LEUCEMIA LINFATICA CRONICA, OGGI... ED OLTRE

Il tramonto scritto della chemio-immunoterapia!

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Fondazione Policlinico Universitario A Gemelli,IRCCS, Roma

Cagliari, Hotel Regina Margherita – 16 Ottobre 2024

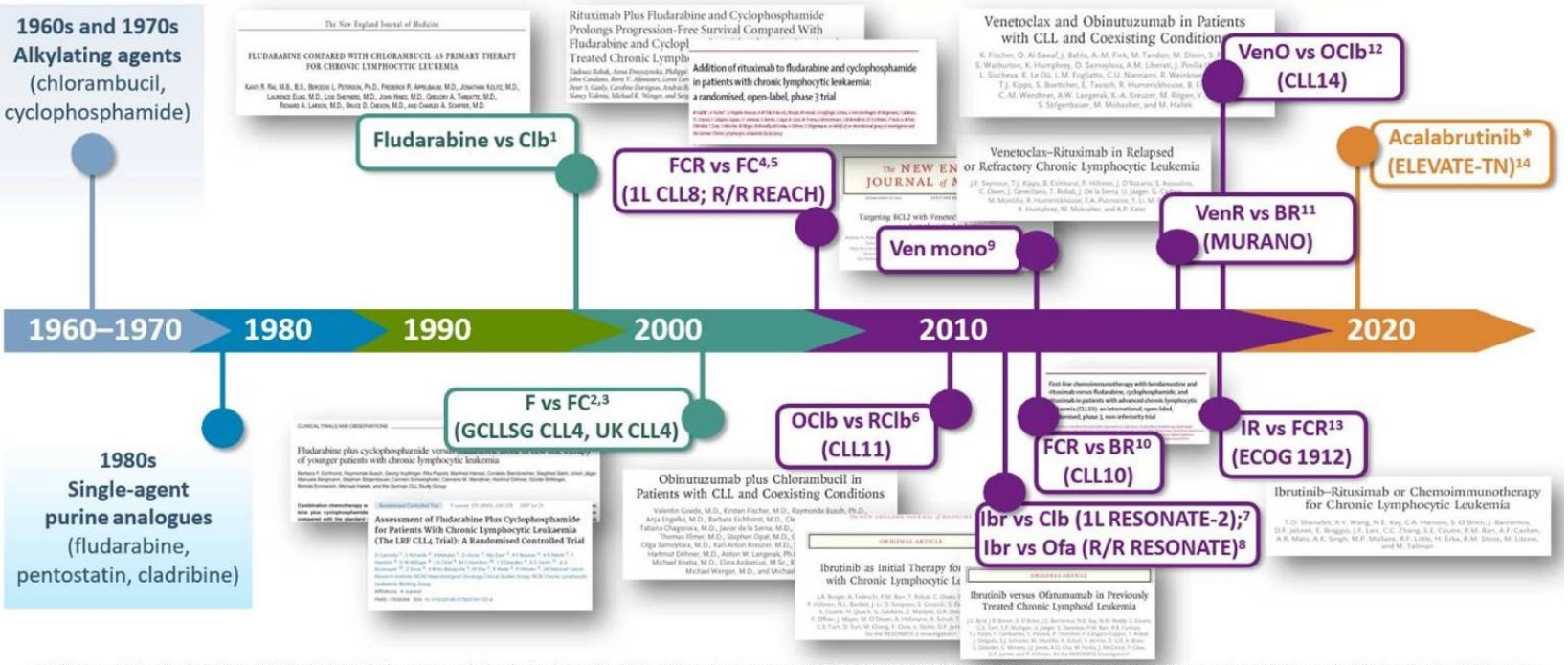
Disclosures of Luca Laurenti

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

Until 2022-23

Until 2022-23

From 2022-23

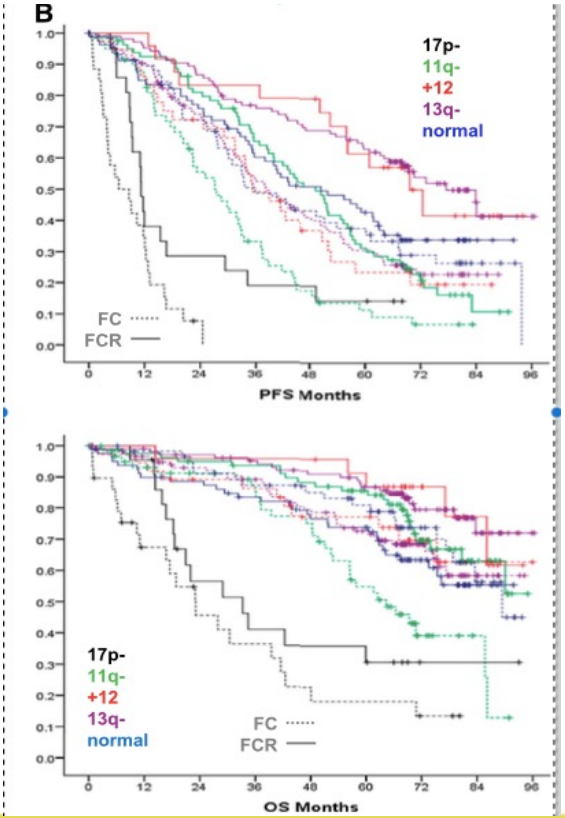


1. Rai KR, *et al. N Engl J Med* 2000; **343:**1750–1757; 2. Eichhorst BF, *et al. Blood* 2006; **114:**3382–3391; 3. Catovsky D, *et al. Lancet* 2007; **370:**230–239; 4. Hallek M, *et al. Lancet* 2010; **376:**1164–1174; 5. Robak T, *et al. J Clin Oncol* 2010; **8:**1756–1765; 6. Goede V, *et al. N Engl J Med* 2014; **370:**1101–1110; 7. Burger JA, *et al. N Engl J Med* 2015; **373:**2425–2437; 8. Byrd JC, *et al. N Engl J Med* 2014; **372:**213–223; 9. Roberts AW, *et al. N Engl J Med* 2016; 10. Eichhorst B, *et al. Lancet Oncol* 2016; **17:**928–942; 11. Seymour JF, *et al. N Engl J Med* 2018; **378:**1107–1120; 12. Fischer K, *et al. N Engl J Med* 2019; **380:**2225–2236; 13. Shanafelt TD, *et al. N Engl J Med* 2019; **381:**432–443; 14. Sharman JP, *et al. Lancet* 2020; **379:**1278–1291.

CLINICAL TRIALS AND OBSERVATIONS

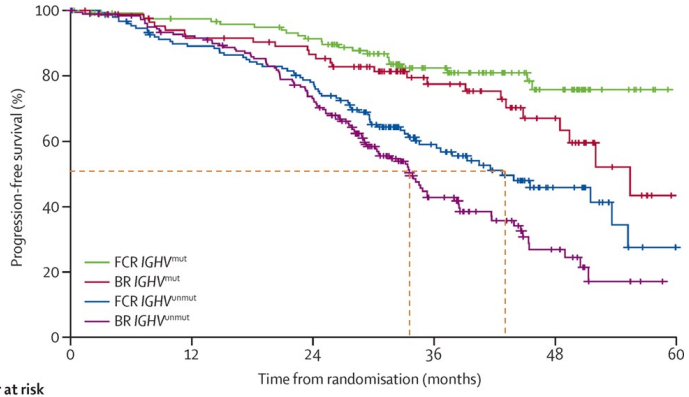
Gene mutations and treatment outcome in chronic lymphocytic leukemia: results from the CLL8 trial

Stephan Stilgenbauer,[1] Andrea Schnaiter,[1] Peter Paschka,[1] Thorsten Zenz,[1,2] Marianna Rossi,[3] Konstanze Döhner,[1] Andreas Bühler,[1] Sebastian Böttcher,[4] Matthias Ritgen,[4] Michael Kneba,[4] Dirk Winkler,[1] Eugen Tausch,[1] Patrick Hoth,[1] Jennifer Edelmann,[1] Daniel Mertens,[1,5] Lars Bullinger,[1] Manuela Bergmann,[1] Sabrina Kless,[1] Silja Mack,[1] Ulrich Jäger,[6] Nancy Patten,[7] Lin Wu,[7] Michael K. Wenger,[8] Günter Fingerle-Rowson,[8,9] Peter Lichter,[10] Mario Cazzola,[3] Clemens M. Wendtner,[9,11] Anna M. Fink,[9] Kirsten Fischer,[9] Raymonde Busch,[12] Michael Hallek,[9] and Hartmut Döhner[1]



