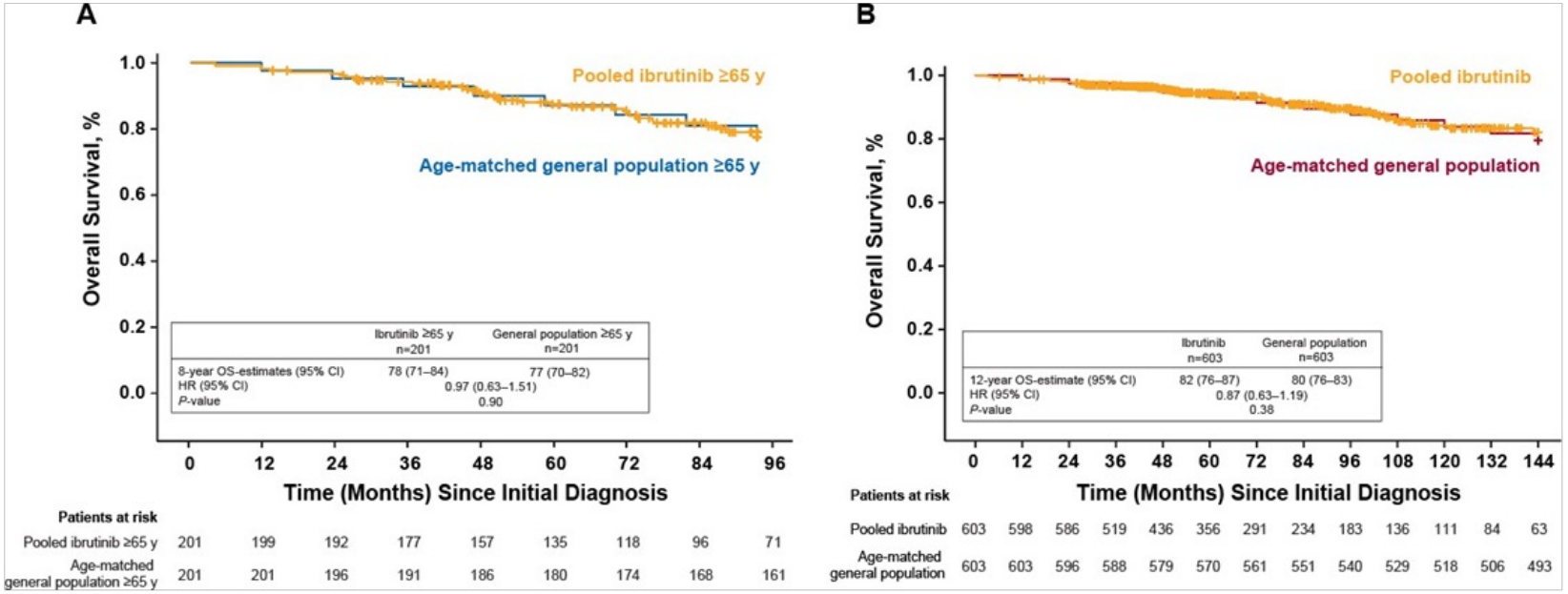
- CLL OS rates have improved over the last 20 years, starting with the use of CT/CIT, then with the introduction of novel agents such as ibrutinib, a once-daily BTKi.[1–5]
  - 1L ibrutinib has shown superiority to standard CT/CIT across a range of previously untreated patient populations, with demonstrated significant OS benefit in multiple randomized phase 3 studies.
  - Recent 8-year follow-up data from RESONATE-2 demonstrated that 59% of previously untreated unfit patients remain progression-free.[5]
- The ideal goal of any therapeutic regimen is to cure patients of their disease, but the first step is to provide enough effective therapeutic options to allow patients to live with their disease.[5-7]
  - Continuous treatment with ibrutinib is possible without toxicity limiting its ongoing use in most patients.
  - Dose management for AEs allows patients to continue to benefit from ibrutinib.
- Given the size of the program and the length of follow-up, there is a unique opportunity to assess whether the initiation of 1L ibrutinib could essentially remove the survival hazard associated with CLL vs the general population.

EM-119078

RESULTS (CONTINUED)

Figure 3. Similar OS Estimate for Pooled Ibrutinib-Treated Patients ≥65 years[a] (A) and Overall Pooled Ibrutinib-Treated Patients[b] (B) vs Age-Matched General Population Population

- 201 ibrutinib-treated patients ≥65 years were included in the analysis; median time on treatment was 44 months, with a median follow-up from initial diagnosis of 6.8 years.
  - OS estimate (8-year) was comparable for the ibrutinib-treated patients ≥65 years vs age-matched general population (**Figure 3A**).
- We also conducted the analysis in the total pooled population of 603 ibrutinib-treated patients; median time on treatment was 39 months, with a median follow-up from initial diagnosis of 5.9 years.
  - OS estimate (12-year) was also comparable for the overall ibrutinib-treated vs age-matched general population (**Figure 3B**).



