



# References

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# LIVING AHEAD OF THE CURVE<sup>1-2</sup>

imbruvica® + venetoclax  
(ibrutinib)

## Superior efficacy



9 out of 10 patients do not require 2L therapy 3.5 years after starting I+V therapy<sup>3</sup>

## Fixed duration, chemo-free therapy



The only all-oral, once-daily, fixed duration therapy in 1L CLL<sup>1,3,4</sup>

## Favorable safety profile



Well tolerated combination reducing the risk of TLS<sup>2,5</sup>

MoA: mode of action; 1L: first line; 2L: second line; CLL: chronic lymphocytic leukemia; I+V: ibrutinib + venetoclax; TLS: tumor lysis syndrome



Mode of Action

Efficacy

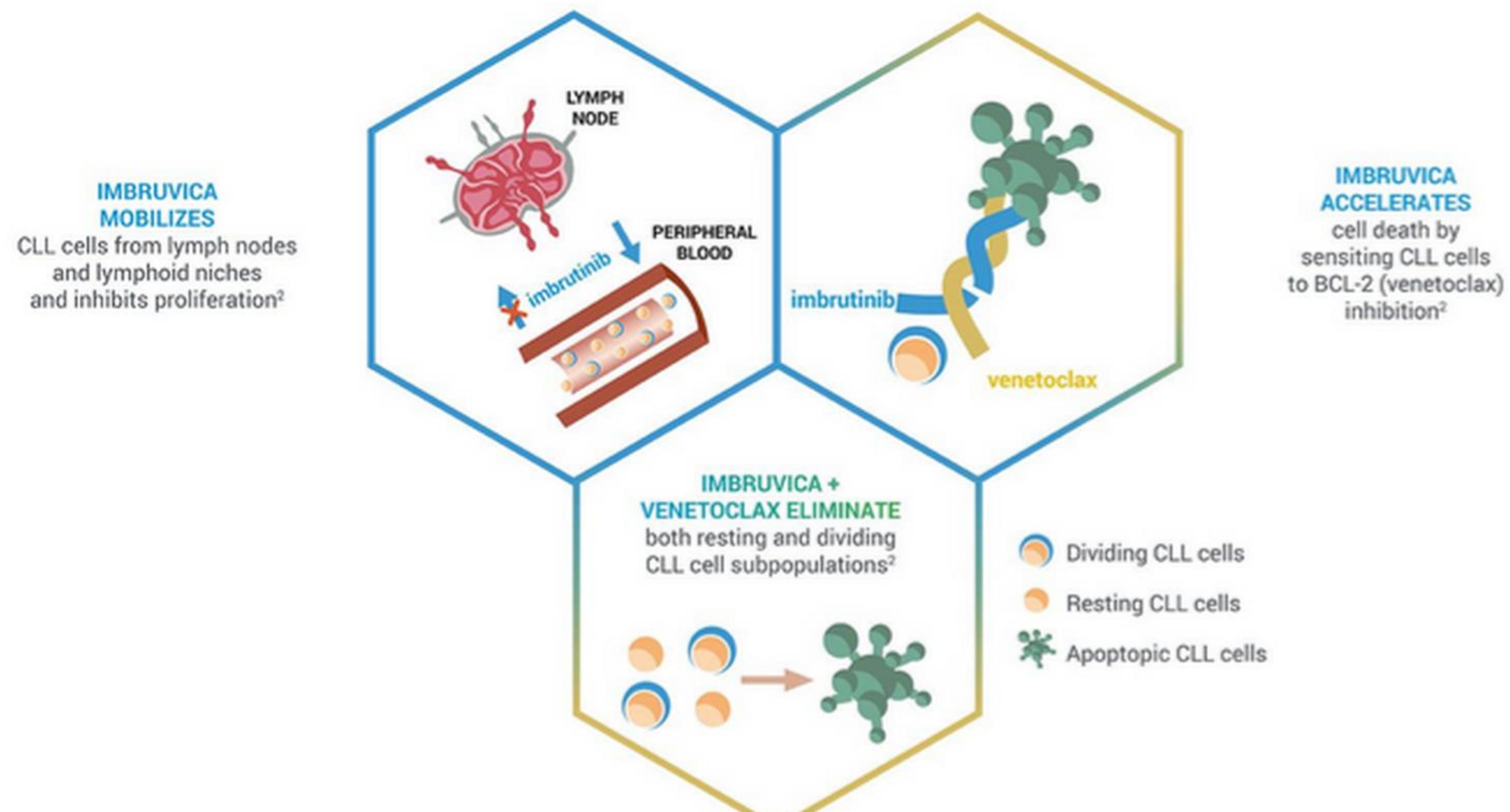
Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

# Strength through synergy by combining 2 powerful targeted therapies<sup>2</sup>



Adapted from Kater AP, et al. 2022

BCL-2 = B-cell lymphoma - 2; CLL = chronic lymphocytic leukemia



## The strength of superior efficacy with IMBRUVICA® + venetoclax<sup>3-5</sup>

### GLOW trial – Elderly population<sup>3</sup>



OS-rate

at 3,5 years<sup>3</sup>

PFS-rate

### CAPTIVATE trial – Young/fit population<sup>4</sup>



OS-rate

at 4 years<sup>4</sup>

PFS-rate

### TIME-TO-NEXT TREATMENT<sup>3</sup>

**9 out of 10**

patients do not require  
2L therapy 3.5 years after  
starting I+V treatment<sup>3</sup>



STUDY DESIGN



STUDY DESIGN

OS: overall survival; PFS: progression-free survival; CLb+O: chlorambucil + obinutuzumab; 2L: second line; I+V: ibrutinib+venetoclax



Mode of Action

Efficacy

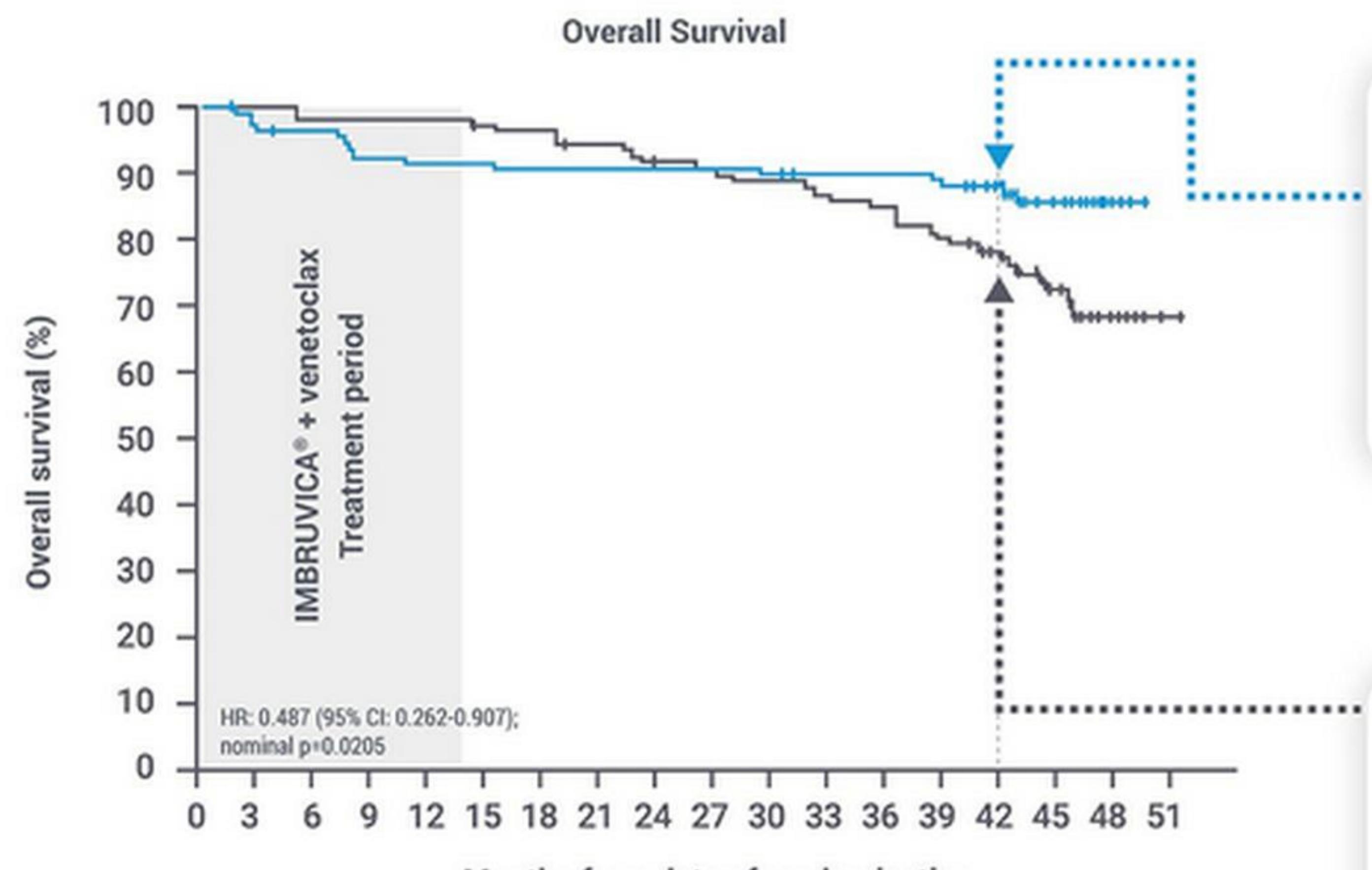
Safety

Dosing

Summary

**imbruvica® + venetoclax**  
(ibrutinib)

## Superior OS with IMBRUVICA® + venetoclax versus Clb+O<sup>3</sup>



87.5%

Estimated 3.5-year OS  
with IMBRUVICA®  
+ venetoclax<sup>3</sup>

77.6%

Estimated 3.5-year OS  
with Clb+O<sup>3</sup>

Median study follow up: 46 months

Adapted from Niemann C, et al. 2022<sup>3</sup>

<sup>3</sup>Median OS was not reached in the Clb+O arm.<sup>3</sup> The statistical testing hierarchy for secondary end points, in order, was uMRD rate in bone marrow, complete response rate, overall response rate, and overall survival. The overall response rate as assessed by IRC was similar between treatment arms (86.8% vs. 84.8%); therefore, testing of subsequent secondary end points according to the prespecified testing hierarchy was exploratory.<sup>3</sup>

OS: overall survival; CLb+O: chlorambucil + obinutuzumab; HR: hazard ratio; CI: confidence interval



Mode of  
Action

Efficacy

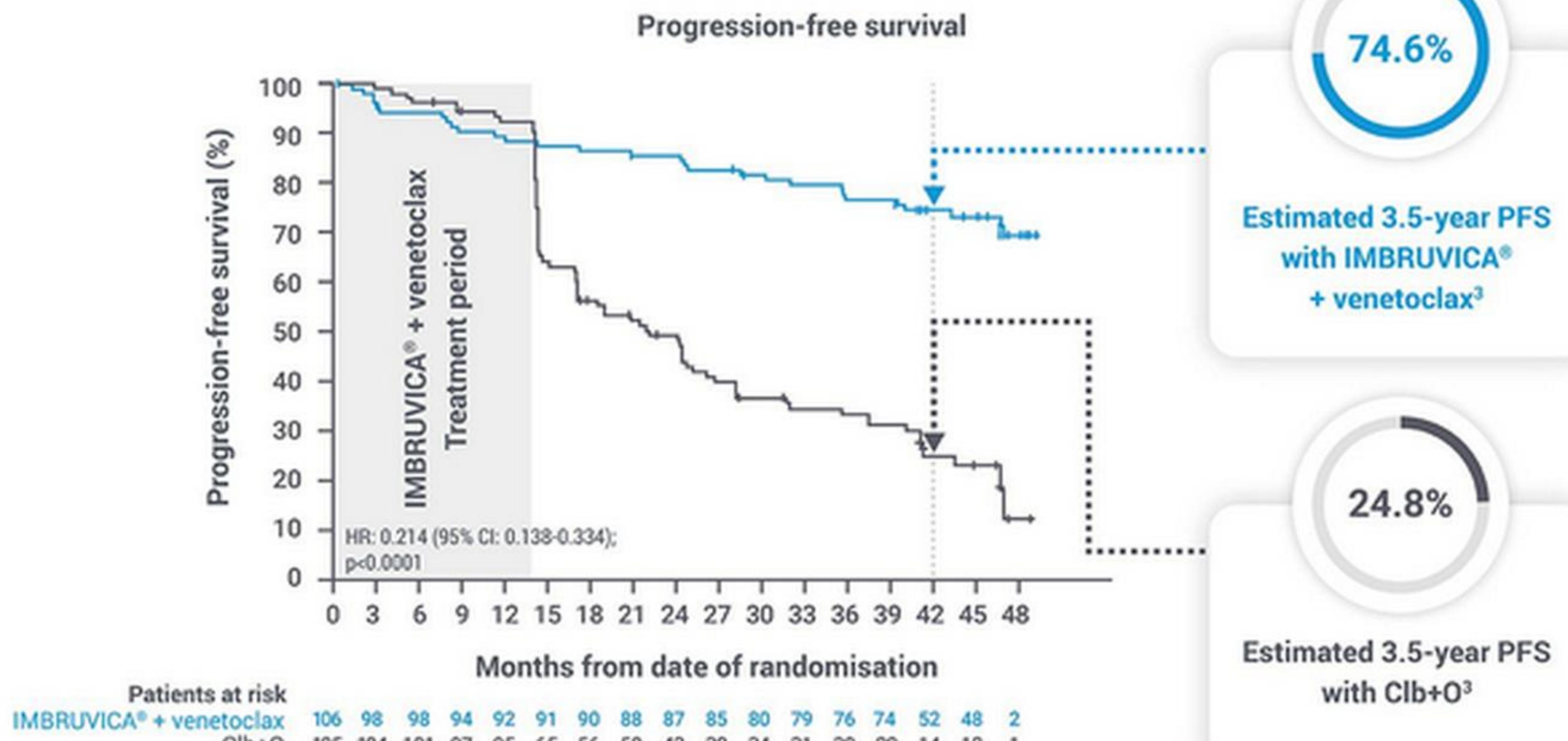
Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## Superior PFS with IMBRUVICA® + venetoclax versus Clb+O<sup>3</sup>



Adapted from Niemann C, et al. 2022<sup>3</sup>

Almost 75% of previously untreated older and comorbid patients were alive and progression free at 3.5 years with all oral, once daily, fixed duration IMBRUVICA® + venetoclax<sup>3</sup>

PFS: progression-free survival; Clb+O: chlorambucil + obinutuzumab; HR: hazard ratio; CI: confidence interval



Mode of Action

Efficacy

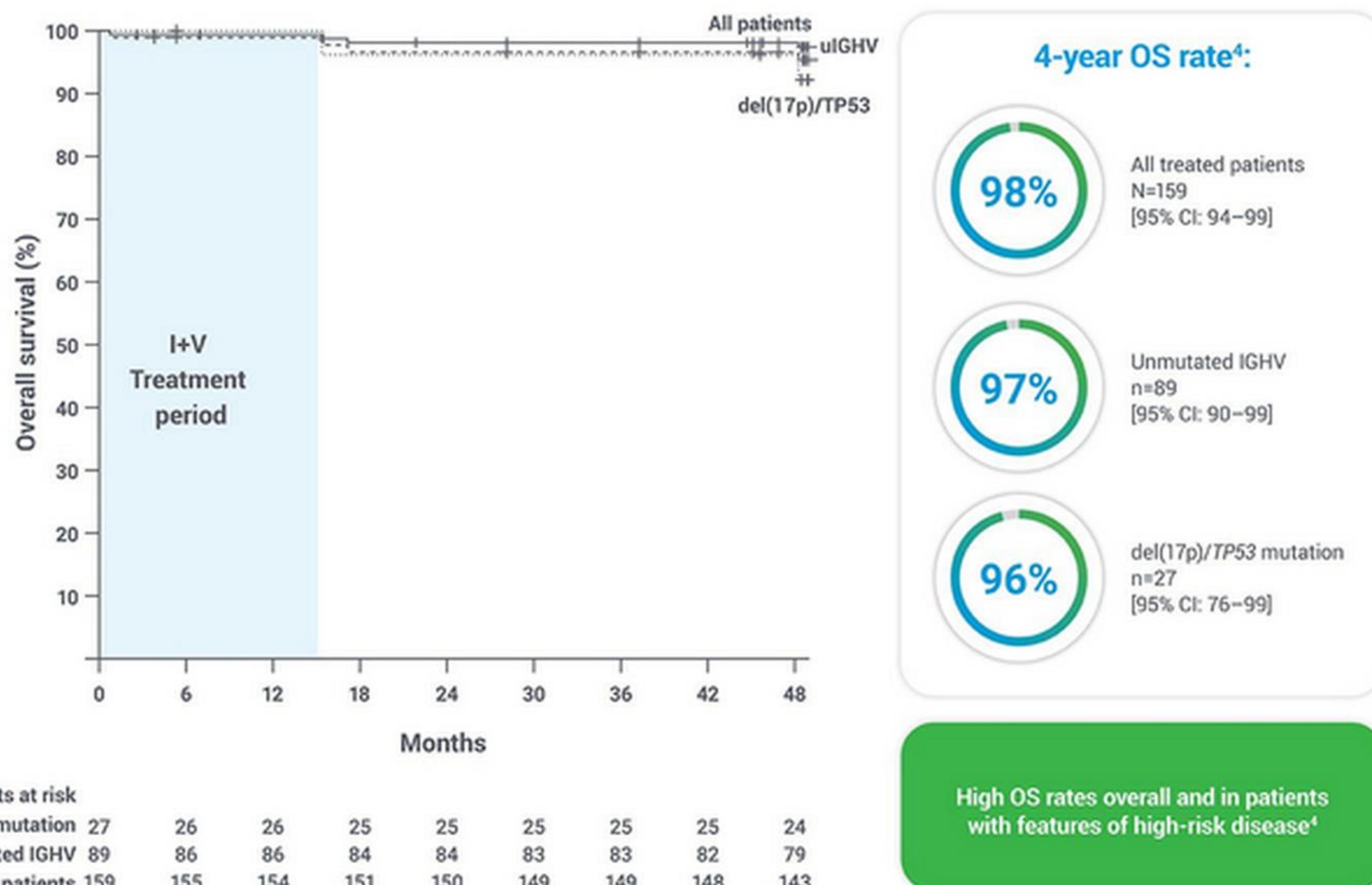
Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## Durable and high overall survival rates with IMBRUVICA® + venetoclax<sup>4</sup>