First-line chemoimmunotherapy with bendamustine and rituximab versus fludarabine, cyclophosphamide, and rituximab in patients with advanced chronic lymphocytic leukaemia (CLL10): an international, open-label, randomised, phase 3, non-inferiority trial

Barbara Eichhorst, Anna-Maria Fink, Jasmin Bahlo, Raymonde Busch, Gabor Kovacs, Christian Maurer, Elisabeth Lange, Hubert Köppler, Michael Kiehl, Martin Sökler, Rudolf Schlag, Ursula Vehling-Kaiser, Georg Köchling, Christoph Plöger, Michael Gregor, Torben Plesner, Marek Trneny, Kirsten Fischer, Harmut Döhner, Michael Kneba, Clemens-Martin Wendtner, Wolfram Klapper, Karl-Anton Kreuzer, Stephan Stilgenbauer, Sebastian Böttcher, Michael Hallek, on behalf of an international group of investigators and the German CLL Study Group (GCLLSG)



Number at risk						
FCR $IGHV^{mut}$	196	112	86	44	13	0
BR $IGHV^{mut}$	86	129	94	37	9	0
FCR $IGHV^{unmut}$	155	74	57	31	12	0
BR $IGHV^{unmut}$	108	161	106	33	8	0

Historical Data (TRIAL OR RWE)

17p/TP53	7% of 1st line pts
U-IGHV	60% of 1st line pts
M-IGHV	30% of 1st line pts

mPFS 17p/TP53	1 Year
mPFS uIGHV	< 4 Years
mPFS mIGHV	up to 9 Years

Stilgenbauer et al. Blood 2014; Eichhorst et al, Lancet Oncol 2016

November 2013

2015

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib as Initial Therapy for Patients with Chronic Lymphocytic Leukemia

J.A. Burger, A. Tedeschi, P.M. Barr, T. Robak, C. Owen, P. Ghia, O. Bairey, P. Hillmen, N.L. Bartlett, J. Li, D. Simpson, S. Grosicki, S. Devereux, H. McCarthy, S. Coutre, H. Quach, G. Gaidano, Z. Maslyak, D.A. Stevens, A. Janssens, F. Offner, J. Mayer, M. O'Dwyer, A. Hellmann, A. Schuh, T. Siddiqi, A. Polliack, C.S. Tam, D. Suri, M. Cheng, F. Clow, L. Styles, D.F. James, and T.J. Kipps, for the RESONATE-2 Investigators*

2014

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Ibrutinib versus Ofatumumab in Previously Treated Chronic Lymphoid Leukemia