- *[a]Data after 96 months is not represented in the KM curve; [b]Data after 144 months is not represented in the KM curve*

EM-119078

Continuous therapy

Ibrutinib / Acalabrutinib / Zanubrutinib

- Logistically easy to administer
- Long follow-up support efficacy and tolerability (I)
- Preferred option in patients with high-risk disease (especially *TP53* aberrations)

Fixed-duration therapy

Venetoclax+Obi / Venetoclax+Ibrutinib

- Undetectable MRD in up to ≈75% of cases
- Prolonged treatment-free interval
- Drug-related AE rare after end of treatment

Ibrutinib / Acalabrutinib / Zanubrutinib

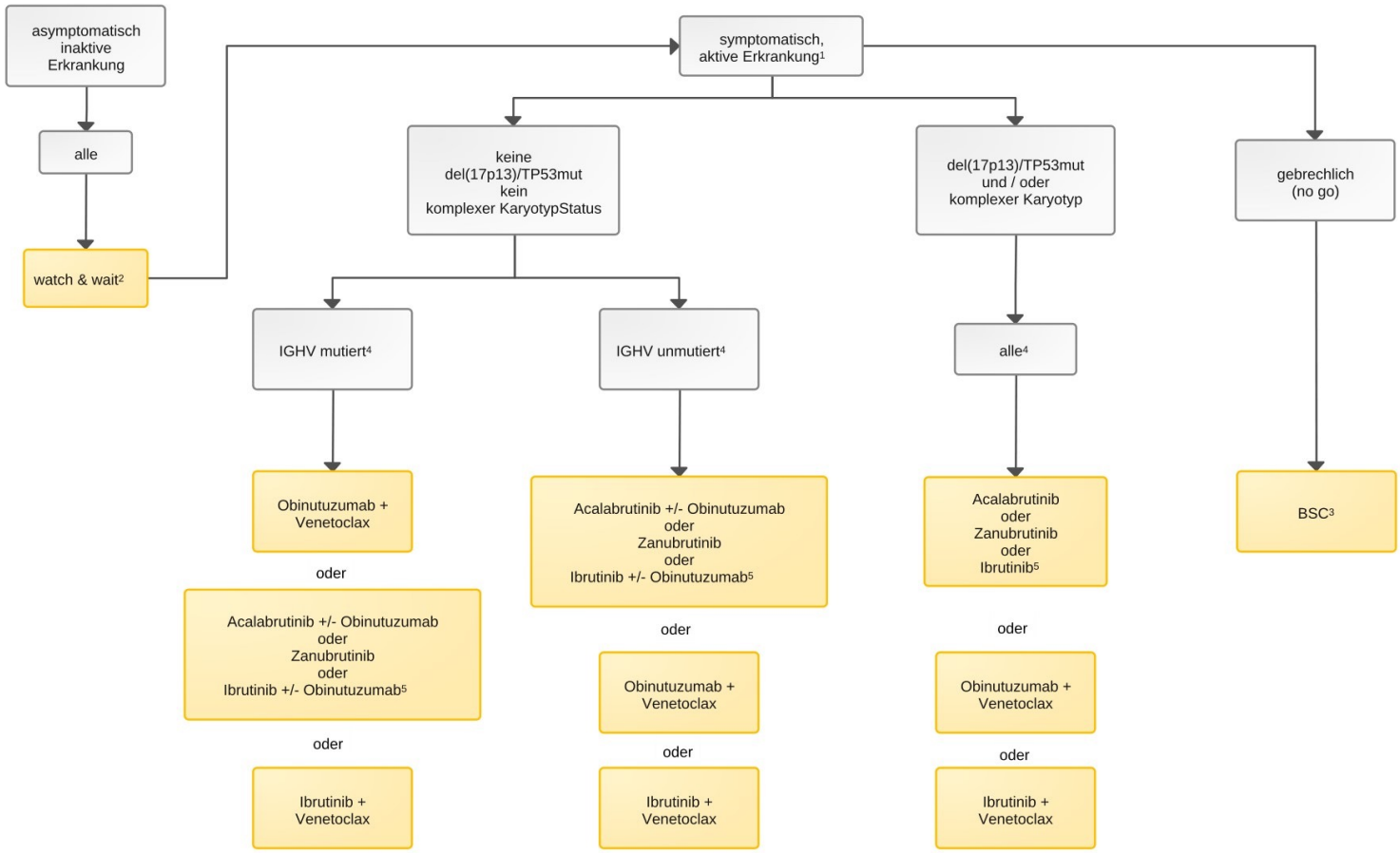
- Afib/VA (< with A and Z)
- Hypertension (< with A)
- Hemorrhage (< with A)
- Anticoagulants
- Arthralgia (< with A and Z)
- Cumulative incidence of AE over time

Venetoclax+Obi

- Grade 3-4 infusion reactions
- Need monitoring TLS
- Neutropenia
- Shorter PFS in high-risk disease

Venetoclax+Ibrutinib

- Afib/VA
- Hypertension
- Neutropenia
- Short follow-up
- Subsequent treatment?