Adapted from Tedeschi A, et al. 2023

OS: overall survival; FD: fixed-duration; IGHV: immunoglobulin heavy chain variable; I+V: ibrutinib + venetoclax; CI: confidence interval



Mode of Action

Efficacy

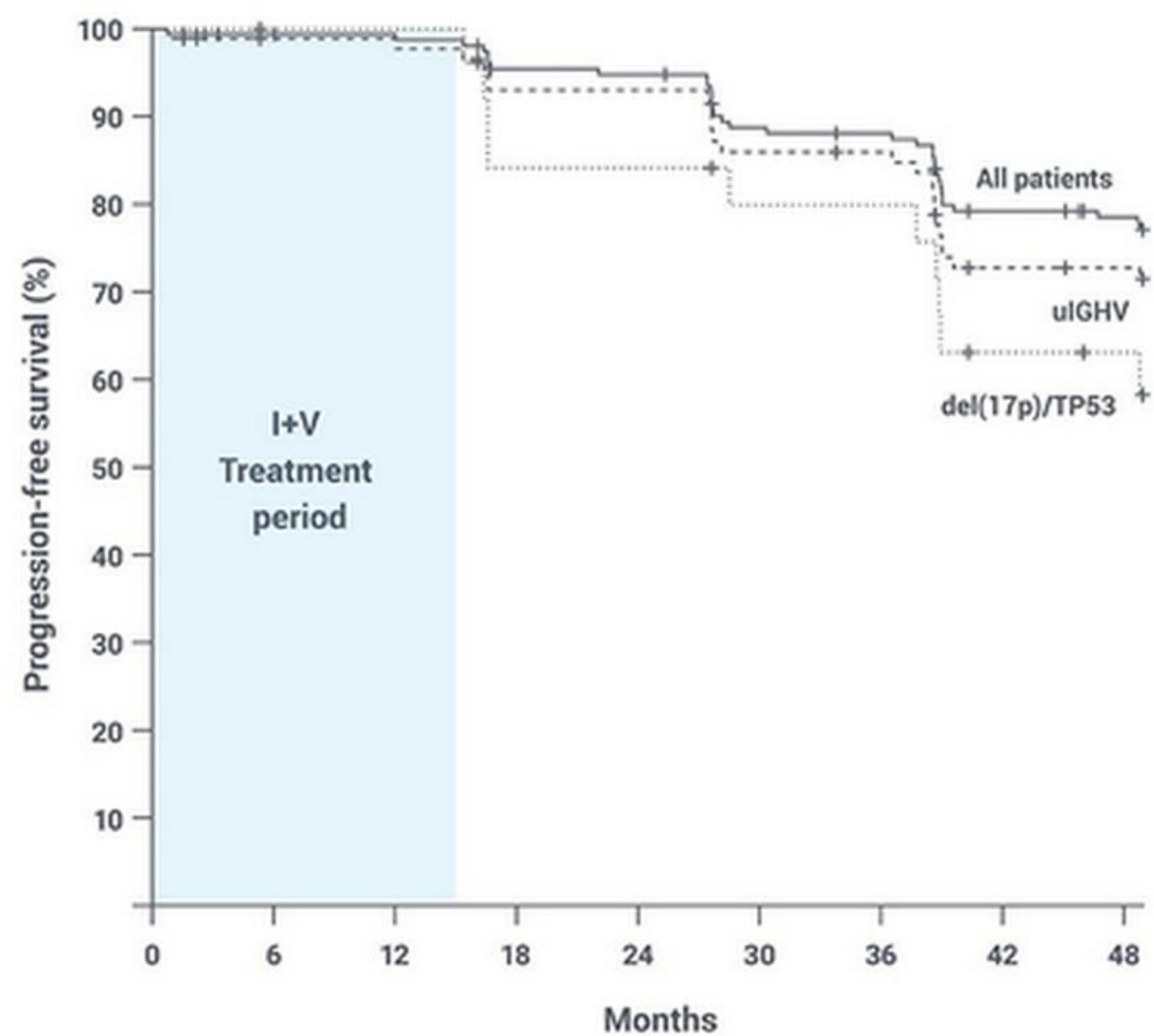
Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## Durable and high progression-free survival rates with IMBRUVICA® + venetoclax<sup>4</sup>



Patients at risk									
del(17p)/TP53 mutation	27	26	26	21	21	19	19	14	13
Unmutated IGHV	89	85	85	79	79	73	72	59	58
All treated patients	159	153	152	144	143	132	130	115	111

Adapted from Tedeschi A, et al. 2023

dMRD=detectable minimal residual disease; FD=fixed duration; I+V=IMBRUVICA® + venetoclax; IGHV=immunoglobulin heavy chain variable; PFS=progression-free survival; uIGHV=unmutated IGHV; uMRD=undetectable minimal residual disease.

### 4-year PFS rate<sup>4</sup>:



All treated patients  
N=159  
[95% CI: 71–84]



Unmutated IGHV  
n=89  
[95% CI: 62–81]



del(17p)/TP53 mutation  
n=27  
[95% CI: 41–79]

Landmark PFS rates at 48 months were:

90% in patients who had uMRD in peripheral blood 3 months posttreatment<sup>4</sup>

66% in those with dMRD in peripheral blood 3 months posttreatment<sup>4</sup>



Mode of Action

Efficacy

Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## GLOW phase III study design<sup>3</sup>



### Eligibility criteria

- Previously untreated CLL
- ≥65 years of age or <65 years
- with CIRS >6 or CrCl <70 mL/min
- No del(17p) or known TP53 mutation
- ECOG PS 0–2

N = 211

Randomised  
1:1

Stratified by IGHV  
mutational status and  
presence of del11q

Imbruvica 420 mg daily for 3-cycle lead-in  
followed by Imbruvica + venetoclax  
for 12 cycles  
(venetoclax ramp-up 20–400 mg over 5 weeks  
beginning C4)

chlorambucil  
0.5 mg/kg on D1 and  
D15 for 6 cycles  
+  
obinutuzumab  
1000 mg on D1-2, D8, D15  
of C1, and D1 of C2-6

Primary end point: PFS (IRC)

Key secondary end points: Undetectable MRD in BM, CR rate (IRC), ORR (IRC), OS; safety was also evaluated

MRD assessed in responders by NGS and 8-color flow cytometry (<1 CLL cell per 10,000 leukocytes; <0.01%)

BM: bone marrow; C: cycle; CIRS: Cumulative Illness Rating Scale score; CR: complete response. CrCl: creatinine clearance; D: day; ECOG PS: Eastern Cooperative Oncology Group performance status; IGHV: immunoglobulin heavy-chain variable; IRC: independent review committee; MRD: minimal residual disease; NGS: next generation sequencing; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.



Mode of  
Action

Efficacy

Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## CAPTIVATE phase II study design<sup>4</sup>



The CAPTIVATE FD cohort is an open-label, single-arm cohort evaluating FD treatment with IMBRUVICA® + venetoclax.

### **Patients (N=159)**

- Previously untreated CLL/SLL
- Active disease requiring treatment per iwCLL criteria
- Aged ≤70 years
- ECOG PS 0–2
- High-risk features including uIGHV and del(17p)/TP53

**IMBRUVICA® Lead-in**  
IMBRUVICA® 420mg  
once daily (3 cycles)



**IMBRUVICA® + venetoclax**  
IMBRUVICA® 420mg once daily +  
venetoclax 5-week ramp-up to 400mg  
once daily (12 cycles)

**Primary end point:** Rate of CR, including CRI, per investigator assessment in patients without del(17p).

– Supporting analyses were conducted in the all-treated population.

**Key secondary end points:** ORR, DOR, uMRD rates (<10<sup>-4</sup> by flow cytometry), PFS, OS, reduction in TLS risk category, and safety.

CR=complete response; CRI=complete response with incomplete recovery; DOR=duration of response; ECOG PS= Eastern Cooperative Oncology Group performance status; FD=fixed duration; IwCLL=International workshop on chronic lymphocytic leukemia; PFS=progression-free survival; OS=overall survival; ORR=overall response rates; TLS=tumour lysis syndrome; uIGHV=unmutated IGHV; uMRD=undetectable minimal residual disease.

1. Wierda G, et al. Fixed-duration ibrutinib + venetoclax for first-line treatment of chronic lymphocytic leukemia/small lymphocytic lymphoma: 3-year follow-up from the FD cohort of the phase 2 CAPTIVATE study. Oral abstract presented at ASCO 2022. #7519.



Mode of Action

Efficacy

Safety

Dosing

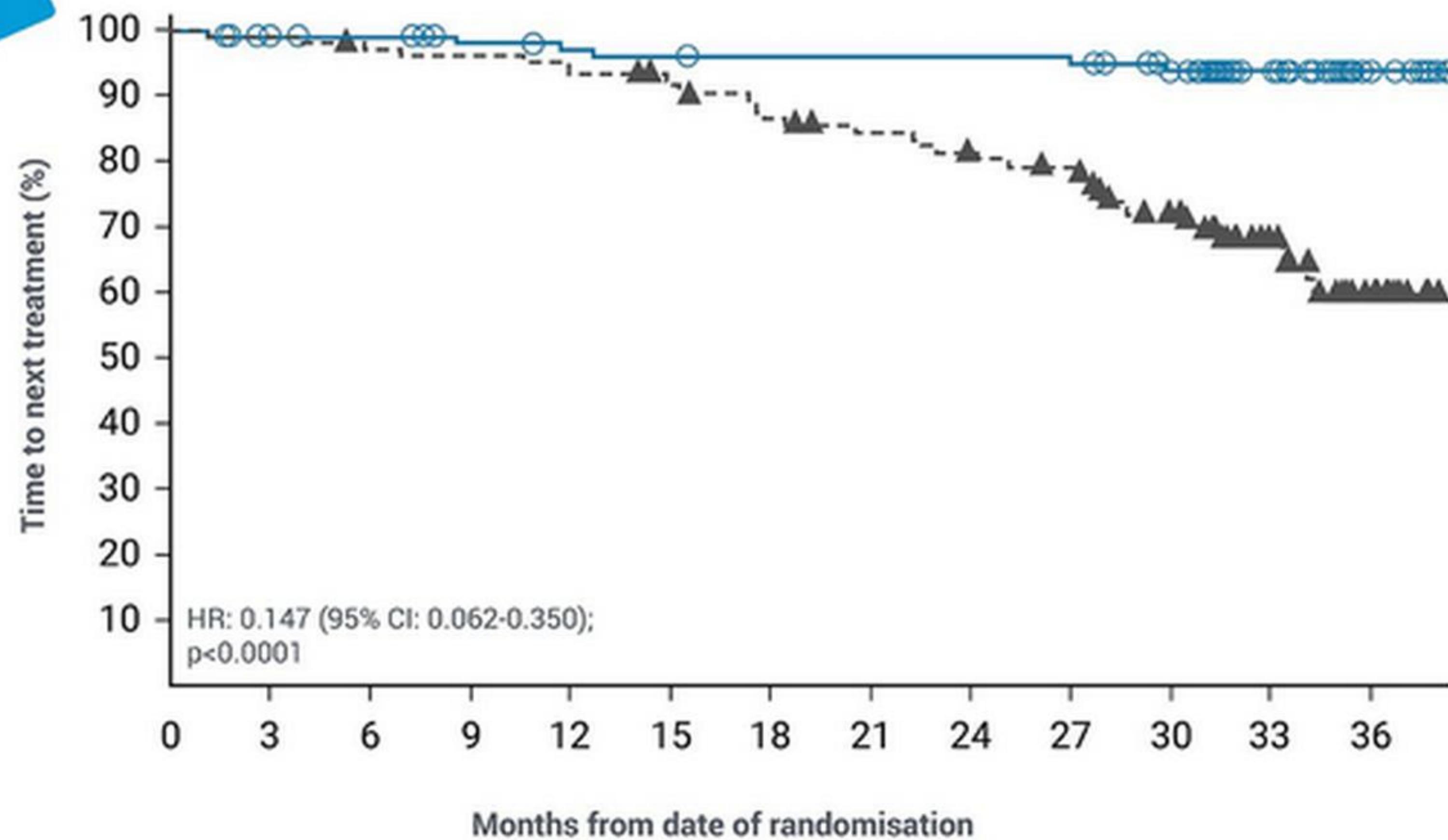
Summary

imbruvica® + venetoclax  
(ibrutinib)

## The strength to prolong time-to-next-treatment with IMBRUVICA® + venetoclax<sup>7\*</sup>



GLOW



No. at risk:													
IMBRUVICA® + venetoclax	106	100	99	95	93	92	91	91	91	90	84	54	12
Chlorambucil + obinutuzumab	105	104	101	100	97	94	87	83	79	76	63	38	12

Adapted by Munir T, et al. 2023

I + V\*\*



V + O

Clb+O=chlorambucil + obinutuzumab; HR= hazard ratio; CI= confidence interval.

\*vs Clb+O at median follow-up of 34.1 months.<sup>7</sup>

\*\*Indirect trial comparison of different studies



Mode of Action

Efficacy

Safety

Dosing

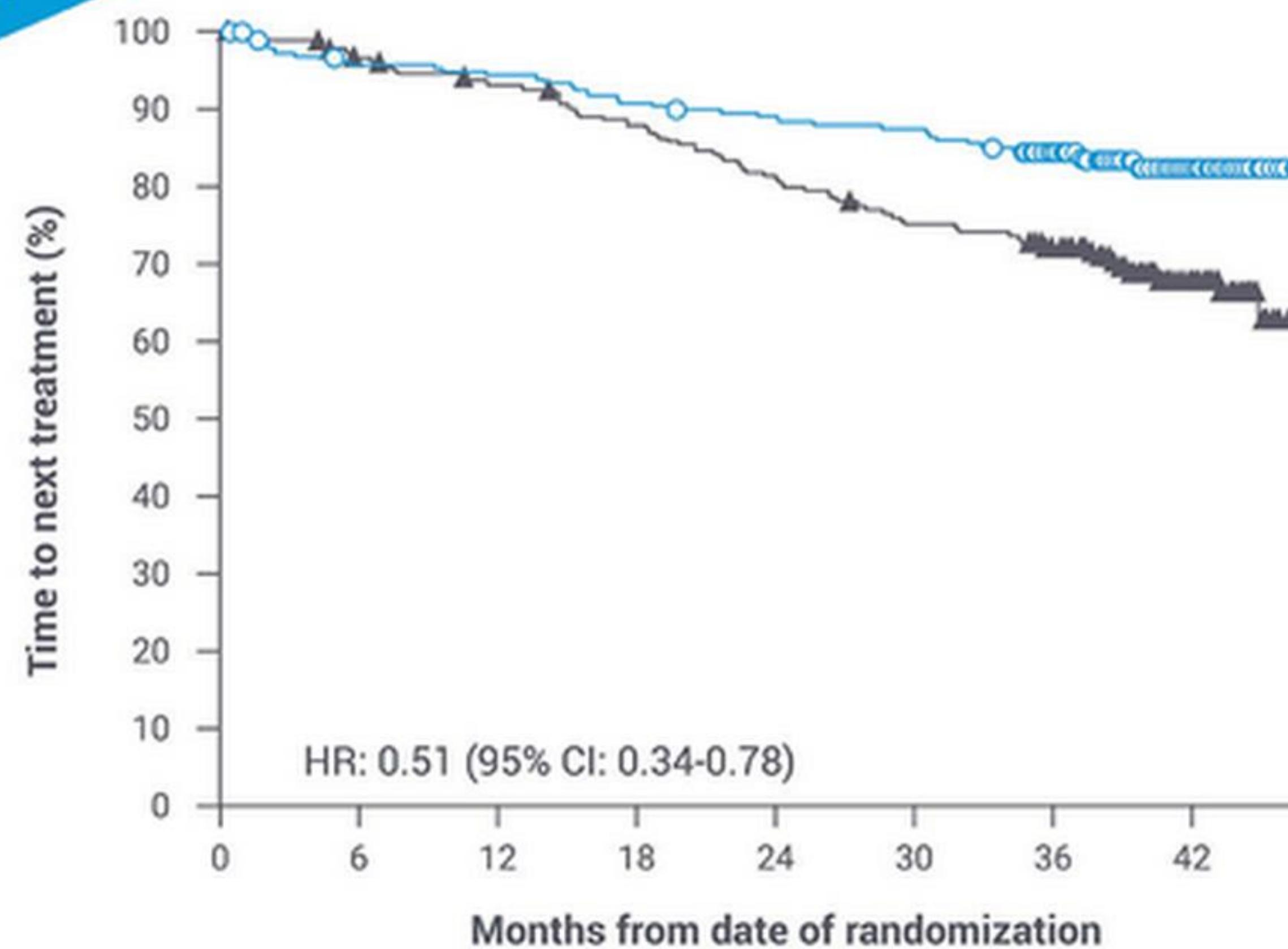
Summary

imbruvica® + venetoclax  
(ibrutinib)

## Time to next treatment of venetoclax + obinituzumab versus Clb+O<sup>6</sup>



CLL 14



Venetoclax +  
obinituzumab reduced  
the risk of needing  
second-line therapy by

49%

at a median follow-up of  
39,6 months<sup>6</sup>

Patients at risk	
V + O	216
Clb + O	216

Adapted from Al-Sawaf O, et al. 2020

I + V

V + O\*\*

V+O: venetoclax + obinituzumab; Clb+O: chlorambucil + obinituzumab; HR: hazard ratio; CI: confidence interval

\*\*Indirect trial comparison of different studies



Mode of  
Action

Efficacy

Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

## The strength to provide a favorable safety profile with IMBRUVICA® + venetoclax<sup>2,5</sup>

### Reduced risk of TLS

**94%**  
of patients with  
high tumor burden at  
baseline had a **reduced  
tumor burden** by tumor  
debulking with the 3  
cycles of lead-in with  
IMBRUVICA<sup>®5</sup>

### Favorable safety profile

No new safety signals  
with IMBRUVICA® +  
venetoclax<sup>2,5</sup>



GLOW



CAPTIVATE



Mode of  
Action

Efficacy

Safety

Dosing

Summary

imbruvica<sup>®</sup> + venetoclax  
(ibrutinib)

## The strength to provide a favorable safety profile<sup>2</sup>



### GLOW

Grade 3 or higher AEs in ≥5% of patients<sup>2</sup>

	IMBRUVICA® + venetoclax (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*	34.9	49.5
Infections*	17.0	11.5
Thrombocytopenia	5.7	20.0
Diarrhoea	10.4	1.0
Hypertension	7.5	1.9
Atrial fibrillation	6.6	0
Hyponatremia	5.7	0
TLS	0	5.7



of patients completed  
15 cycles of treatment<sup>2</sup>

Adopted from Kater AP. et al. 2022

AE=adverse events; Clb+O= chlorambucil+obinutuzumab; TLS=tumour lysis syndrome.