J.C. Byrd, J.R. Brown, S. O'Brien, J.C. Barrientos, N.E. Kay, N.M. Reddy, S. Coutre, C.S. Tam, S.P. Mulligan, U. Jaeger, S. Devereux, P.M. Barr, R.R. Furman, T.J. Kipps, F. Cymbalista, C. Pocock, P. Thornton, F. Caligaris-Cappio, T. Robak, J. Delgado, S.J. Schuster, M. Montillo, A. Schuh, S. de Vos, D. Gill, A. Bloor, C. Dearden, C. Moreno, J.J. Jones, A.D. Chu, M. Fardis, J. McGreivy, F. Clow, D.F. James, and P. Hillmen, for the RESONATE Investigators*

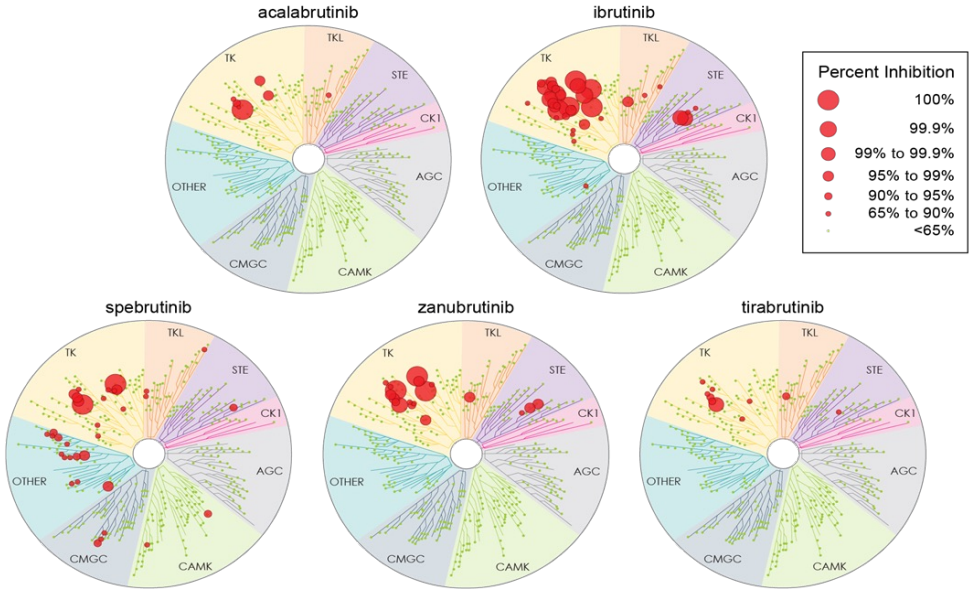
Imbruvica FDA Approval History

Last updated by Judith Stewart, BPharm on Aug 30, 2022.

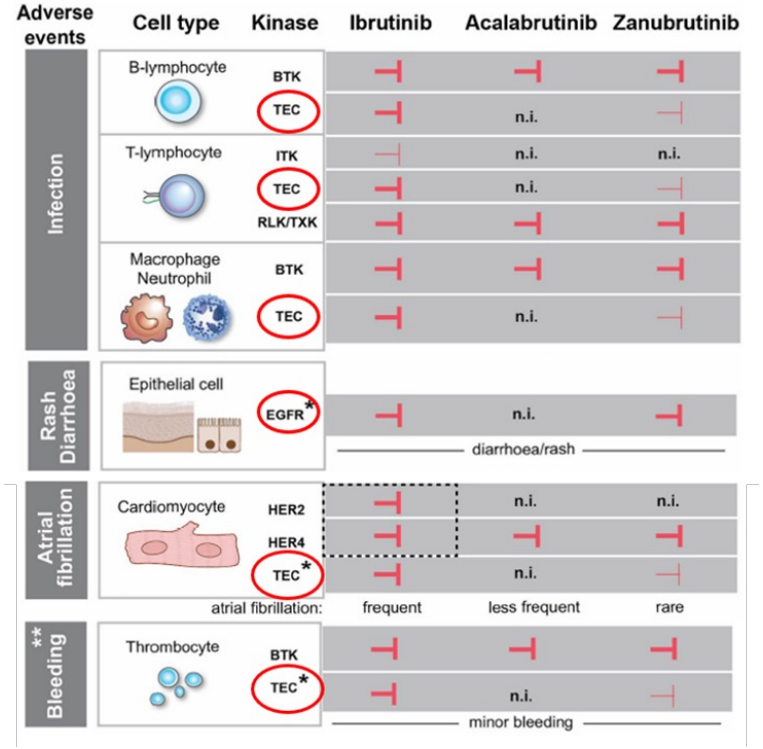
FDA Approved: Yes (First approved November 13, 2013)
Brand name: Imbruvica
Generic name: ibrutinib
Dosage form: Capsules, Tablets and Oral Suspension
Company: AbbVie Inc.
Treatment for: Mantle Cell Lymphoma, Chronic Lymphocytic Leukemia, Waldenström Macroglobulinemia, Graft-versus-host disease, Lymphoma

Imbruvica (ibrutinib) is an oral Bruton's tyrosine kinase (BTK) inhibitor for the treatment of mantle cell lymphoma (MCL), chronic lymphocytic leukemia (CLL)/small lymphocytic lymphoma (SLL), Waldenström's macroglobulinemia (WM), marginal zone lymphoma (MZL), and chronic graft versus host disease (cGVHD).