Legende:

palliativer Therapieansatz

[1] *aktive Erkrankung nach Kriterien des IWCLL 2018 [13];*

[2] *watch & wait – abwartendes Verhalten;*

[3] *BSC – beste supportive Behandlung (best supportive care)*

[4] *Die Reihung der nachfolgenden Therapien stellt eine Möglichkeit dar (siehe Kapitel 6.1.1.1, Kapitel 6.1.1.2 und Kapitel 6.1.1.3.). Aufgrund der aktuellen Datenlage ist sie nicht verbindlich. Das individuelle Komorbiditätsprofil, Adhärenzaspekte, Applikationsaufwand/ Logistik der therapeutischen Intervention und die Patientenpräferenz für die finale Therapiefestlegung sollten berücksichtigt werden.*

[5] *bei Kontraindikation gegen bzw. Nicht-Verfügbarkeit von Acalabrutinib oder Zanubrutinib stellt Ibrutinib (+/- Obinutuzumab) weiterhin eine Therapieoption unter Beachtung von erhöhten kardialen Nebenwirkungen dar. Acalabrutinib bzw. Zanubrutinib wurden nicht systematisch bei jüngeren/ fitten Patienten in der Erstlinientherapie evaluiert.*

UPDATE IN EMATOLOGIA

19 Dicembre 2023

Genova

GRAZIE

OSPEDALE POLICLINICO SAN MARTINO

Unita di Ematologia e Trapianti di Midollo

Direttore
Emanuele ANGELUCCI

Dipartimento di Medicina Sperimentale

Franco Fais
Giovanna Cutrona
Monica Colombo
Mariella Dono
Davide Bagnara
Andrea Mazzarello
Silvia Bruno
.....

CLL17

A PROSPECTIVE, RANDOMIZED, OPEN-LABEL, MULTICENTRE PHASE-III TRIAL OF **IBRUTINIB** VERSUS **VENETOCLAX PLUS OBINUTUZUMAB** VERSUS **IBRUTINIB PLUS VENETOCLAX** FOR PATIENTS WITH PREVIOUSLY UNTREATED CHRONIC LYMPHOCYTIC LEUKAEMIA

V+I not reimbursed in Italy

Patients with previously untreated CLL

Incl. fit and unfit patients
Incl. patients with del17p/TP53 mut

1:1:1 Randomization

Stratification according to fitness, del17p/TP53, IGHV

Ibrutinib

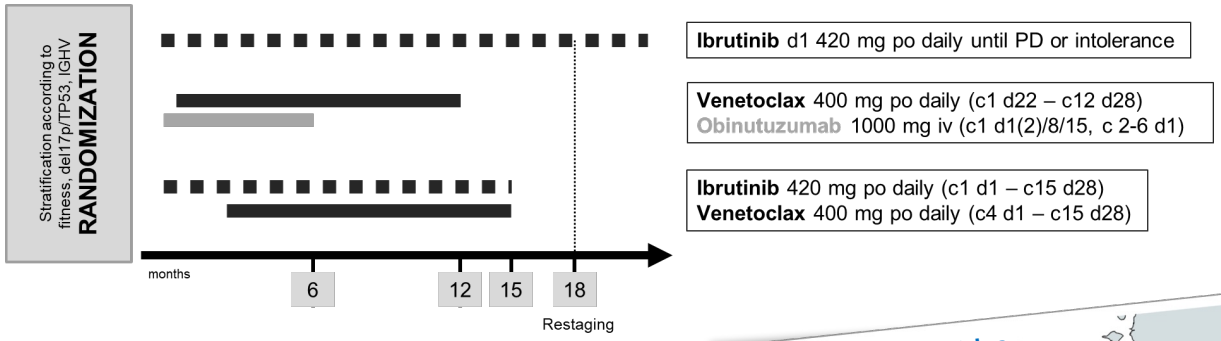
Venetoclax Obinutuzumab

Venetoclax Ibrutinib

897 patients

Primary endpoint:
Progression-free survival

TREATMENT SCHEDULE



TIMELINES

Start of recruitment	Q1/2
Expected end of recruitment	Q4/2
End of study	Q1/2

Molte grazie per il vostro impegno!