\*No new safety signals when comparing adverse events on IMBRUVICA® + venetoclax combination therapy versus either as monotherapy in CLL. \*Includes 'neutrophil count decreased'; grade ≥3 febrile neutropenia: 1.9% for I+V vs 2.9% for Clb+O.2 <sup>2</sup>Includes multiple preferred terms.<sup>2</sup>



Mode of  
Action

Efficacy

Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)

The strength to provide a favorable safety profile<sup>5</sup>



## CAPTIVATE

Adverse events from the primary analysis CAPTIVATE study, n(%) at 27.9 months median follow-up.<sup>5</sup>

All treated patients, N=159

Grade 3/4 AEs ( $\geq 5\%$ )	
Neutropenia	52 (33)
Hypertension	9 (6)
Neutrophil count decreased	8 (5)
AEs of clinical interest (any grade)	
Atrial fibrillation	7 (4)
Major haemorrhage <sup>†</sup>	3 (2)
Any serious AE	
	36 (23)
Fatal AEs	
	1 (1) <sup>‡</sup>

92%  
(147/159)

of patients completed  
15 cycles of treatment<sup>5</sup>

AE=adverse events.

\*No new safety signals when comparing adverse events on IMBRUVICA® + venetoclax combination therapy versus either as monotherapy in CLL.<sup>5</sup> <sup>†</sup>Major hemorrhage was identified using the Standardized MedDRA Query for Hemorrhage, excluding laboratory terms. <sup>‡</sup>Sudden death in 1 patient during IMBRUVICA® lead-in.<sup>5</sup>



Mode of Action

Efficacy

Safety

Dosing

Summary

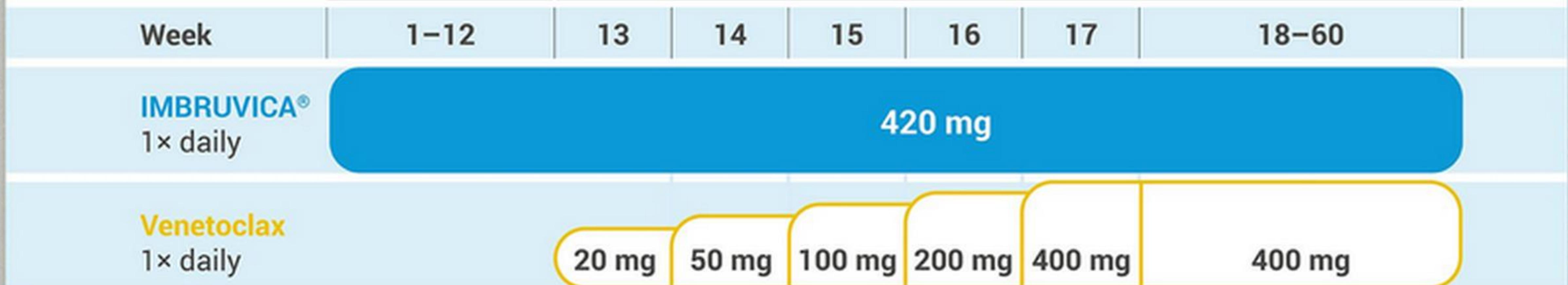
imbruvica® + venetoclax  
(ibrutinib)

# The strength to provide a convenient all-oral fixed-duration treatment in 1L CLL<sup>1,3,4</sup>



Induction  
therapy with  
IMBRUVICA®  
3 cycles of  
28 days

12 cycles of 28 days



Therapy with IMBRUVICA® + venetoclax is comprised of 15 cycles.

Please also take note of the dosage and administration instructions in the IMBRUVICA® and venetoclax summaries of product characteristics.<sup>1</sup>

1L: first line; CLL: chronic lymphocytic leukemia



Mode of  
Action

Efficacy

Safety

Dosing

Summary

imbruvica® + venetoclax  
(ibrutinib)



## References

1. Imbruvica, Sažetak opisa svojstava lijeka, rujan 2023
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**imbruvica®**  
(ibrutinib)

CLL

LIVING  
AHEAD  
OF THE  
CURVE

with

imbruvica®

imbruvica®  
+  
venetoclax

CLL=chronic lymphocytic leukaemia

SAMO ZA ZDRAVSTVENE RADNIKE

CP-413109

IMB-CRO-eDA-019-18/09/2023

Date of preparation: rujan 2023.

# LIVING AHEAD OF THE CURVE WITH IMBRUVICA® 1-5

Because life is the ultimate endpoint<sup>6</sup>



## UNPRECEDENTED EFFICACY

The only BTKi with the most established data and real-world experience, including high risk & uIGHV.<sup>1,7,8,11</sup>



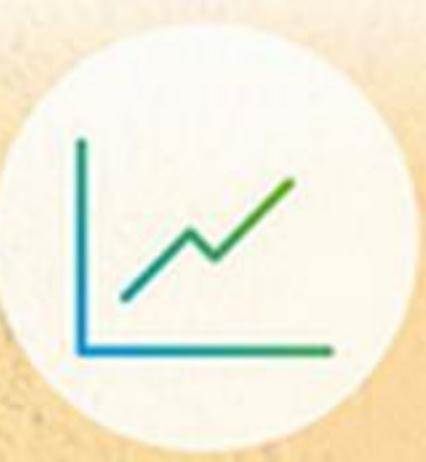
## EFFECTIVE FLEXIBILITY

The only BTKi with a simple and flexible dosing for active therapy management to maximize overall survival benefit.<sup>5,17</sup>

**Proven long-term survival with up to 8 years of clinical experience and with  
>250,000 patients treated worldwide<sup>7</sup>**

REF PI

**RESONATE 2  
PHASE III TRIAL<sup>1\*</sup>**



**IMBRUVICA**

**8 OUT OF 10 PATIENTS  
ALIVE AT 7 YEARS**



**MULTI-CENTER RETROSPECTIVE  
"REAL-WORLD" STUDY VS FCR<sup>§§</sup>**

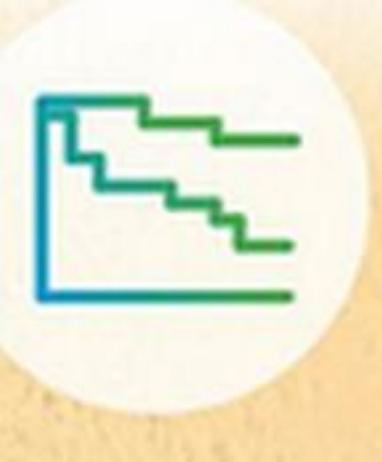


**IMBRUVICA**

**9 OUT OF 10 PATIENTS  
ALIVE AT 3 YEARS**



**ALLIANCE  
PHASE III TRIAL VS BR<sup>¶</sup>**



**IMBRUVICA**

**64%**

**reduction in risk of progression  
or death vs BR  
(HR: 0.36 [95% CI: 0.26-0.52])<sup>¶</sup>**



FCR: fludarabine, cyclophosphamide and rituximab, BR: bendamustine and rituximab, HR: hazard ratio, CI: confidence interval, OS: overall survival.

\* RESONATE-2 is a phase III open-label, multicentre, international, randomised study investigating the long-term efficacy and safety of IMBRUVICA® vs chlorambucil in patients with previously untreated CLL (N=269). Median OS was not reached for patients on IMBRUVICA® vs 89 months with chlorambucil (HR: 0.453 [95% CI: 0.276–0.743]).<sup>1</sup>

§ Multi-center retrospective "real-world" study to compare the efficacy of front-line ibrutinib monotherapy versus standard FCR in patients with CLL in 235 patients. OS was better with ibrutinib than with FCR, with a 3-year OS of 96.8% vs. 87.5%, respectively (HR=3.52, 95% CI [1.04-11.92], p=0.031).<sup>8</sup>



**Efficacy**

**High-risk  
patients**

**Real-world  
evidence**

**Life expectancy**

**Time to next  
treatment**

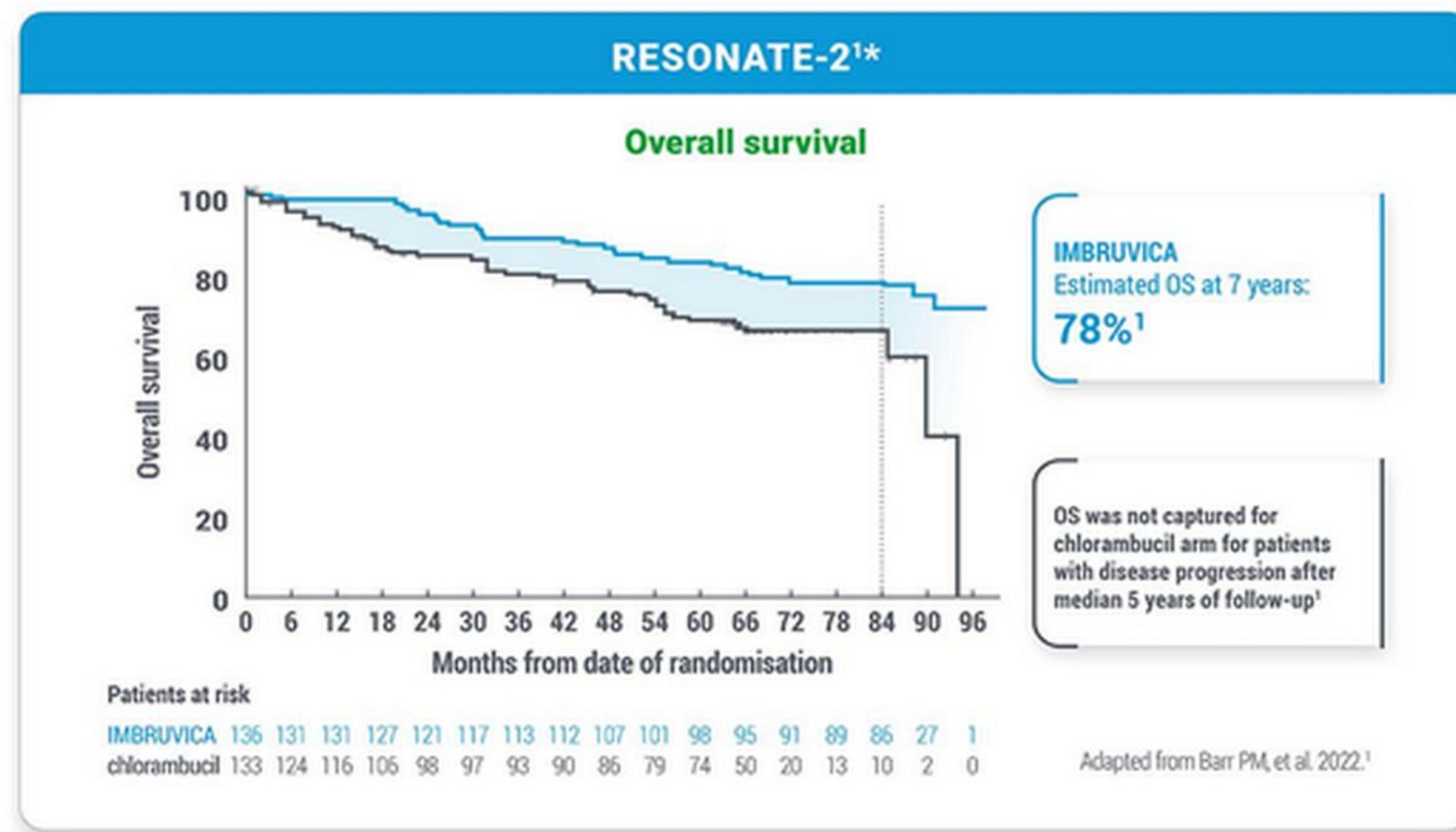
**Safety**

**Dosing**

**imbruvica<sup>®</sup>  
(ibrutinib)**



## IMBRUVICA® demonstrates OS benefits vs chlorambucil at 7 years<sup>1\*</sup>



Median OS was not reached for patients on IMBRUVICA® vs 89 months with chlorambucil (HR: 0.453 [95% CI: 0.276-0.743]).

CI=confidence interval; HR=hazard ratio; OS=overall survival.

\*RESONATE-2 is a Phase III open-label, multicentre, international, randomised study investigating the long-term efficacy and safety of IMBRUVICA® vs chlorambucil in patients with previously untreated CLL (N=269).



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

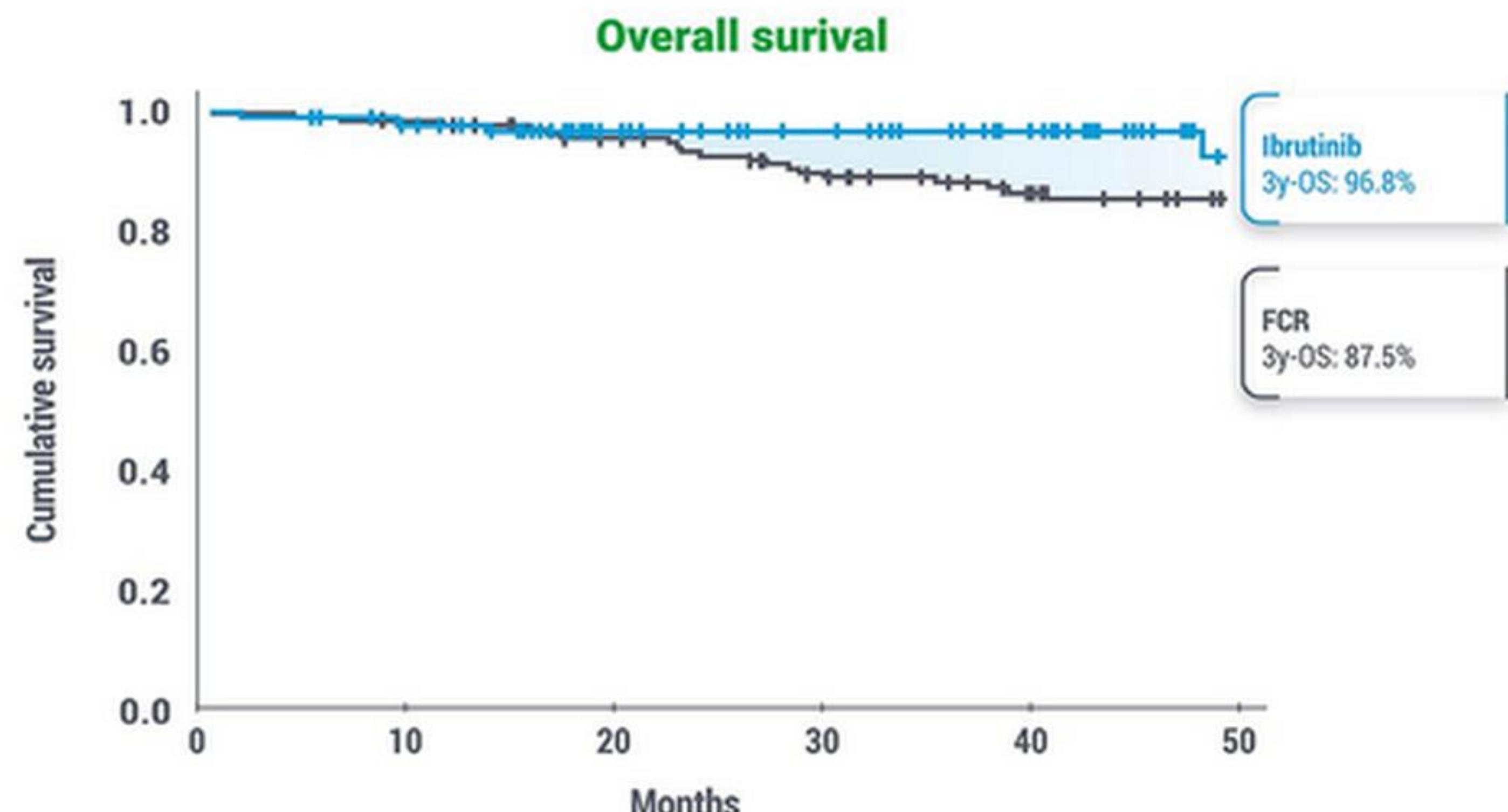
Dosing

imbruvica<sup>®</sup>  
(ibrutinib)



## IMBRUVICA® demonstrates OS superiority vs FCR<sup>8\*</sup>

### MULTICENTER "REAL-WORLD" STUDY OF FRONT-LINE IBRUTINIB VS FCR<sup>8\*</sup>



FCR=fludarabine; cyclophosphamide and rituximab; OS=overall survival.