Acalabrutinib Selectivity as a strength



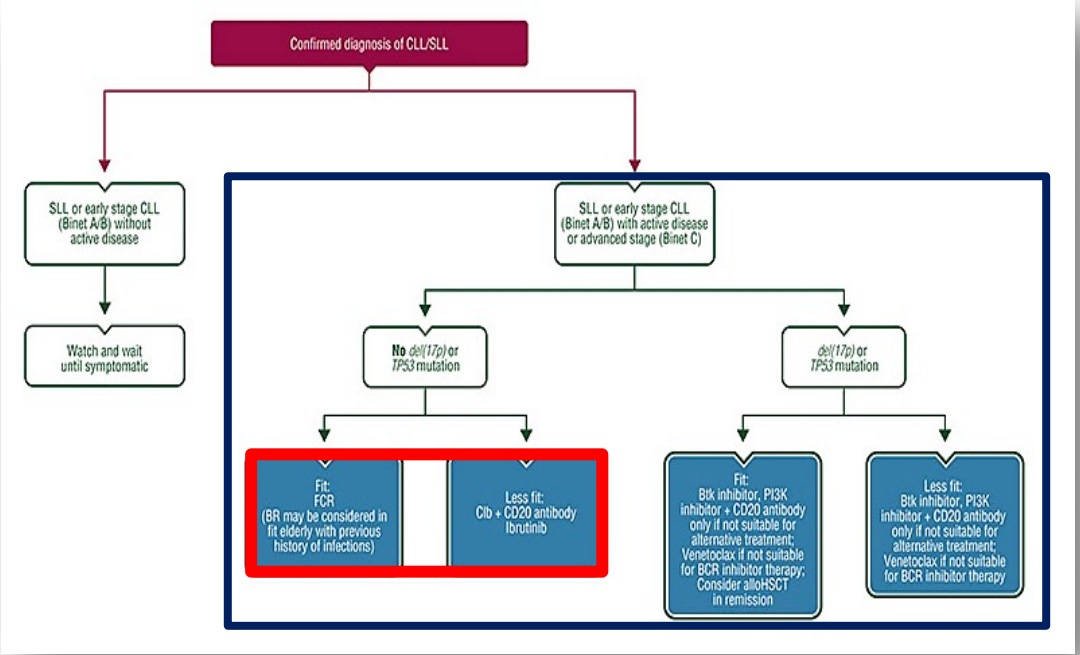
Herman SEM, et al.. ClinCancer Res. 2017



Estupinan et al. Frontiers in Cell and Dev Biology 2021

ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

Welcome to the **EUROPEAN SOCIETY FOR MEDICAL ONCOLOGY**, the leading European professional organisation for medical oncology.

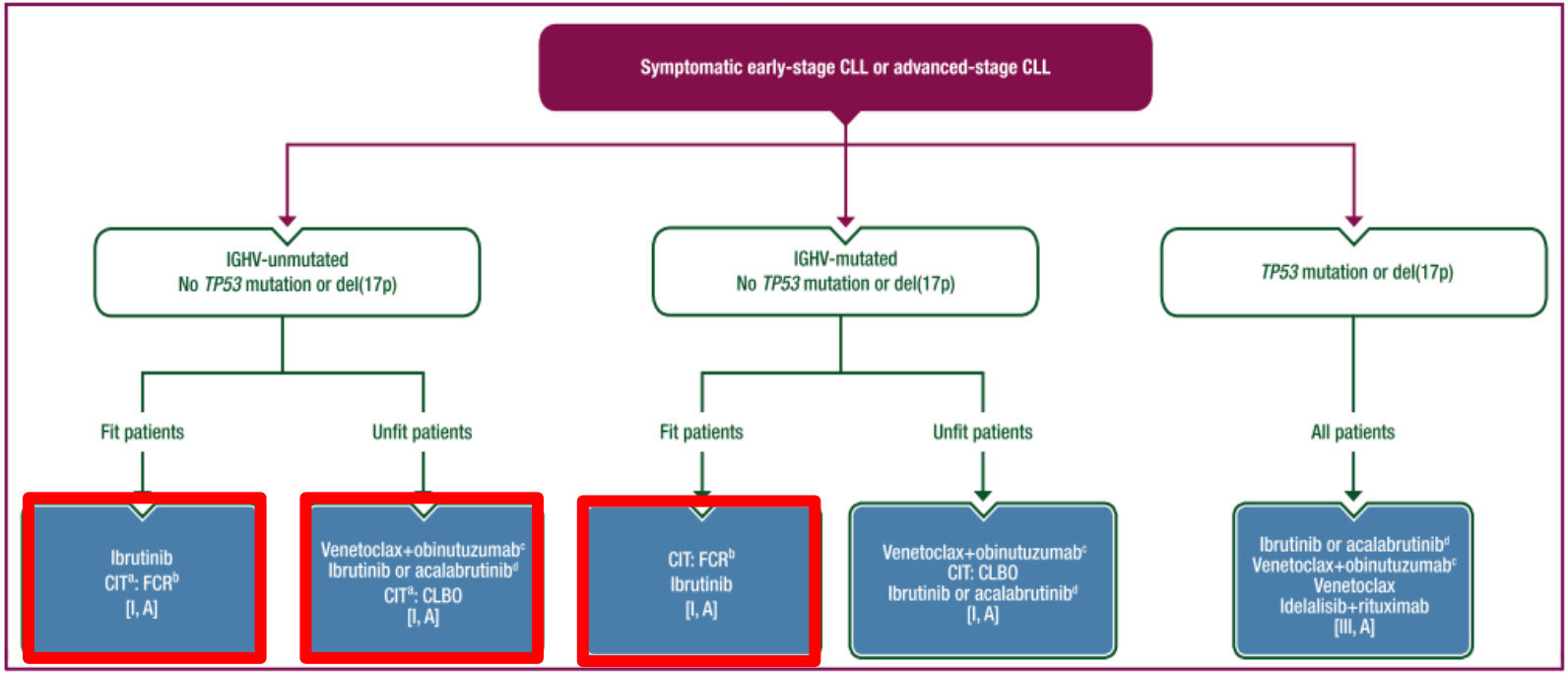


Frontline CLL

- **ESMO guidelines recommend analysis for the detection of del(11q) and of IGHV mutation status as 'desirable' before the start of therapy**
- **Only patients with del(17p) and/or TP53 mutation are highlighted as needing specific regimens**