\*ECOG-ACRIN 1912 is a Phase III trial comparing IMBRUVICA® and rituximab to FCR in patients with previously untreated CLL, (N=529). At 5 years, 95% of IMBRUVICA® + rituximab patients were estimated to be alive vs 89% with FCR (HR: 0.47 [95% CI: 0.25-0.89] p=0.018).<sup>8</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

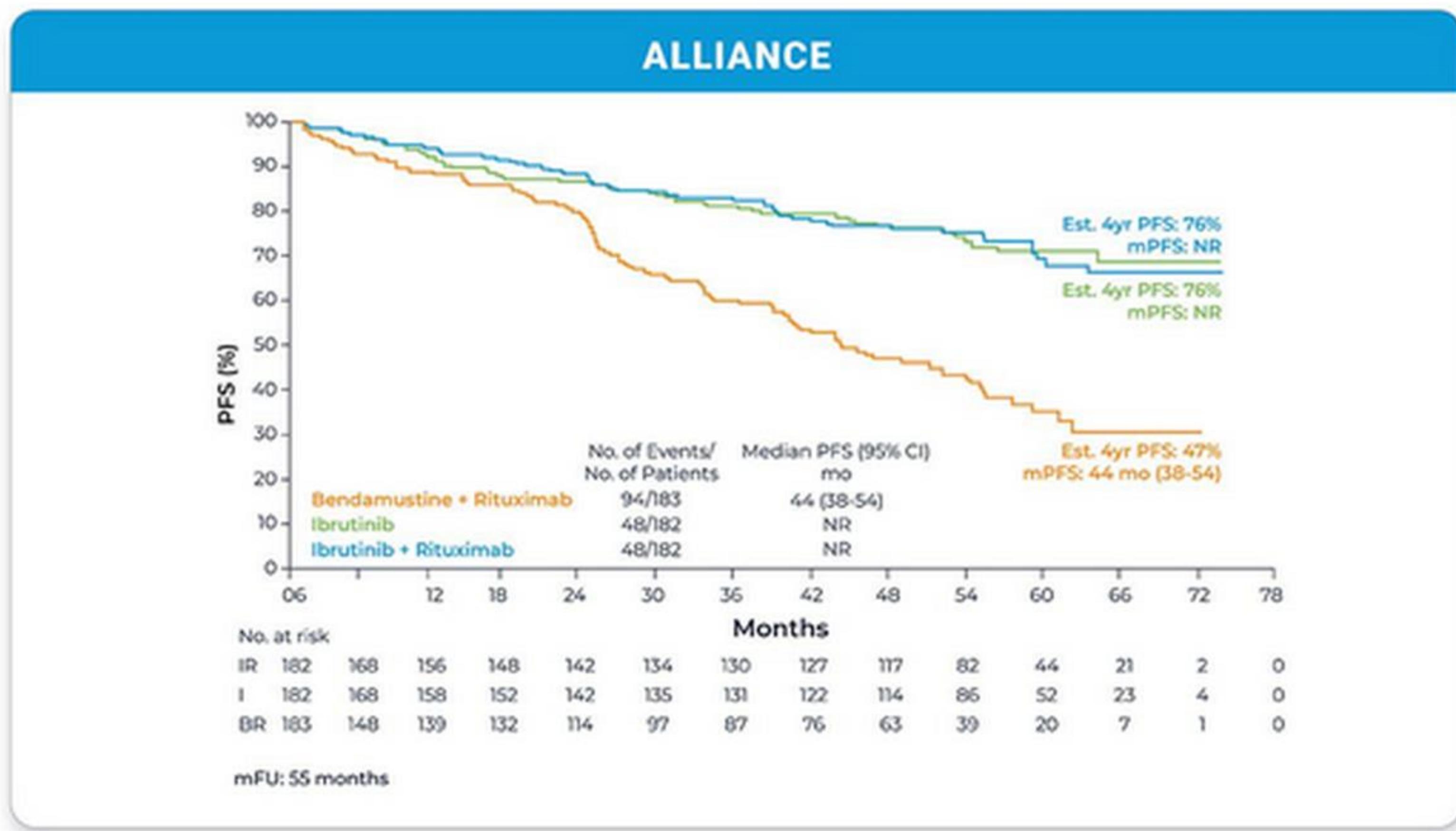
Safety

Dosing

imbruvica<sup>®</sup>  
(ibrutinib)



## IMBRUVICA® demonstrated superiority vs BR with a risk of reduction of disease progression of 64%<sup>9</sup>



There was no significant difference in PFS between the IR and ibrutinib arms HR 0.99 (95% CI, 0.66 - 1.48; p = 0.96)<sup>9</sup>

PFS was significantly longer with ibrutinib vs BR; HR 0.36 (95% CI, 0.26 - 0.52; p<0.0001)<sup>9</sup>

PFS was significantly longer with IR vs BR; HR = 0.36 (95% CI, 0.26 - 0.52; p<0.0001)<sup>9</sup>

Adapted from Woyach J.A. et al. 2022.  
BR: bendamustine and rituximab, IR: ibrutinib and rituximab, HR: hazard ratio, CI: confidence interval, mFU: median follow-up, PFS: progression-free, NR: not reached.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

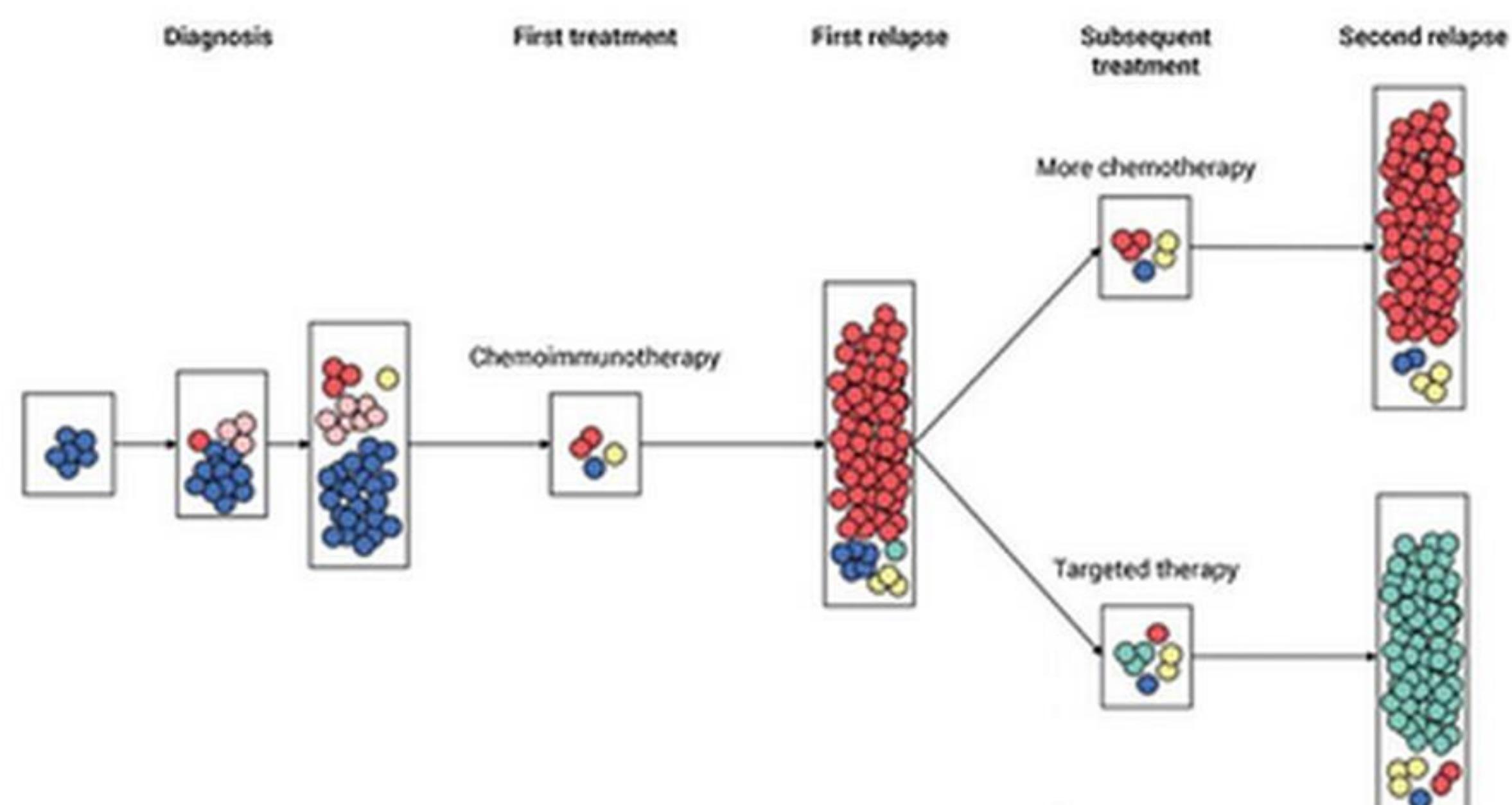
Dosing

imbruvica<sup>®</sup>  
(ibrutinib)



The use of CIT in 1L CLL can cause further DNA damage that may lead to high risk clones, reducing the effectiveness of subsequent therapies, such as IMBRUVICA®<sup>10</sup>

**AN EXAMPLE OF POSSIBLE CLONAL EVOLUTION SCENARIOS ACROSS THE COURSE OF DISEASE IN CHRONIC LYMPHOCYTIC LEUKEMIA<sup>10</sup>**



Genomic diversification of CLL occurs through sequential acquisition of gene mutations, represented by clones of different colors. Treatment may reduce or eliminate the incumbent clone, shifting the clonal architecture in favor of one or more aggressive subclones. Different therapies may preferentially provide selective advantages for different mutations. For example, the red circles are TP53-mutated clones, which have been selected for by chemotherapy, whereas the turquoise clones would have acquired resistance to the targeted therapy.<sup>10</sup>

Adapted from Campo E, et al. 2018.

1L: first line, CLL: chronic lymphocytic leukemia, CIT: chemoimmunotherapy



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica<sup>®</sup>  
(ibrutinib)

**IMBRUVICA® is the BTKi with the most established data across all high-risk patient subtypes (del(17p)/TP53 and uIGHV)<sup>1,4,11</sup>**

**Del(17p)/TP53 POPULATION<sup>11</sup>**

Del17p  
TP53

IMBRUVICA

8 OUT OF 10 PATIENTS  
ALIVE AND PROGRESSION FREE  
AT 4 YEARS<sup>11</sup>



POOLED ANALYSIS

**uIGHV POPULATION<sup>1,4</sup>**

uIGHV

IMBRUVICA

6 OUT OF 10 PATIENTS  
ALIVE AND PROGRESSION FREE  
AT 7 YEARS<sup>1</sup>



RESONATE-2



ECOG 1912

BTKi=Bruton's tyrosine kinase inhibitor; PFS=progression-free survival; uIGHV=unmutated immunoglobulin heavy chain variable.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

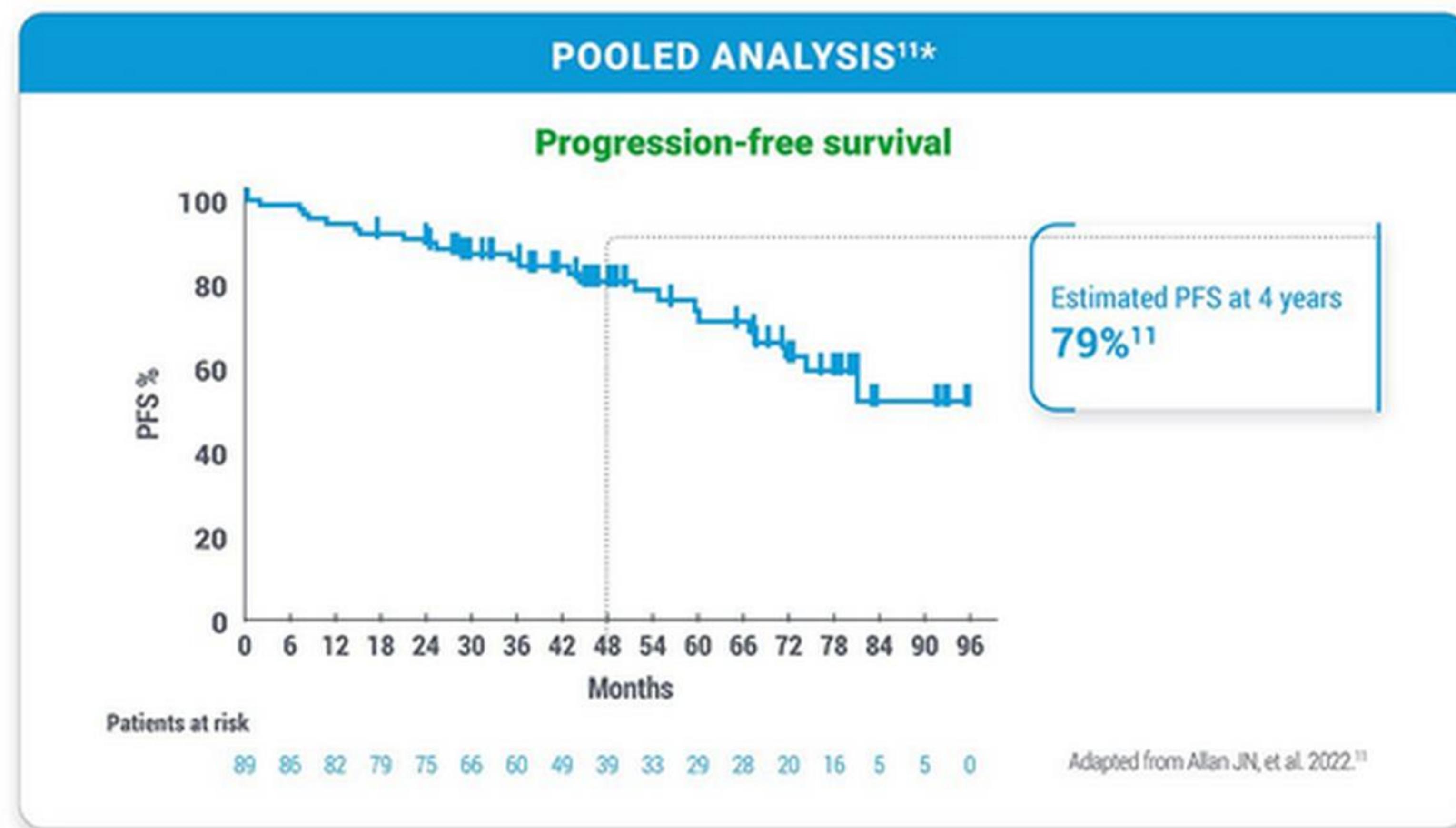
Safety

Dosing

**imbruvica**  
(ibrutinib)



## Sustained PFS demonstrated in IMBRUVICA®-treated patients with del(17p)/TP53 mutation<sup>11\*</sup>



PFS=progression-free survival.

\*Pooled across 4 clinical trials in CLL/SLL: PCYC-1122e, PCYC-1130, ECOG-ACRIN 1912 and RESONATE-2 (N=89). The estimated 4-year PFS rate was 79% [95% CI: 68–87]. Of 89 patients, 47 (53%) had del(17p); of the 58 patients with TP53 sequencing results available, 53 (91%) had a TP53 mutation.<sup>11</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

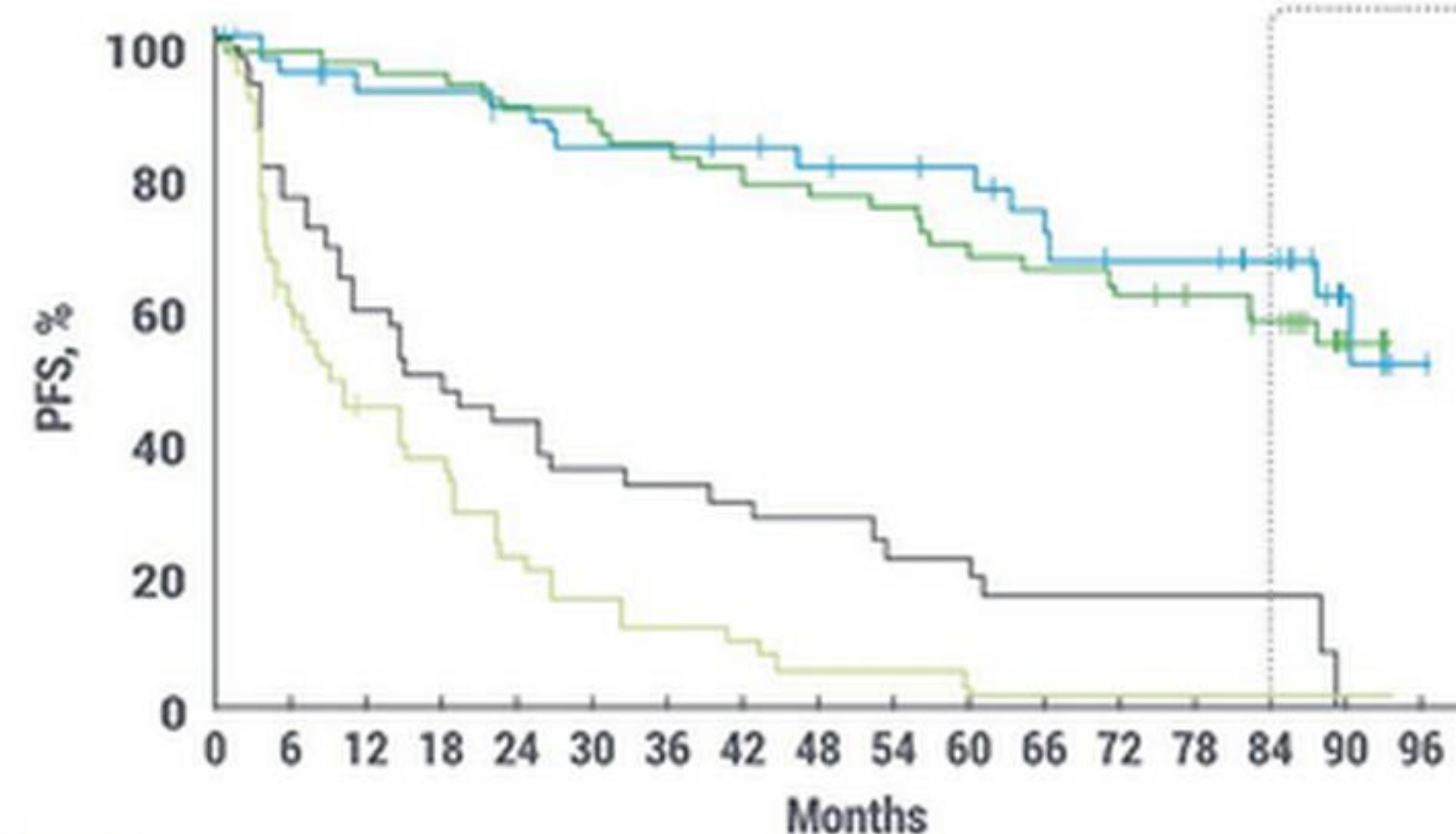
imbruvica<sup>®</sup>  
(ibrutinib)



## IMBRUVICA® is superior to chemo-immuno therapy regimens in CLL high risk patients with uIGHV<sup>1\*</sup>

### RESONATE-2<sup>1\*</sup>

#### Progression-free survival



IMBRUVICA®, mutated IGHV  
PFS at 7 years  
**68%<sup>1</sup>**

IMBRUVICA®, unmutated IGHV  
PFS at 7 years  
**58%<sup>1</sup>**

Chlorambucil, mutated IGHV  
PFS at 7 years  
**17%<sup>1</sup>**

Chlorambucil, unmutated IGHV  
PFS at 7 years  
**2%<sup>1</sup>**

Adapted from Barr PM, et al. 2022.<sup>1</sup>

#### Patients at risk

IMBRUVICA®, mutated IGHV	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
IMBRUVICA®, unmutated IGHV	58	57	56	53	49	48	46	43	42	41	36	35	32	30	27	10	0
Chlorambucil, mutated IGHV	42	32	25	21	18	15	14	12	11	8	8	5	4	4	3	0	0
Chlorambucil, unmutated IGHV	60	33	23	19	11	8	6	5	3	3	2	1	1	1	1	1	0

PFS=progression-free survival; uIGHV=unmutated immunoglobulin heavy chain variable.

\*RESONATE-2 is a Phase III open-label, multicentre, international, randomised study investigating the long-term efficacy and safety of IMBRUVICA® vs chlorambucil in patients with previously untreated CLL (N=269). At 7 years, PFS rates for IMBRUVICA® (n=58) and chlorambucil (n=60) for patients with uIGHV were 58% and 2% (HR: 0.112 [95% CI: 0.065–0.192]).<sup>1</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

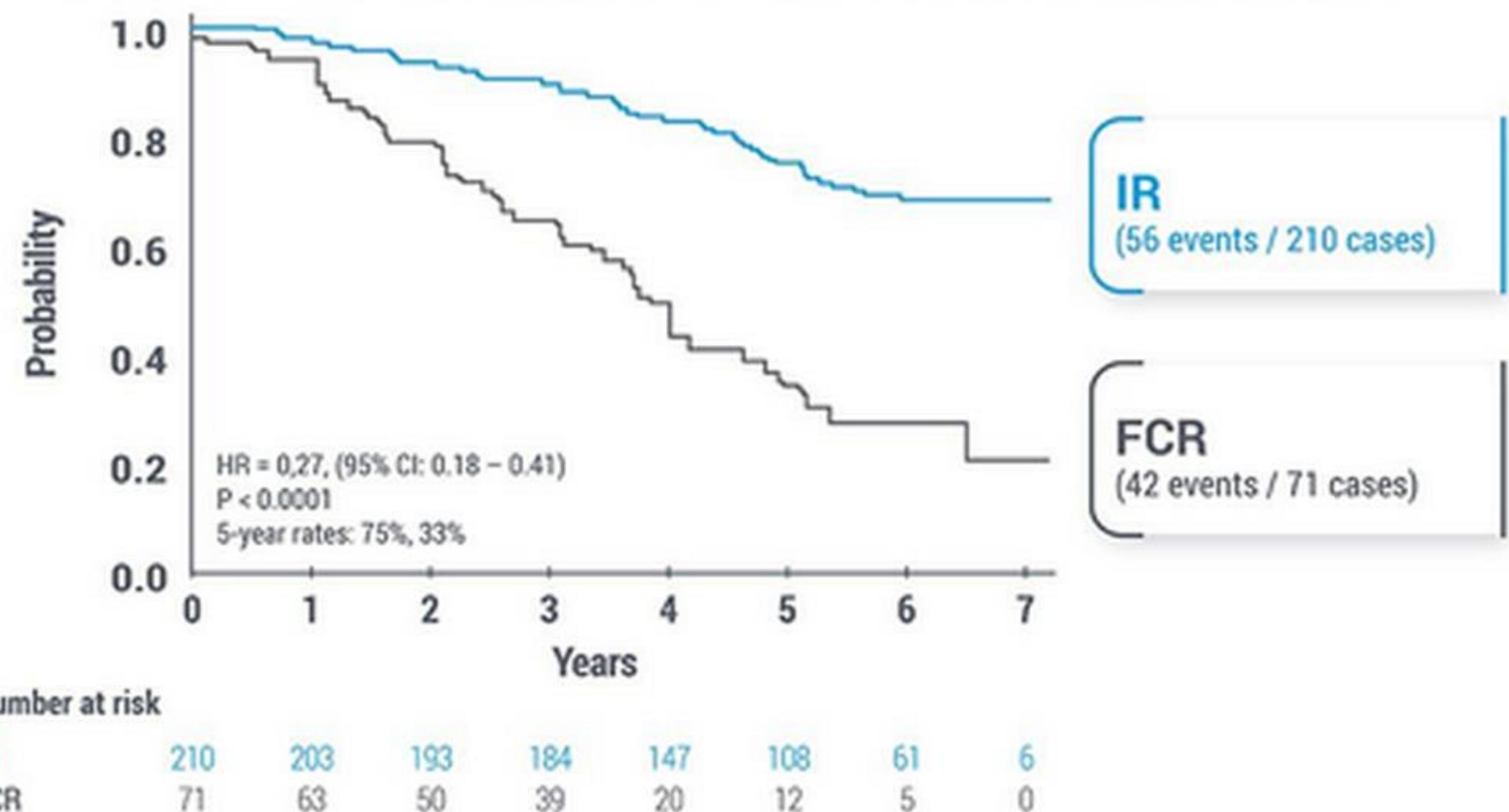
imbruvica<sup>®</sup>  
(ibrutinib)

## Sustained PFS achieved with IMBRUVICA® in patients with uIGHV CLL<sup>4\*</sup>



ECOG 1912 - IMBRUVICA VS FCR<sup>4\*</sup>

### Progression free survival among unmutated IGHV patients



Adapted from Shanafelt TD, et al, 2022<sup>4</sup>

PFS=progression-free survival; IGHV=immunoglobulin heavy chain variable; HR=hazard ratio; CI=confidence interval.

\*ECOG-ACRIN 1912 is a Phase III trial comparing IMBRUVICA® and rituximab to FCR in patients with previously untreated CLL (N=529).<sup>2</sup> At 5 years, PFS rates for IMBRUVICA® (n=210) and FCR (n=71) for patients with unmutated IGHV were 75% and 33% (HR: 0.27 [95% CI:0.18-0.41]).<sup>2</sup> At 5 years, PFS rates for IMBRUVICA® (n=70) and FCR (n=44) for patients with mutated IGHV were 83% and 68% (HR: 0.27 [95% CI:0.11-0.62]).<sup>2</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica<sup>®</sup>  
(ibrutinib)

## IMBRUVICA® has extensive real-world experience<sup>8, 12-16</sup>

### IBRORS<sup>12</sup>



Elderly, high risk



### FIRE<sup>13</sup>



1L and R/R



### BiRD<sup>14</sup>



1L and R/R



### EVIDENCE<sup>15</sup>



1L and 2L



### Multicenter RWE<sup>8</sup>



1L



### REALITY<sup>16</sup>



1L, 2L and 3L



BTKi=Bruton's tyrosine kinase inhibitor; PFS=progression-free survival; uIGHV=unmutated immunoglobulin heavy chain variable.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

**imbruvica**  
(ibrutinib)

## IBRORS



**IMBRUVICA® monotherapy is effective and well tolerated, regardless of age and high-risk genetic features, in line with data from clinical trials.<sup>12</sup>**



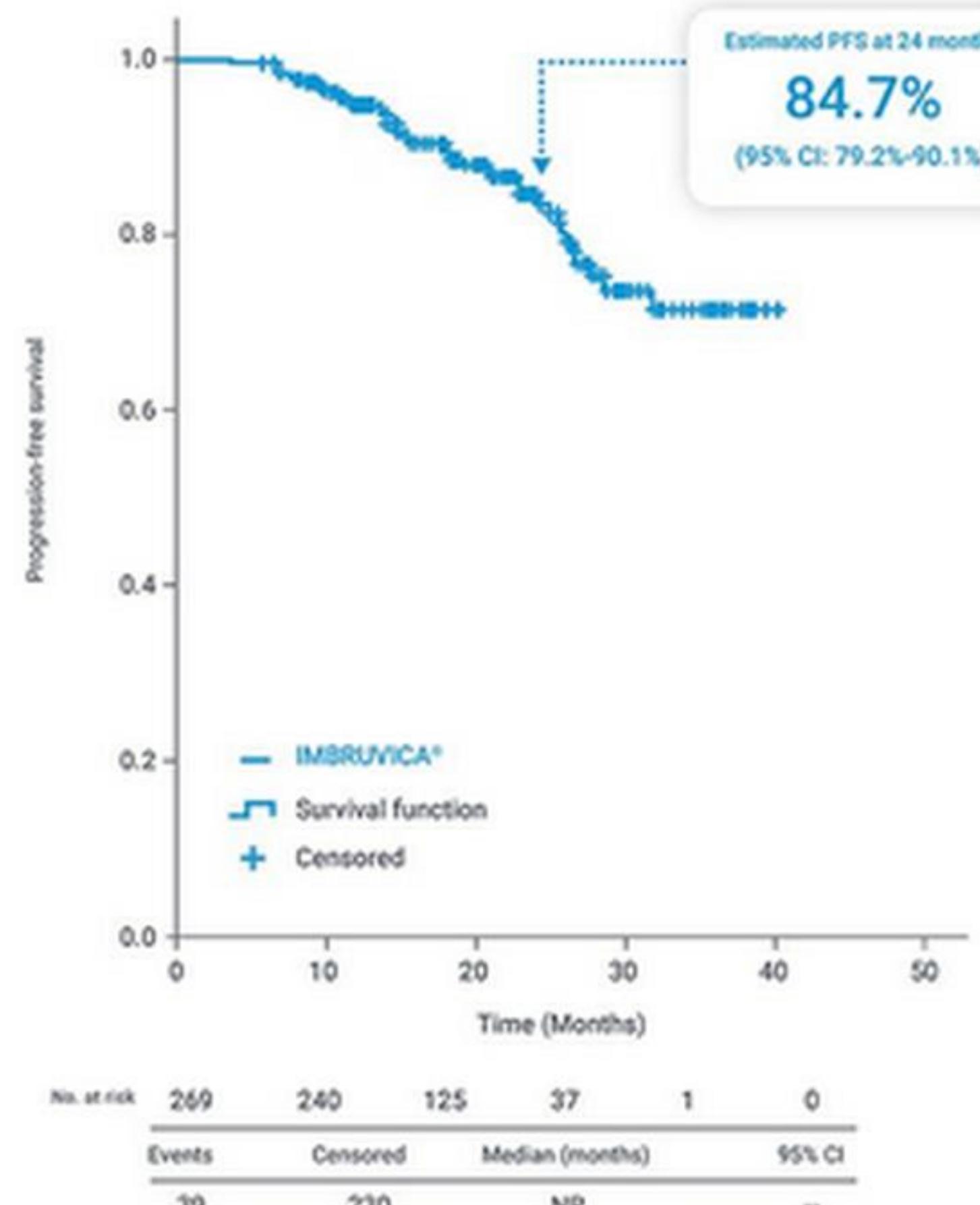
Multicentre, retrospective, observational study exploring outcomes in patients in Spain treated with IMBRUVICA® in early lines of CLL therapy.<sup>12</sup>

The study aimed to discover the molecular characteristics of this population in real-world practice, in addition to measuring response, overall survival and tolerability in an elderly cohort. It included patients with **high-risk genetic features and significant baseline comorbidities.**<sup>12</sup>

In patients receiving single-agent IMBRUVICA® in the 1L (n=84) and 2L (n=121) settings:

- 6% and 12.7% had complex karyotype, respectively
- 88.1% and 66.1% had high risk features, respectively<sup>12</sup>

### IBRORS – ELDERLY, HIGH-RISK<sup>12</sup>



Adapted from Costa PA, et al. 2020.<sup>12</sup>

CI=confidence interval, NR=not reached, PFS=progression-free survival.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica<sup>®</sup>  
(ibrutinib)

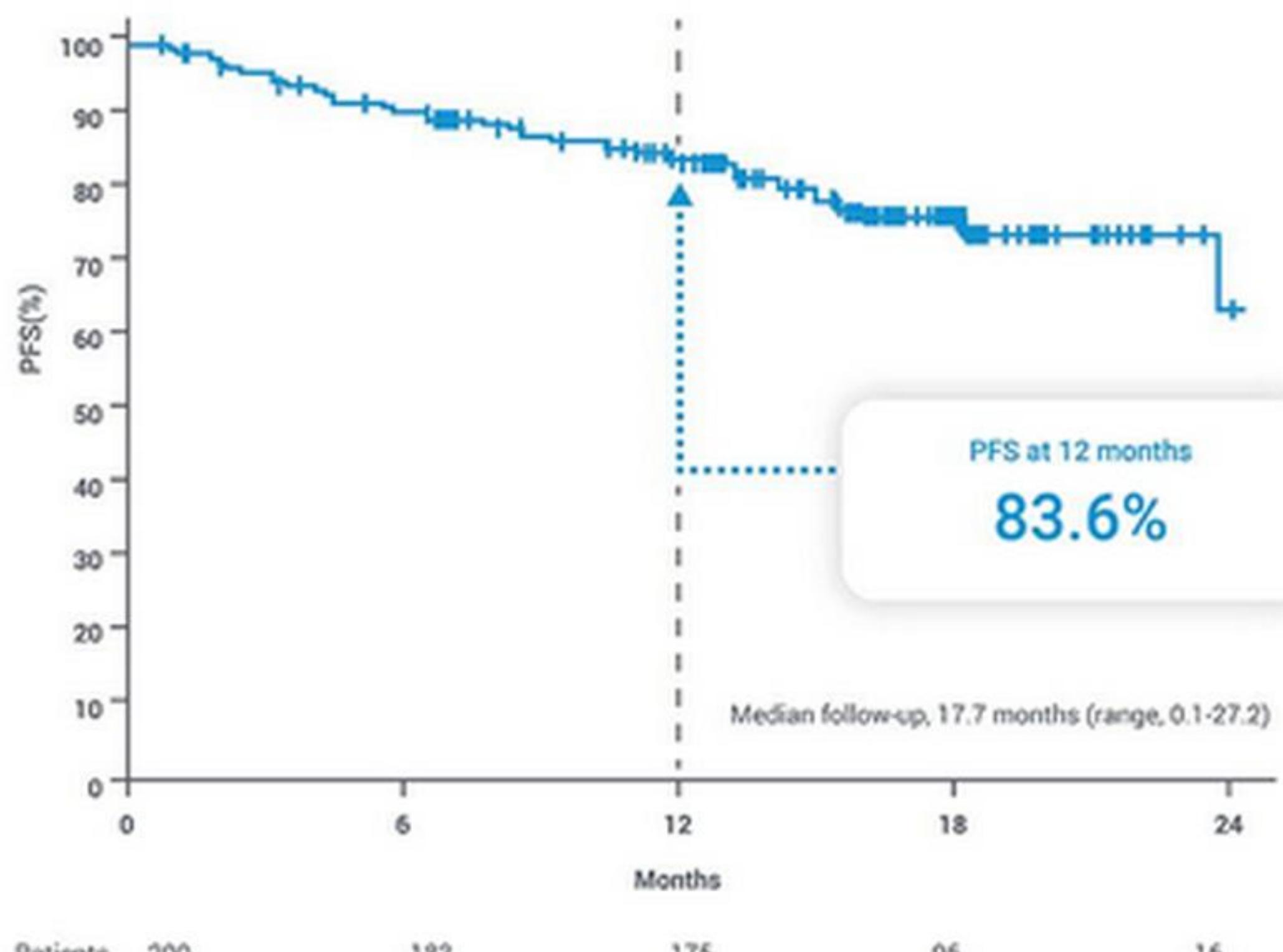
## FIRE



IMBRUVICA® treatment in this large real-world analysis was effective in patients who were mostly R/R with high-risk features.<sup>13</sup>



A retrospective and prospective, noninterventional, multicentre study investigating real-world effectiveness and safety of IMBRUVICA® in patients with previously untreated (n=35) and R/R CLL/SLL (n=165) in France, including those with high-risk features.<sup>13</sup>

FIRE – 1L AND R/R<sup>13</sup>

Adapted from Dartigues C, et al. 2022.