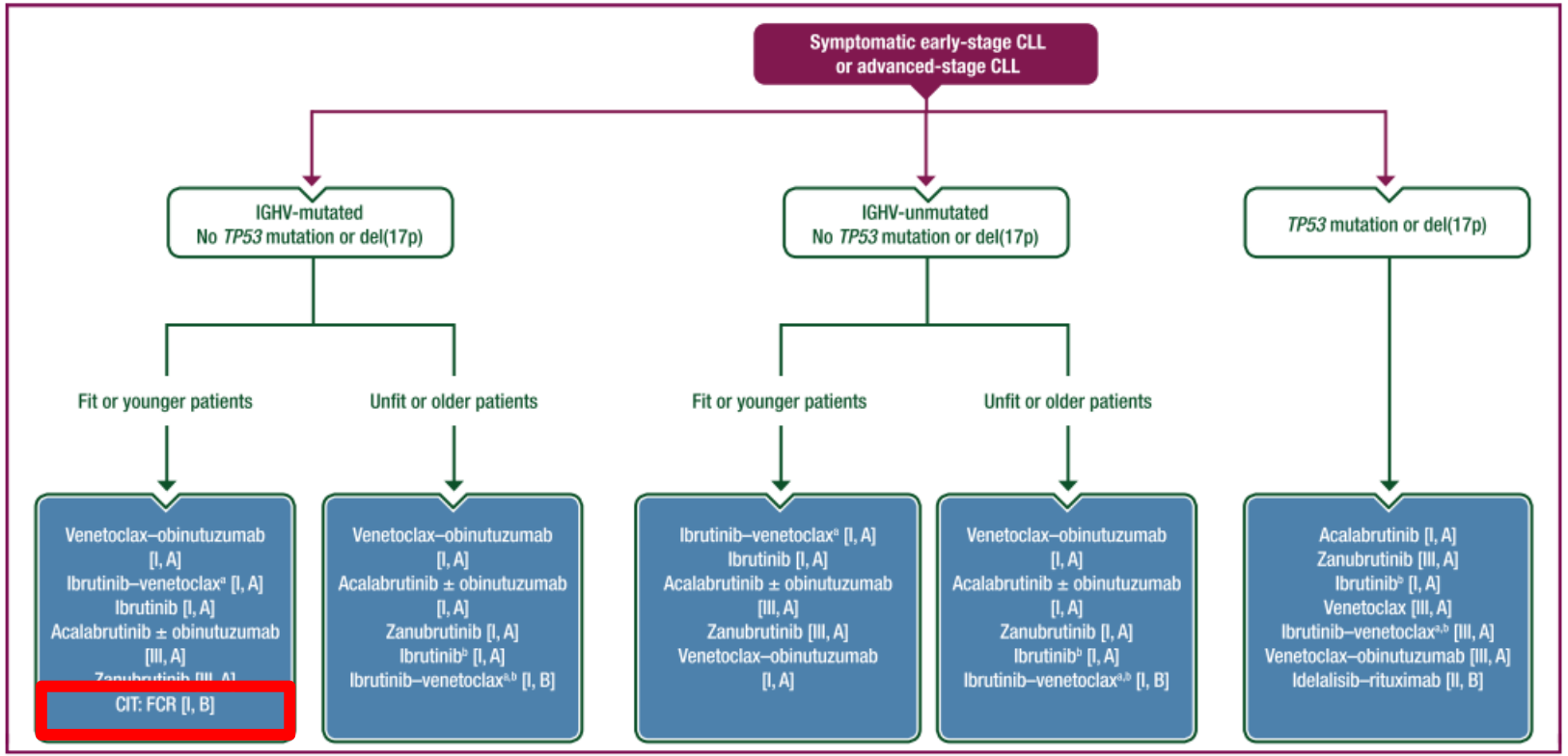
Published: 27 June 2017. Authors: ESMO Guidelines Committee

ESMO 2020



eUpdate ESMO Guidelines Commitee Ann Oncol 2020

Linee Guida ESMO 2024



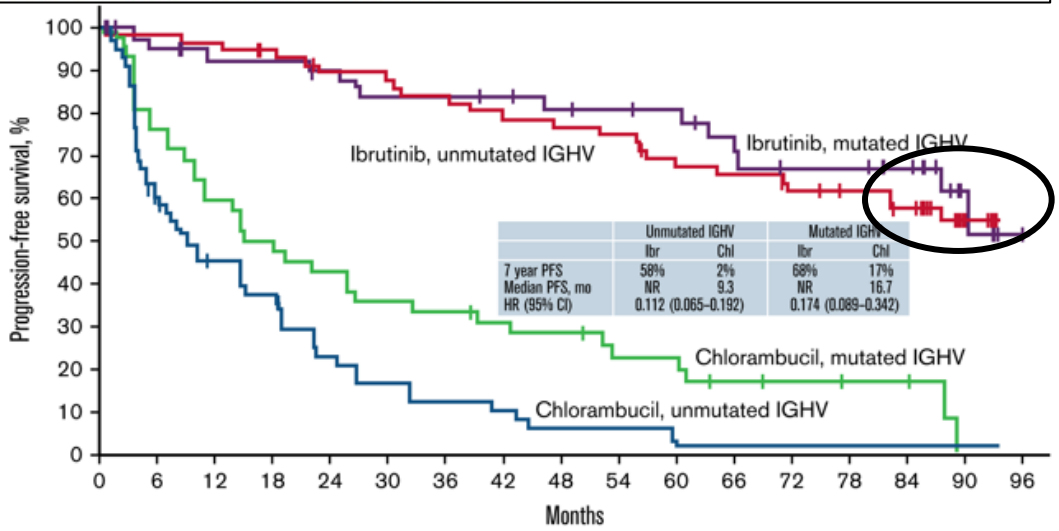
eUpdate ESMO Guidelines Commitee Ann Oncol 2024

Why CIT is unacceptable in 2024 ?