CLL=chronic lymphocytic leukaemia; MCL=mantle cell lymphoma; PFS=progression-free survival;  
R/R=relapsed/refractory; SLL=small lymphocytic leukaemia.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

## BiRD



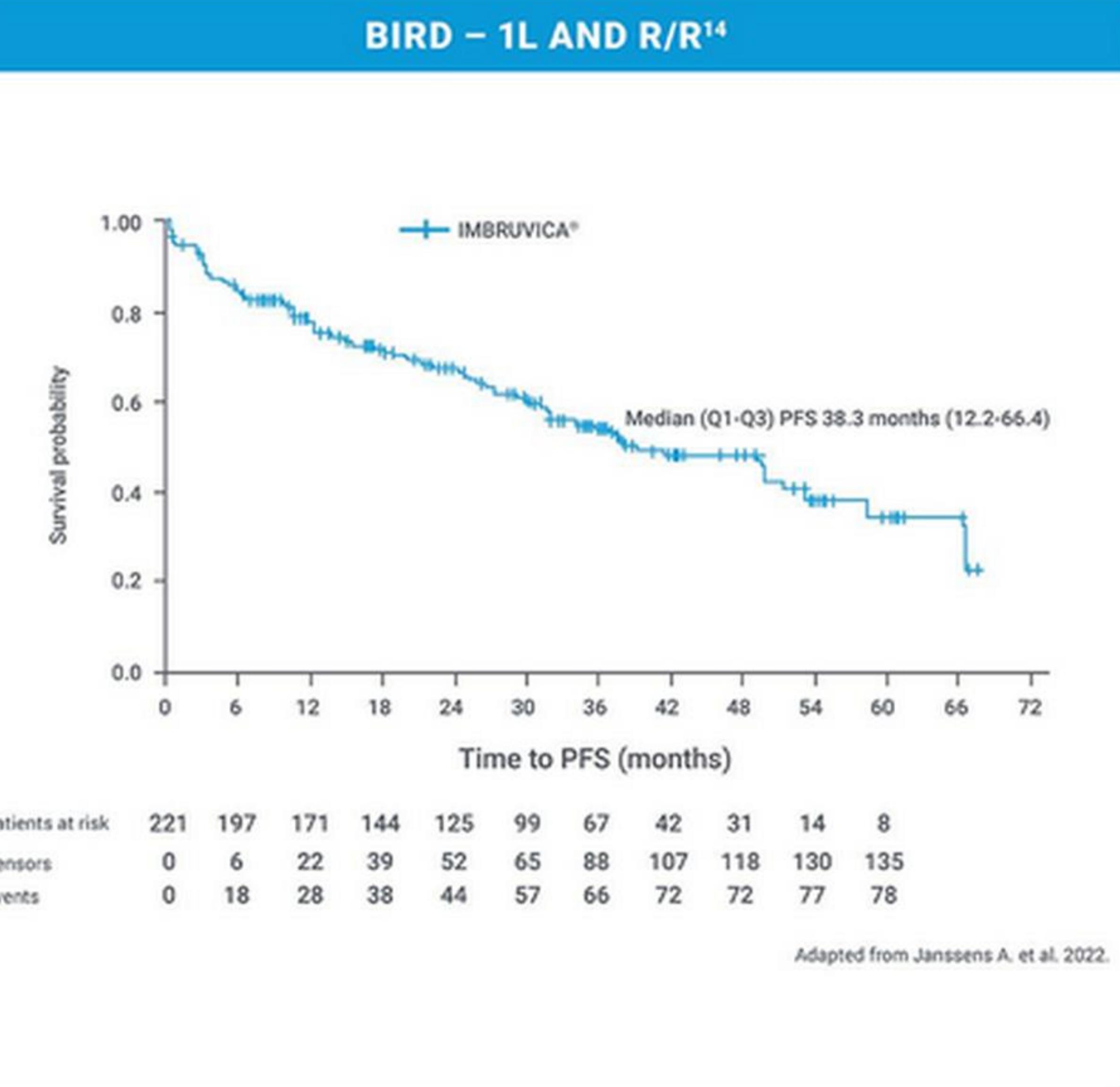
Interim analysis showed IMBRUVICA® to be effective and tolerable, with no new safety signals.<sup>14</sup>



Multicentre, observational study exploring effectiveness and safety of IMBRUVICA® in patients in Belgium with CLL (1L n=60; R/R n=159).<sup>14</sup>

The study included patients either prospectively or retrospectively<sup>14</sup>

With up to 70 months of follow-up, TEAEs were similar to those reported in other real-world studies and single-agent controlled trials, with low rates of discontinuation (11.5%).<sup>14</sup>



1L=first line; CLL=chronic lymphocytic leukaemia; R/R=relapsed/refractory.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

## EVIDENCE



In this real-world study, patients who received IMBRUVICA® as 1L therapy reported the highest 2-year retention rate.<sup>15</sup>



Treatment retention with IMBRUVICA® in an older CLL cohort with CV comorbidities.<sup>15\*</sup>

Multicentre, prospective, non-interventional Italian study in IMBRUVICA® as 1st, 2nd and later lines of treatment for CLL over a 2-year period.<sup>15</sup>

EVIDENCE – 1L AND 2L<sup>15</sup>

1<sup>st</sup> line  
(n=118)

2<sup>nd</sup> line  
(n=127)

PFS AT  
2 YEARS

**85.6%**      **77.9%**

RETENTION RATE  
AT 2 YEARS

**75.4%**      **70%**

PFS and retention rate was highest in the 1L cohort

CLL=chronic lymphocytic leukaemia.

\* At baseline, 63.1% of patients had comorbidities; CV disorder in 33.3%, 46% were on antihypertensive medication and 17.5% were on anticoagulation and/or antiplatelet agents.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

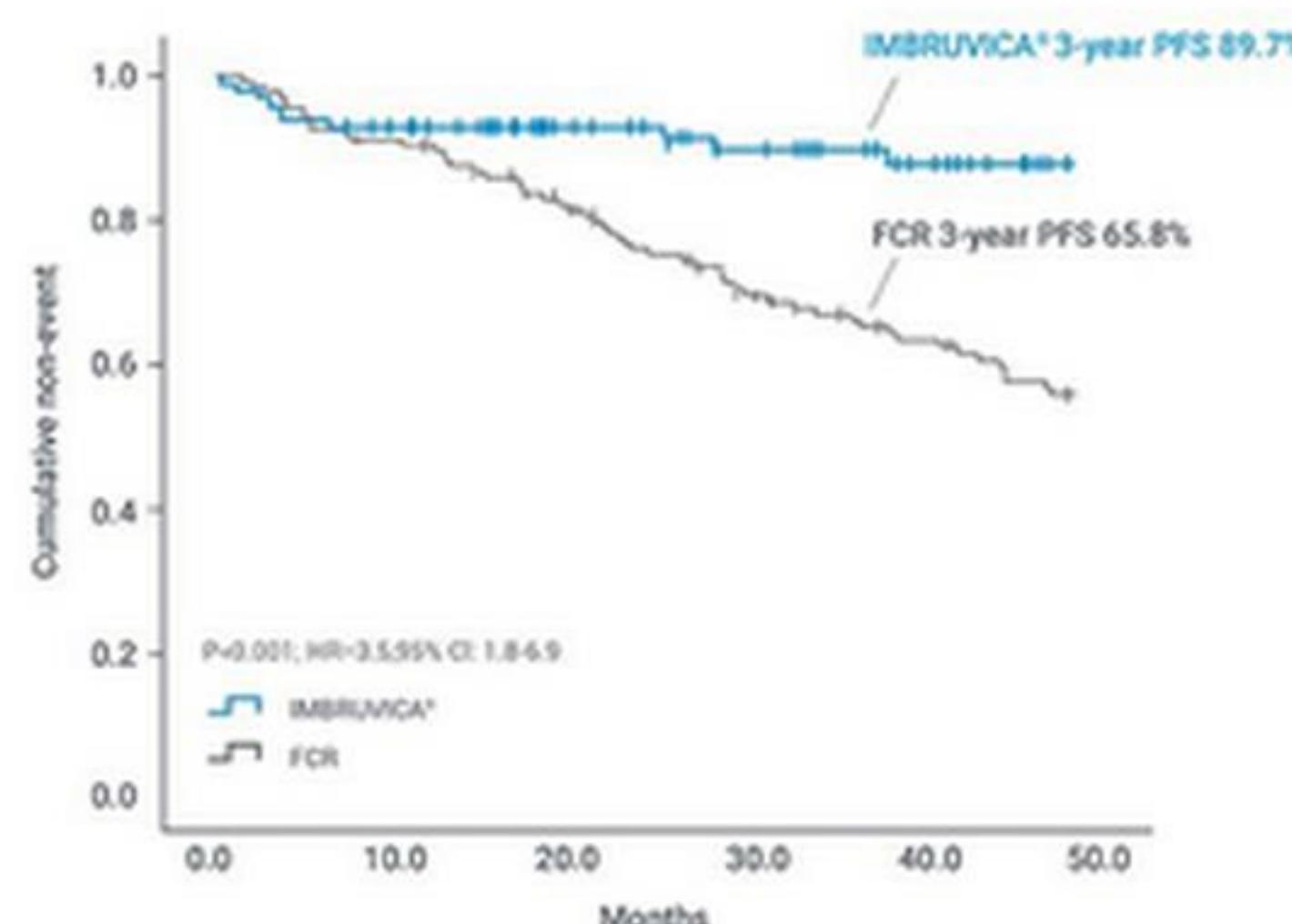
## RWE from Italy &amp; Israel



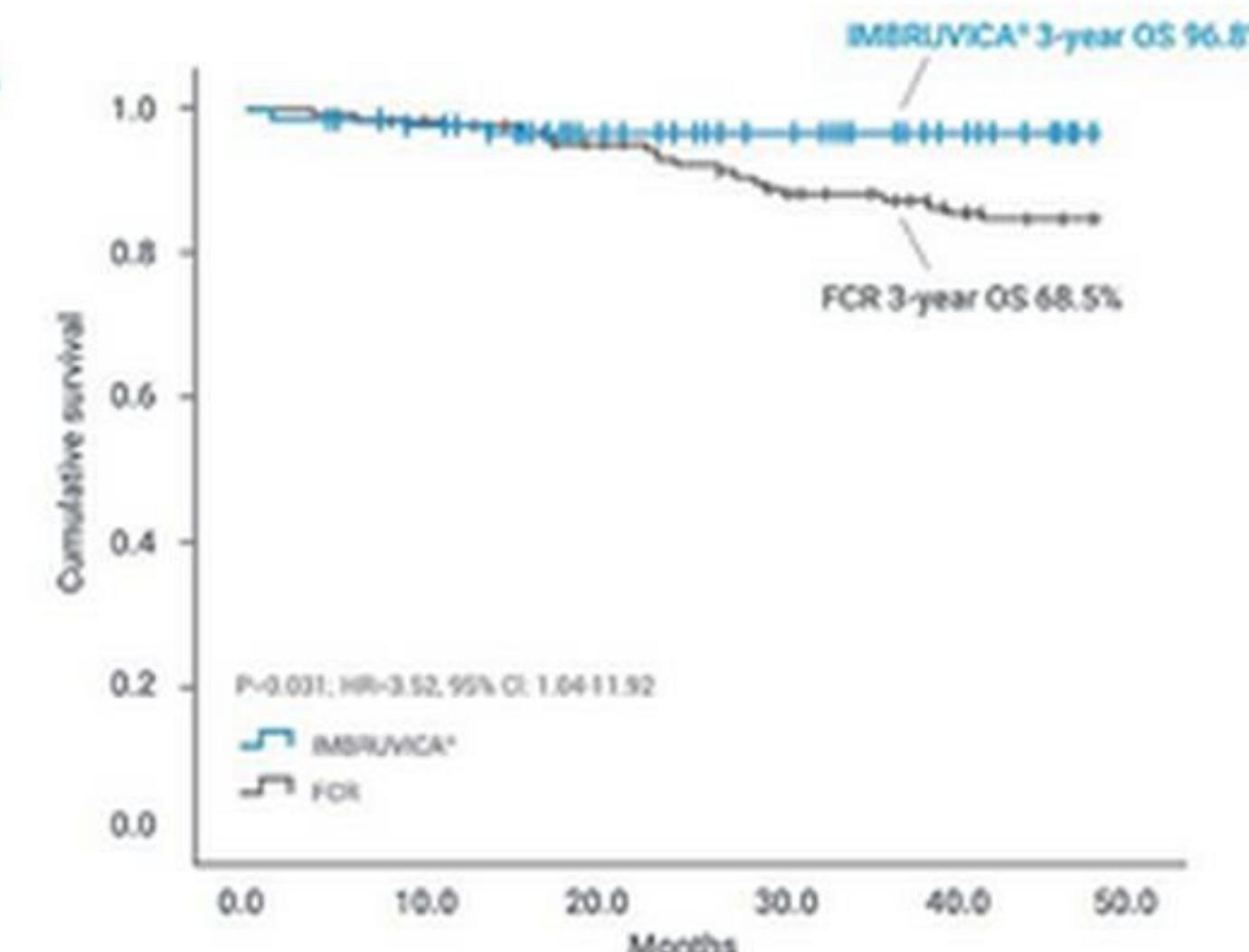
Among a total of 235 patients, PFS and OS were superior with IMBRUVICA® compared to FCR, with PFS benefits in patients with unmutated IGHV<sup>8</sup>



Multicentre, retrospective, real-world study comparing the efficacy of first-line IMBRUVICA® vs FCR in cohorts obtained from the Italian Campus CLL network and the Israeli CLL study group.<sup>8</sup>

MULTICENTER RWE – 1L<sup>8</sup>PFS by treatment protocol<sup>8</sup>

Adapted from Herishanu Y, et al. 2022.

OS by treatment protocol<sup>8</sup>

Adapted from Herishanu Y, et al. 2022.

CLL=chronic lymphocytic leukaemia, RWE= real world evidence.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

## REALITY

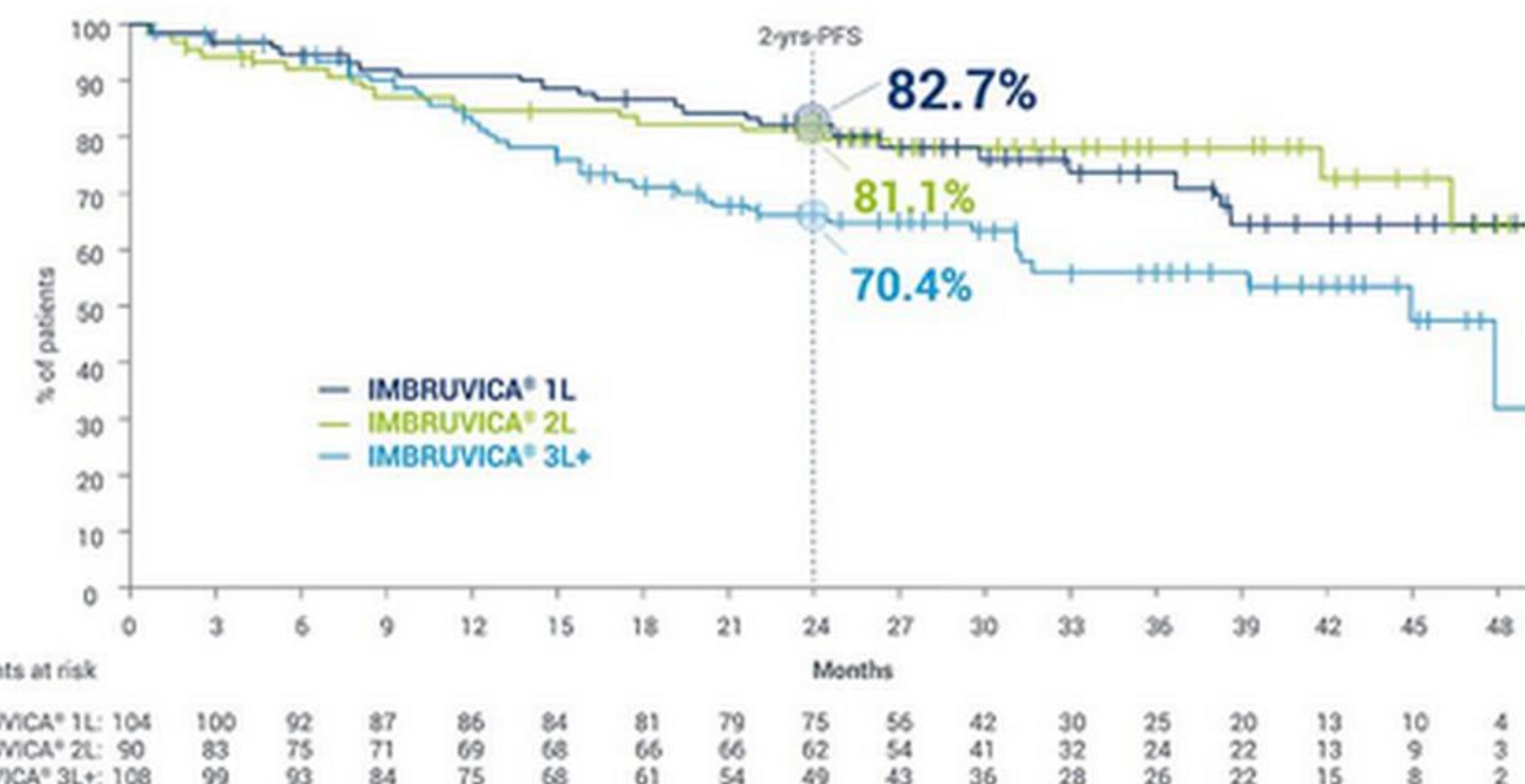


**IMBRUVICA® is proven to be a highly effective treatment option for CLL, especially in the first line<sup>16</sup>**



Multicentre, prospective, non-interventional, real-world study evaluating the efficacy and safety of single agent IMBRUVICA® as 1st (n=104), 2nd (n=90), or 3rd line (n=108) CLL treatment in routine clinical practice in Germany.<sup>16</sup>

8 out of 10 CLL 1L patients were progression free at 2 years follow-up.<sup>16</sup>

REALITY - 1L, 2L AND 3L<sup>16</sup>

Adapted from Welslau M, et al. 2022.

1L=first line; CLL=chronic lymphocytic leukaemia; FU=follow-up; OS=overall survival; PFS=progression-free survival; RWE=real-world evidence.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

**IMBRUVICA® can provide 1L CLL patients the chance of a standardised life expectancy<sup>17\*</sup>**

REF PI

Pooled analysis of RESONATE-2,  
ECOG1912 and iLLUMINATE: ASH 2022

Previously untreated patients with CLL had an overall survival estimate similar to that of an age-matched general population<sup>17\*</sup>

OVERALL SURVIVAL AT 12 YEARS

IMBRUVICA®

82%



(95% CI, 76-87)

AGE-MATCHED GENERAL POPULATION\*

80%



(95% CI, 76-83)

VS.



**IMBRUVICA® improves OS vs CIT >**

**AE management >**

1L=first-line; AE=adverse event; ASH=American Society of Hematology; CI=confidence interval; CIT=chemoimmunotherapy; CLL=chronic lymphocytic leukaemia; OS=overall survival.