- Efficacy of target therapies

Up to 8-year follow-up from RESONATE-2: first-line ibrutinib treatment for patients with chronic lymphocytic leukemia

Paul M. Barr,[1] Carolyn Owen,[2] Tadeusz Robak,[3] Alessandra Tedeschi,[4] Osnat Bairey,[5] Jan A. Burger,[6] Peter Hillmen,[7] Steve E. Coutre,[8] Claire Dearden,[9] Sebastian Grosicki,[10] Helen McCarthy,[11] Jian-Yong Li,[12] Fritz Offner,[13] Carol Moreno,[14] Cathy Zhou,[15] Emily Hsu,[16] Anita Szoke,[16] Thomas J. Kipps,[17] and Paolo Ghia[18]



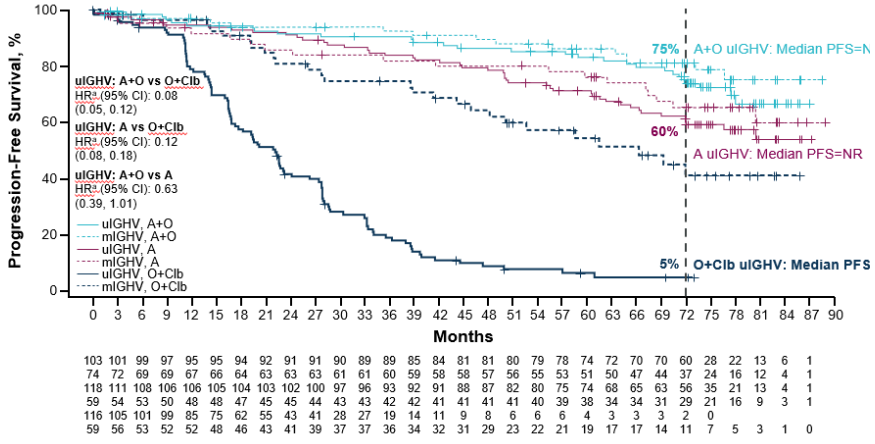
Patients at risk

Ibrutinib, mutated IGHV:	40	37	34	34	32	30	30	29	27	26	25	22	19	19	16	6	1
Ibrutinib, 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