\*OS data for IMBRUVICA-treated patients with previously untreated CLL/SLL were pooled (n=603) from the RESONATE-2, E1912, and iLLUMINATE clinical studies (which evaluated IMBRUVICA® alone (n=136)<sup>1</sup> or in combination with 6 cycles rituximab (n=354)<sup>4</sup> or with 6 cycles obinutuzumab (n=113)<sup>17</sup>, and compared with OS from an age-matched US general population (OS estimated from the CDC life table for total US population in 2019).<sup>17</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

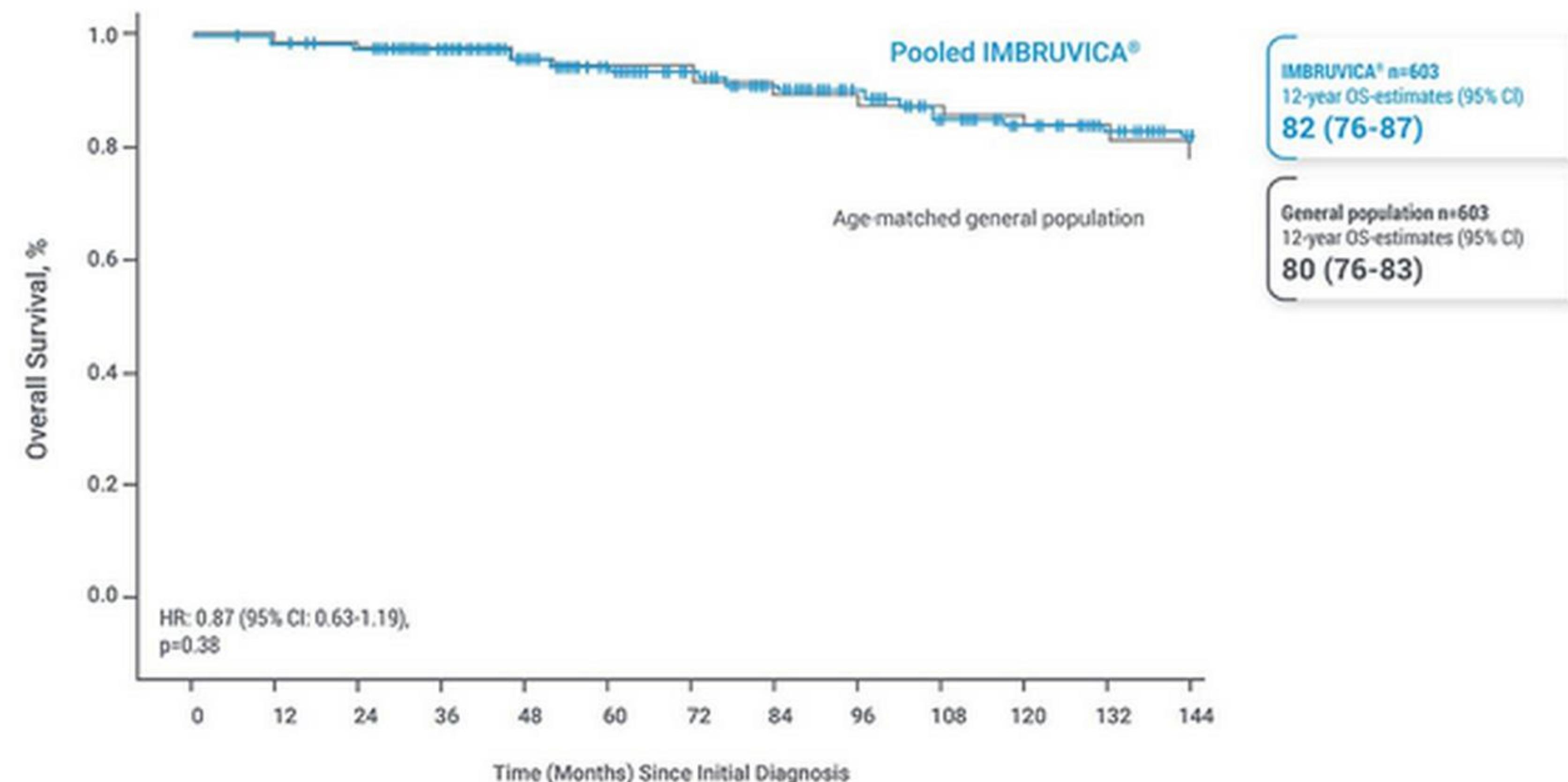
Safety

Dosing

**imbruvica**  
(ibrutinib)



## Overall pooled IMBRUVICA®-treated patients vs age-matched general population have similar survival estimates<sup>17</sup>



Adapted from Ghia P et al. 2022.

BTKi=Bruton's tyrosine kinase inhibitor; CLL=chronic lymphocytic leukaemia; CT/CIT=chemotherapy and chemoimmunotherapy; IGHV=immunoglobulin heavy chain variable region; HR=hazard ratio; OS=overall survival; CI=confidence interval.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

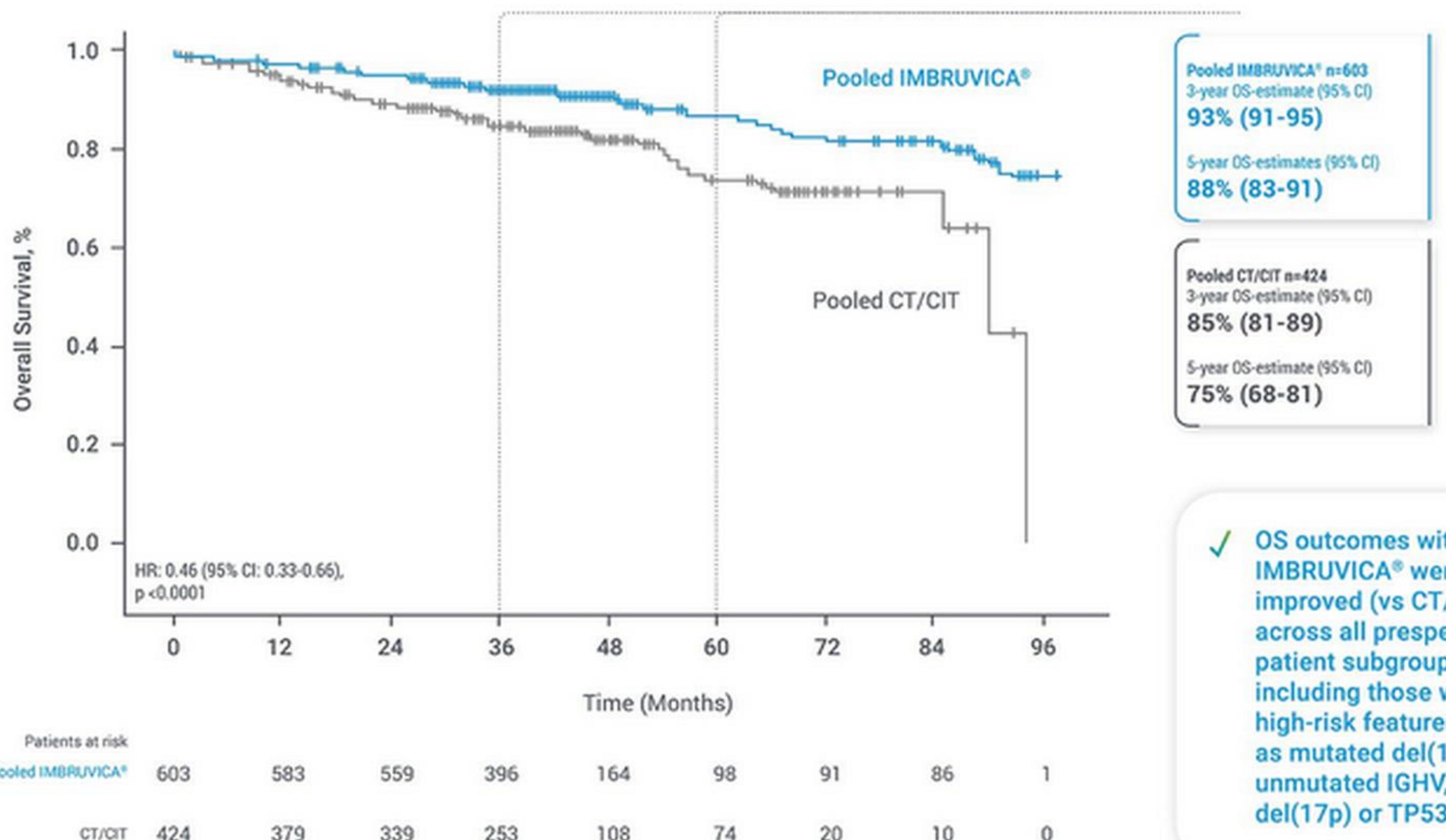
Safety

Dosing

imbruvica®  
(ibrutinib)



## Initiating therapy with 1L IMBRUVICA® improves OS vs traditional CT/CIT regardless of age or fitness<sup>17</sup>



✓ OS outcomes with IMBRUVICA® were improved (vs CT/CIT) across all prespecified patient subgroups, including those with high-risk features such as mutated del(11q), unmutatedIGHV, and del(17p) or TP53 mutation

Adapted from Ghia P, et al. 2022

CLL=chronic lymphocytic leukaemia; CT/CIT=chemotherapy and chemoimmunotherapy; IGHV=immunoglobulin heavy chain variable region; HR=hazard ratio; OS=overall survival; CI=confidence interval.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

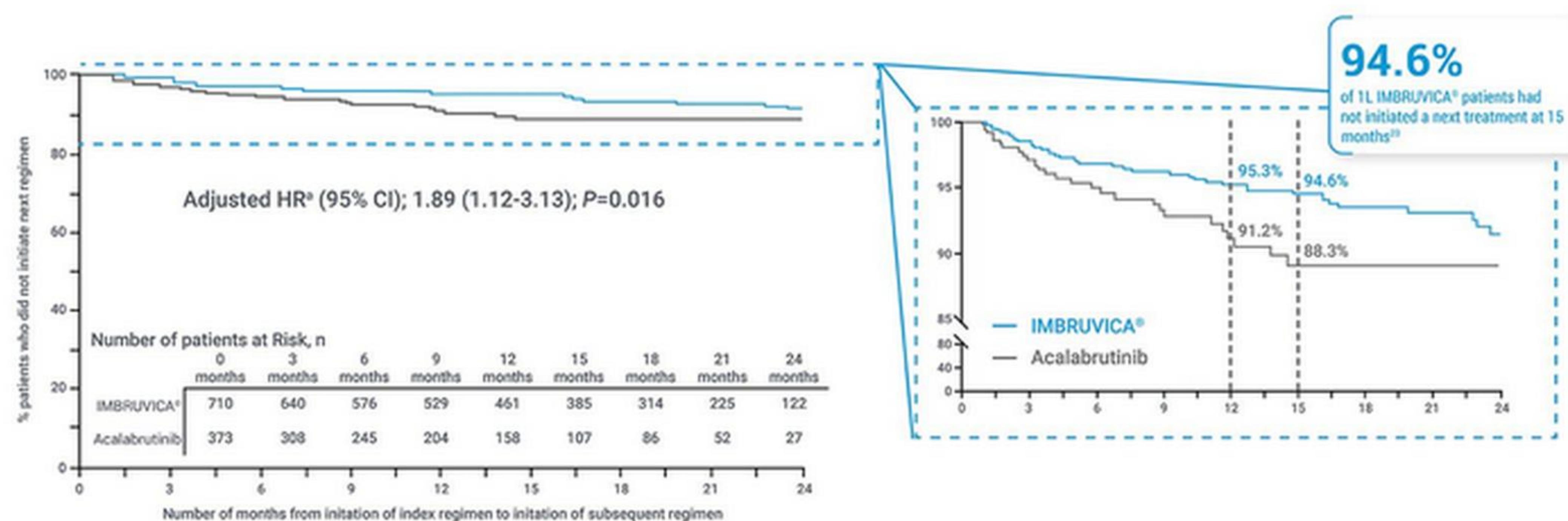
imbruvica®  
(ibrutinib)

## Time to next treatment with IMBRUVICA®<sup>23</sup>

REF PI

In the absence of head-to-head studies comparing BTKIs, time to next treatment (TTNT) is a well-established measure in real-world data and is a clinically meaningful end point to determine progression in real-world clinical practice.<sup>23</sup>

### PATIENTS TREATED WITH 1L ACALABRUTINIB WERE 89% MORE LIKELY TO START A NEXT TREATMENT THAN WITH IMBRUVICA®<sup>23</sup>



Adapted from Jacobs R, et al. 2022

BTKI: Bruton's tyrosine kinase inhibitors, HR: hazard ratio, CI: confidence interval.

Adjusted HR were calculated via Cox proportional hazard model. Model was adjusted for age, sex, region, race, year of index date, Quan-Charlson Comorbidity Index, chronic pulmonary disease, peripheral vascular disease, hypertension, atrial fibrillation, metastatic cancer, use of corticosteroid and use of antiplatelets



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

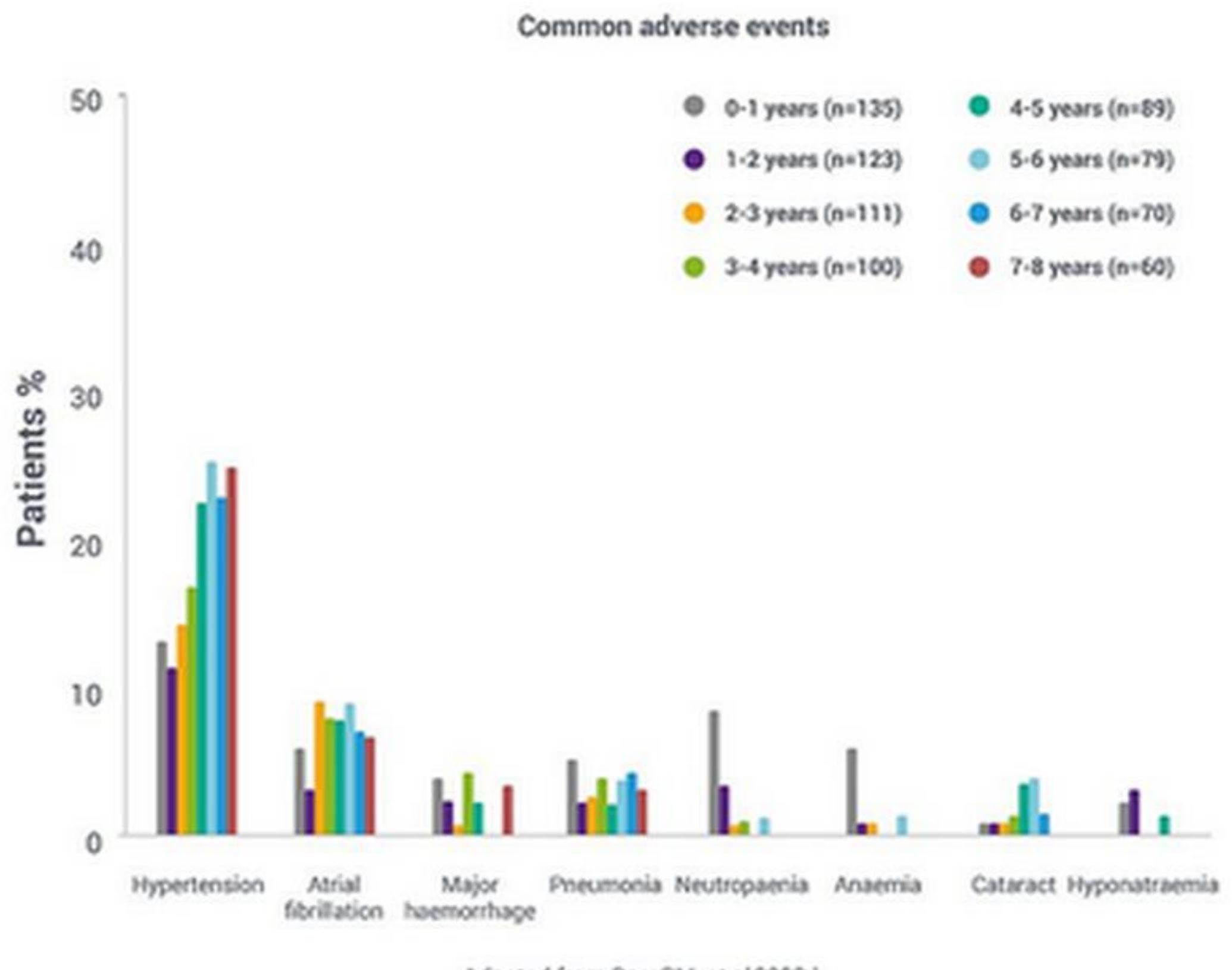
imbruvica<sup>®</sup>  
(ibrutinib)

## IMBRUVICA® is the BTKi with the most extensively studied tolerability profile<sup>1-5</sup>

REF PI

Treatment discontinuations due to AEs generally decreased over time<sup>1\*</sup>

### RESONATE-2



Up to 90% of initial AEs can be resolved with the flexible dose management offered by IMBRUVICA®<sup>17</sup>



New RWE suggests that many adverse events, including CV AEs, may be a class effect of BTK inhibitors<sup>19,20</sup>



AE=adverse event; BTKi=Bruton's tyrosine kinase inhibitor; RWE=real-world evidence; CV=cardiovascular

\*Treatment discontinuations due to AEs generally decreased over time, with 7% of patients (9/135) discontinuing in Year 0–1, 6% (7/121) in Year 1–2, 5% (6/111) in Year 2–3, 6% (6/99) in Year 3–4, 1% (1/88) in Year 4–5, 3% (2/79) in Year 5–6, no patients in Year 6–7, and 2% (1/60) in Year 7–8.<sup>1</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica  
(ibrutinib)



## Active AE management outcomes<sup>17</sup>

Active AE management allows patients to remain on IMBRUVICA® treatment and potentially achieve similar OS as an age-matched general population

### AE MANAGEMENT

Management of AEs with dose reductions resulted in resolution of AE in >90% and prevention of recurrence or worsening for the majority of patients (65%)



AE=adverse event; CDC=Centers for Disease Control; CLL=chronic lymphocytic leukaemia; CT/CIT=chemotherapy and chemoimmunotherapy; OS=overall survival; SLL=small lymphocytic lymphoma; SOC=system organ class.

\*Denominator is patients with any AEs leading to dose reductions.

†The same patients may be counted in more than one category due to multiple events.