No Impact of IGHV on PFS

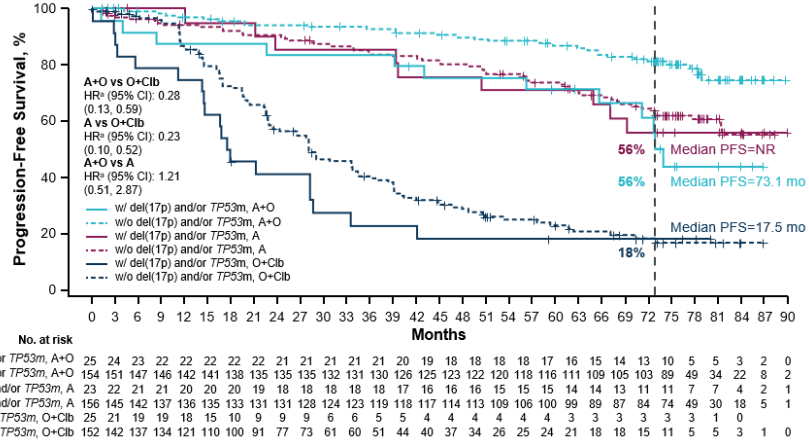
Barr et al, Blood Adv 2022

ELEVATE TN 6y follow-up



mPFS uIGHV

Not Reached



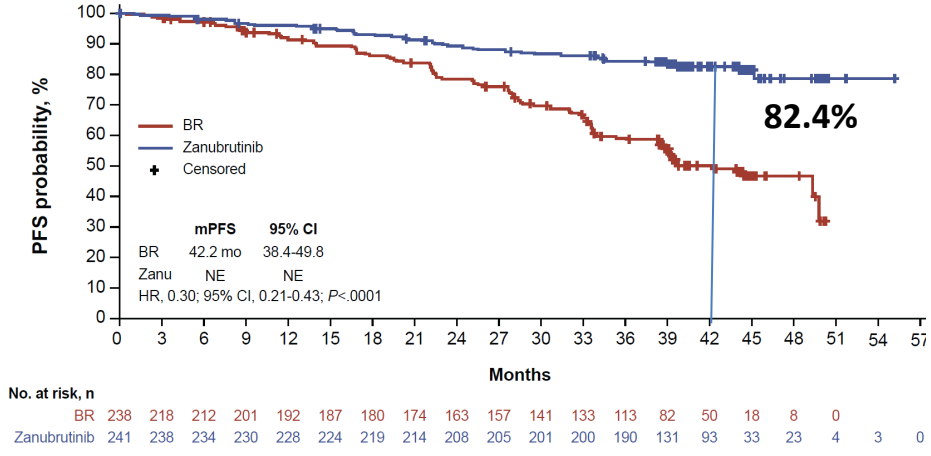
mPFS Del17p and/or TP53

Not Reached

Sharman et al, ASH 2023

SEQUOIA

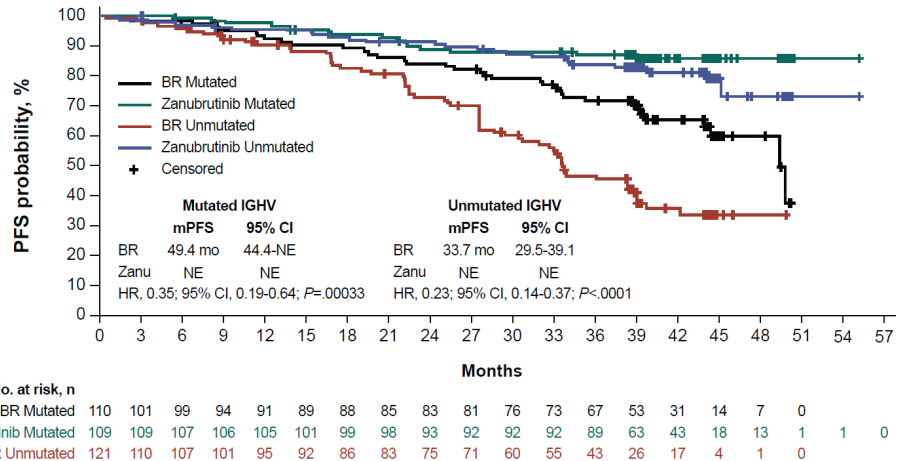
Progression-Free Survival



No. at risk, n

BR	238	218	212	201	192	187	180	174	163	157	141	133	113	82	50	18	8	0	
Zanubrutinib	241	238	234	230	228	224	219	214	208	205	201	200	190	131	93	33	23	4	3	0

Progression-Free Survival by IGHV Mutation Status



No. at risk, n

BR Mutated	110	101	99	94	91	89	88	85	83	81	76	73	67	53	31	14	7	0	
Zanubrutinib Mutated	109	109	107	106	105	101	99	98	93	92	92	92	89	63	43	18	13	1	1	0
BR Unmutated	121	110	107	101	95	92	86	83	75	71	60	55	43	26	17	4	1	0		
Zanubrutinib Unmutated	125	122	120	118	117	117	114	111	111	109	105	104	97	65	47	14	9	2	2	0

In cohort 1, median PFS was not reached in patients who received zanubrutinib; in patients who received BR, median PFS was 42.2 months

Estimated 42-month PFS rates with zanubrutinib and BR were **82.4%** and 50.0%, respectively

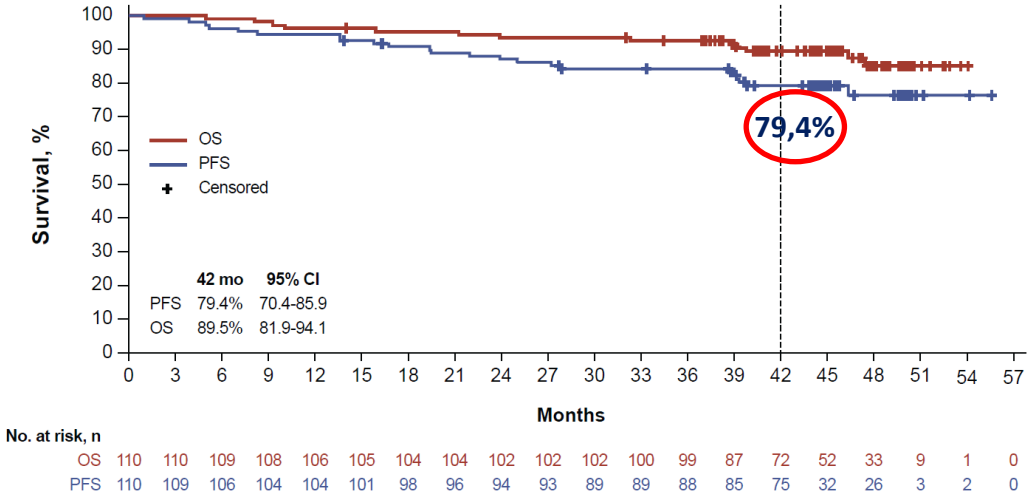
PFS was significantly improved with zanubrutinib vs BR in patients with mutated IGHV (2-sided P=.00033) and unmutated IGHV (2-sided P<.0001)

Data cutoff: 31 October 2022. All *P* values are 2-sided. BR=bendamustine plus rituximab, CI=confidence interval, HR=hazard ratio, NE=not evaluable, PFS=progression-free survival, Zanu=zanubrutinib

Munir T et al. Poster presented at EHA 2023; Abstract number: P639

Progression-Free Survival by del17p/TP53

SEQUOIA – Extended Follow-Up



	Cohort 2 – Del(17p) Zanubrutinib (n=111)
CR / CRi Rate	14.5%

- Median PFS was not reached
- Estimated 42-month PFS rate was 79.4%
- Median OS was not reached
- Estimated 42-month OS rate was 89.5%