AEs leading to dose reduction	Pooled IMBRUVICA®-treated patients N=248
Pts with an AE leading to dose reduction, n (%)	48 (19)
Outcome of first AE leading to dose reduction, n/N (%)*	
Initial AE resolved	45 / 48 (94)
No recurrence or recurred at lower grade	31 / 48 (65)
Recurred at same or higher grade	17 / 48 (35)
AEs of interest by SOC, n (%)†	
Haematologic	15 (5)
Dermatologic	7 (3)
Infection	7 (3)
Cardiac	5 (2)
Gastrointestinal	4 (2)
Musculoskeletal	3 (1)
Grade of AE, n (%)†	
Grade 1	12 (5)
Grade 2	19 (8)
Grade 3	23 (9)
Grade 4	5 (2)



New RWE suggests that hypertension and severe cardiac arrhythmias, including sudden death, may be a class effect of BTK inhibitors<sup>19,20</sup>



For all BTK inhibitors, carrying out a baseline clinical risk assessment is recommended<sup>19,22</sup>



**Full patient history<sup>19,22</sup>**

Including hypertension, CV disease, bleeding risk



**Concomitant medications<sup>5</sup>**

Refer to Summary of Product Characteristics for guidance



**Cardiovascular risk stratification<sup>22</sup>**

Assess BP, HR, echocardiogram  
Optimise treatment of modifiable risks for AF



**Blood tests<sup>22</sup>**

Perform FBC, general biochemistry, LFT



**CHA<sub>2</sub>DS<sub>2</sub>-VASc<sup>22</sup>**

Patients with a score ≥1 should receive anticoagulation based on physician and patient preference

Switching between BTK inhibitors does not always prevent occurrence of BTKi class effects<sup>23</sup>

Stable patients who are tolerating IMBRUVICA® well should not be switched  
and should remain on therapy for optimal benefit<sup>26</sup>

AE=adverse event; AF=atrial fibrillation; BP=blood pressure; BTK=CHA<sub>2</sub>DS<sub>2</sub>-VASc=congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65 to 74 and sex category (female); CV=cardiovascular; FBC=full blood count; HR=heart rate; LFT=liver function test; RWE=real world evidence.



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

Dosing

imbruvica®  
(ibrutinib)

## IMBRUVICA® offers flexible dosing for therapy management with a convenient, once-daily oral tablet<sup>5</sup>

REF PI



The flexibility to dose adjust, if needed, to help manage certain AEs<sup>5†</sup>



Dose modification due to AEs does not impact efficacy outcomes<sup>24</sup>



Stable patients who are tolerating IMBRUVICA® well should not be switched and should remain on therapy for optimal benefit<sup>26</sup>



AE=adverse event.

\*In a review of 13 articles on the various modes of administration for cancer treatment administration, 84.6% (11/13 articles) reported that patients preferred oral treatment over intravenous treatment.<sup>11</sup>

†Dose management available for patients experiencing AEs including Grade ≥3 non-haematological toxicity, Grade ≥3 neutropenia with infection or fever and Grade 4 haematological toxicity.<sup>5</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

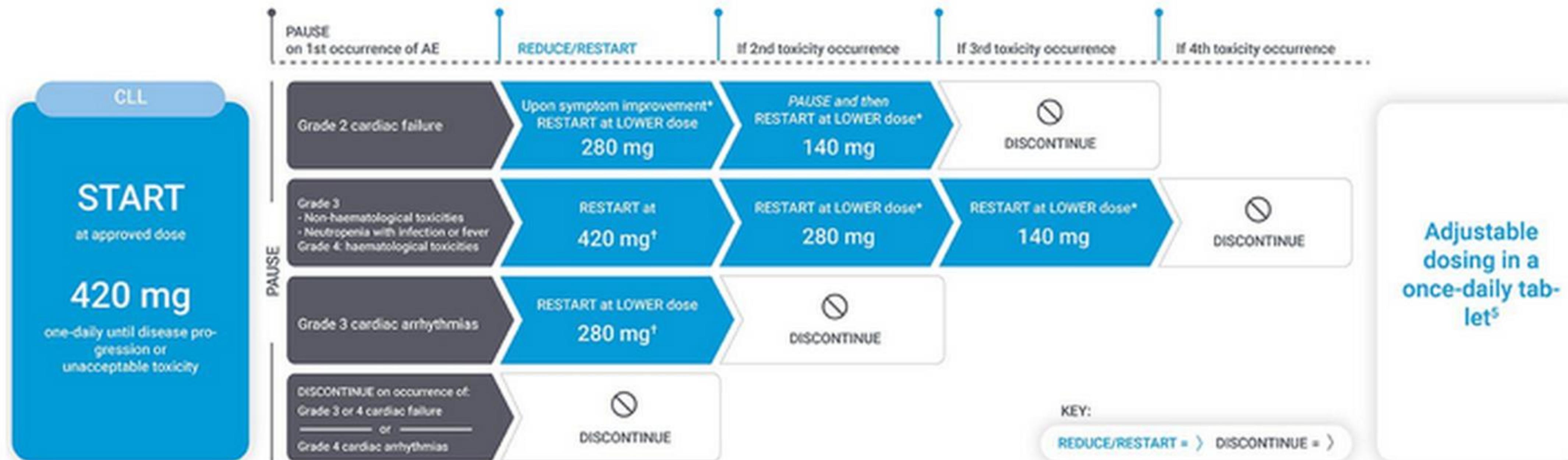
Time to next treatment

Safety

Dosing

imbruvica  
(ibrutinib)

## The flexibility to dose-adjust, if needed, to help manage certain AEs<sup>5</sup>



Active management of AEs with dose reductions or dose holds resulted in AE resolution in the majority (>85%) of patients.<sup>21</sup>

Additionally, dose reductions prevented recurrence or worsening for most patients (75%), allowing many patients to continue to benefit from IMBRUVICA® treatment.<sup>21</sup>

IMBRUVICA® is not contraindicated in patients with hypertension or cardiac comorbidities (please see the Summary of Product Characteristics before prescribing).<sup>14</sup>

AE=adverse event.

<sup>5</sup>Once AE has improved to Grade 1 or baseline, follow the next recommended dose modification.<sup>14</sup>

<sup>†</sup>For Grade 3 or 4 AEs: When resuming treatment, restart at the same or lower dose based on benefit-risk evaluation. If toxicity reoccurs, reduce daily dose by 140 mg.<sup>14</sup>

<sup>14</sup>Evaluate the benefit-risk before resuming treatment.<sup>14</sup>



Efficacy

High-risk patients

Real-world evidence

Life expectancy

Time to next treatment

Safety

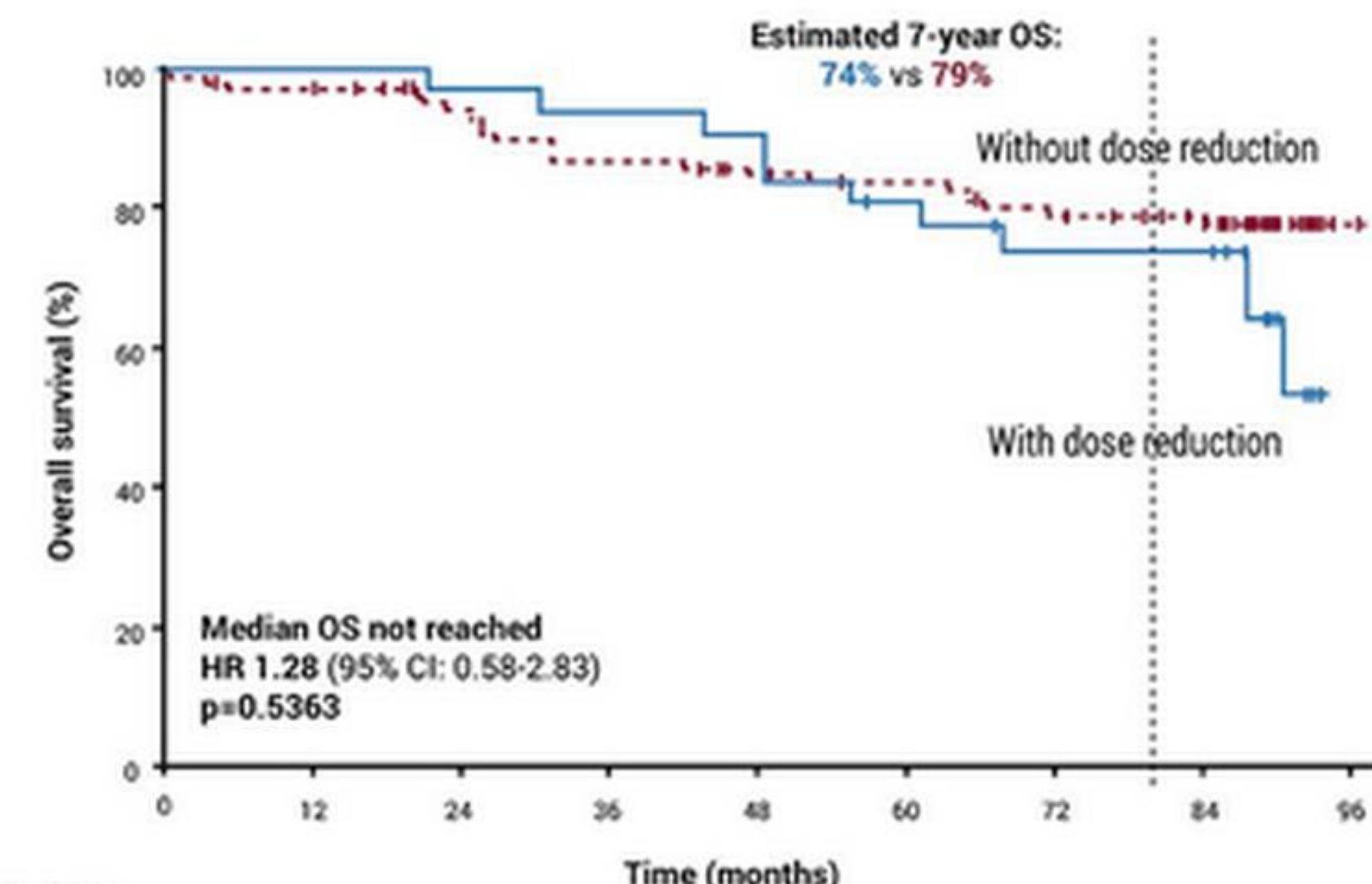
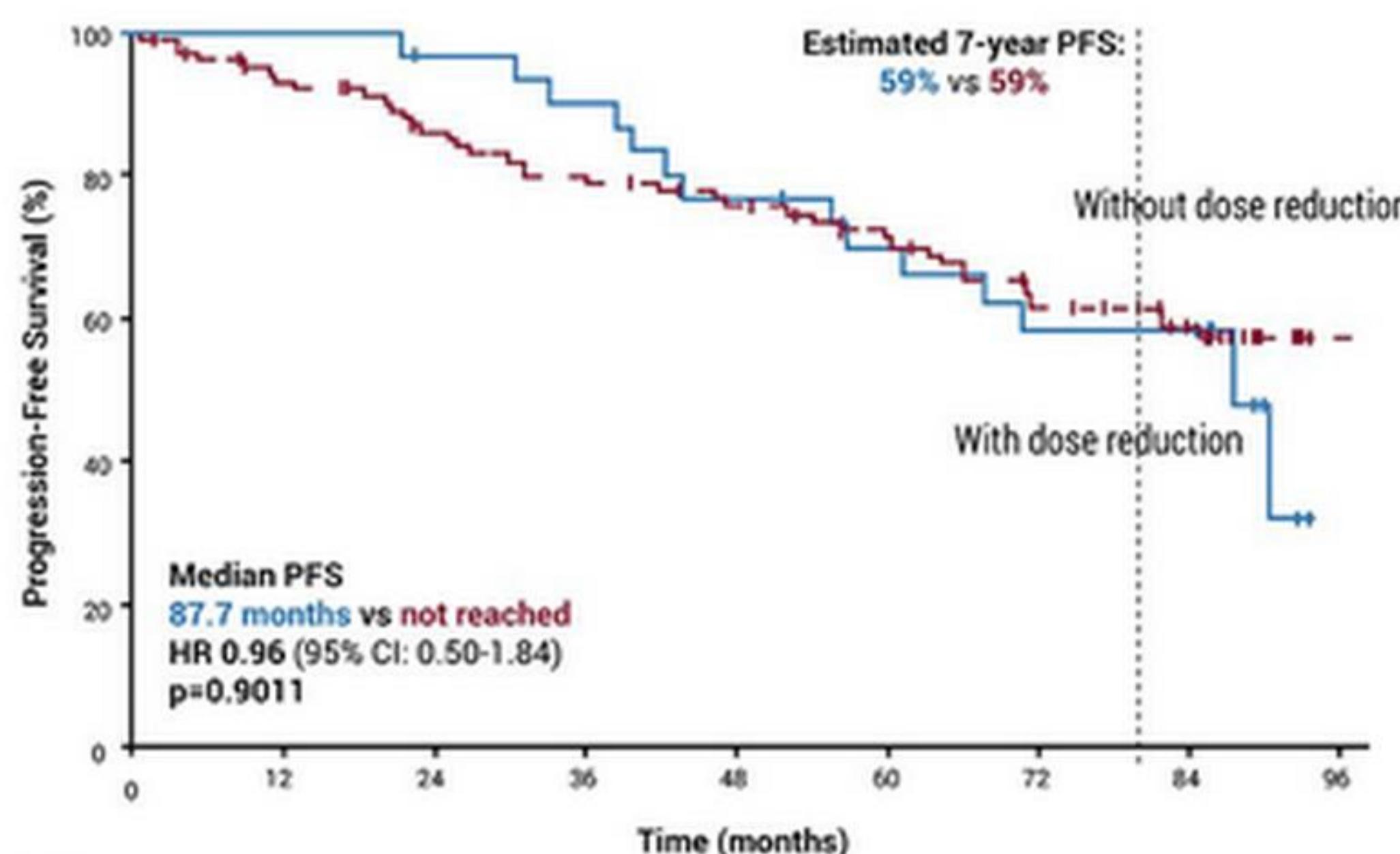
Dosing

imbruvica<sup>®</sup>  
(ibrutinib)

## Dose modification due to AEs does not impact efficacy outcomes<sup>24</sup>

Clinical trial

### RESONATE-2: Post-hoc analysis in patients with dose reductions<sup>24</sup>



Adapted from Wojach J, et al. 2023

HR: hazard ratio, CI: confidence interval, OS: overall survival, PFS: progression-free survival.



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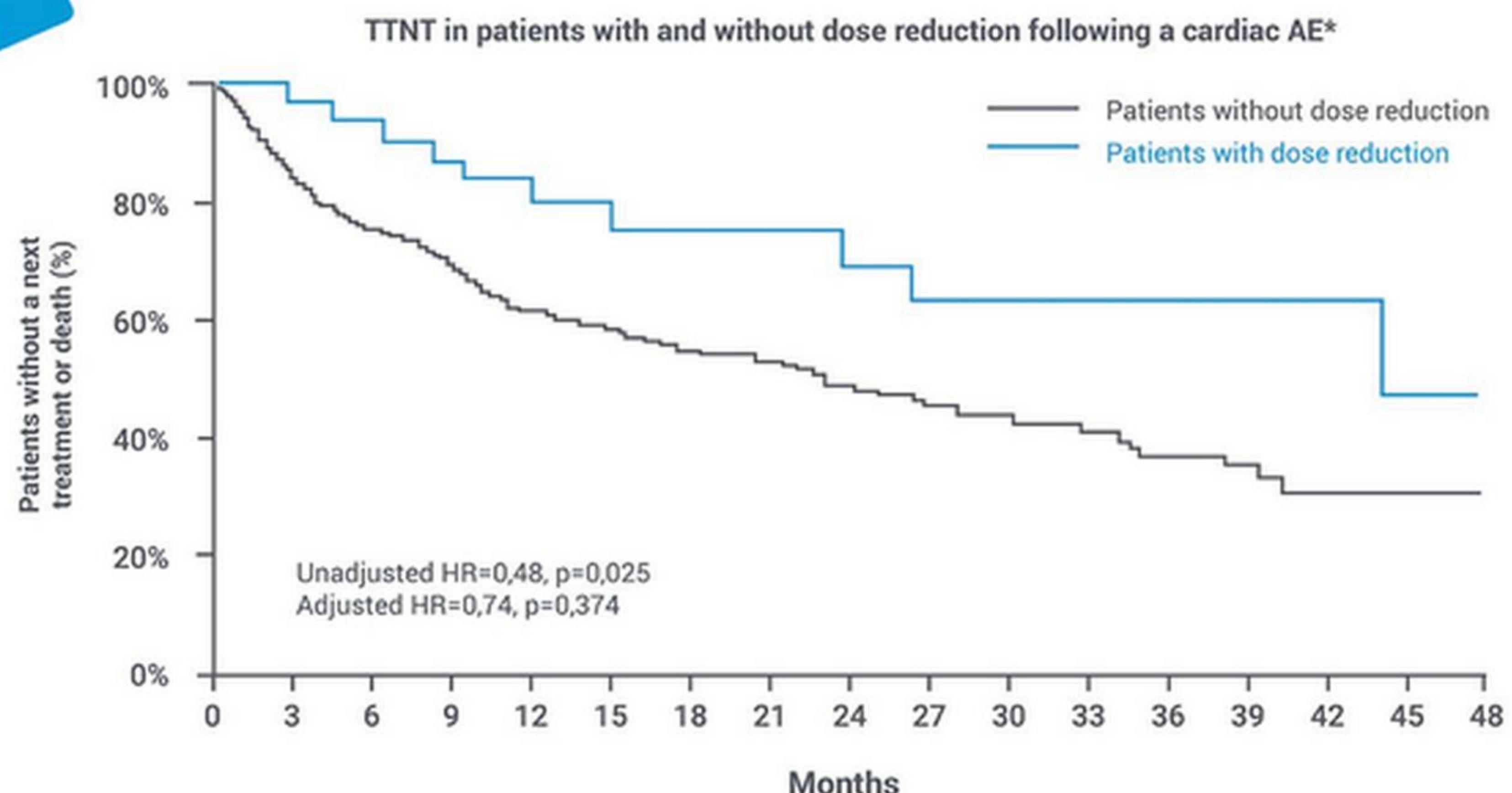
Dosing

imbruvica<sup>®</sup>  
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**Dose reduction with IMBRUVICA® can be an effective strategy to manage AEs and maintain long-term treatment persistence<sup>25</sup>**



Real-world analysis



Adapted from Shadman M, et al. 2023.<sup>25</sup>

AE=adverse event; HR=hazard ratio; TTNT=time to next treatment.

\* TTNT, defined as time from the first incident AE to either first dose of any non-IMBRUVICA® therapy, a gap >90 days between the last day of supply of IMBRUVICA® and the date of the next IMBRUVICA® claim, or death, and evaluated for patients with incidence of cardiac AEs.<sup>25</sup>



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