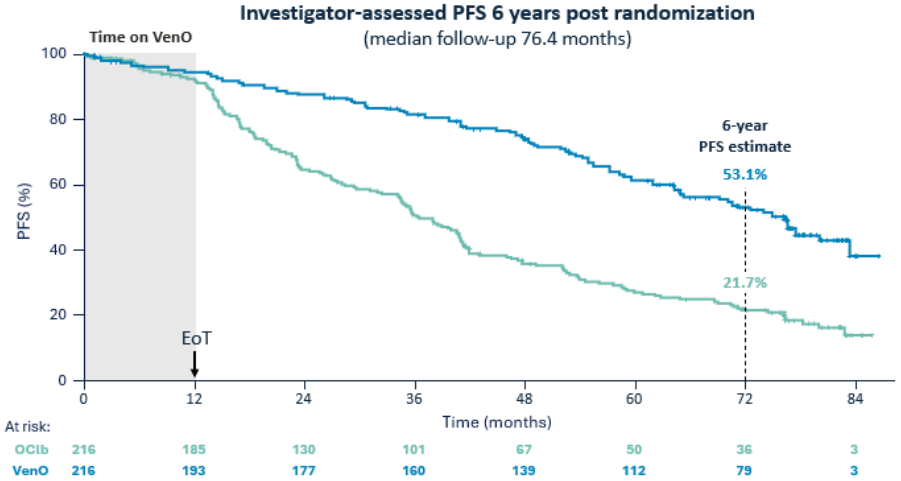
Data cutoff: 31 October 2022. All *P* values are 2-sided.

CI=confidence interval, CR=complete response, CRi=complete response with incomplete hematologic recovery, HR=hazard ratio, NE=not evaluable, OS=overall survival, PFS=progression-free survival,

Munir T et al. Poster presented at EHA 2023; Abstract number: P639

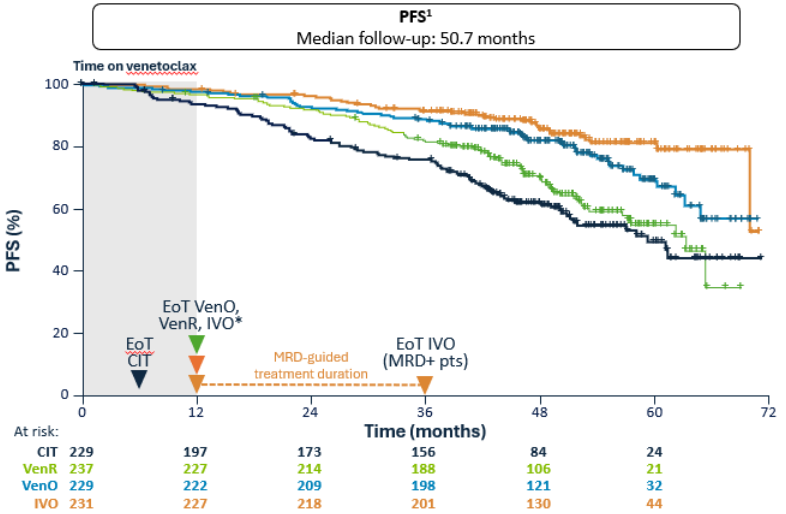
Ven-based regimens:PFS

CLL14



	VenO	OClb
Median PFS, months	76.2	36.4
HR (95% CI), p-value	0.40 (0.31–0.52) p<0.0001*	

CLL13



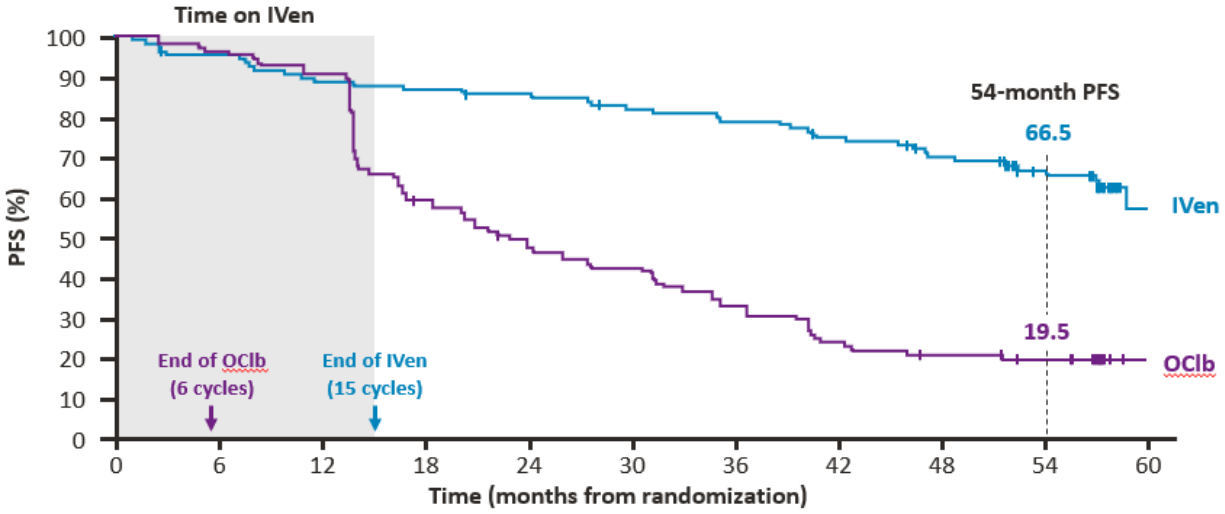
	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value[1]	–	– p=0.10†	0.47 (0.32–0.69) p<0.0001	0.30‡ (0.19–0.47) p<0.0001
4-year PFS, %[1]	62.0	70.1	81.8	85.5
Median PFS, months[2]	59.4	63.2	NR	NR

Al-Sawaf O, *et al. Blood* 2024; doi: 10.1182/blood.2024024631.

1. Fürstenau M, et al. Lancet Oncol 2024; 25:744–759 (incl. suppl.); 2. Fürstenau M, et al. ASH 2023. Abstract 635

GLOW study: PFS

PFS by INV-assessment (ITT population)[1]
(Median follow-up: 57.3 months)



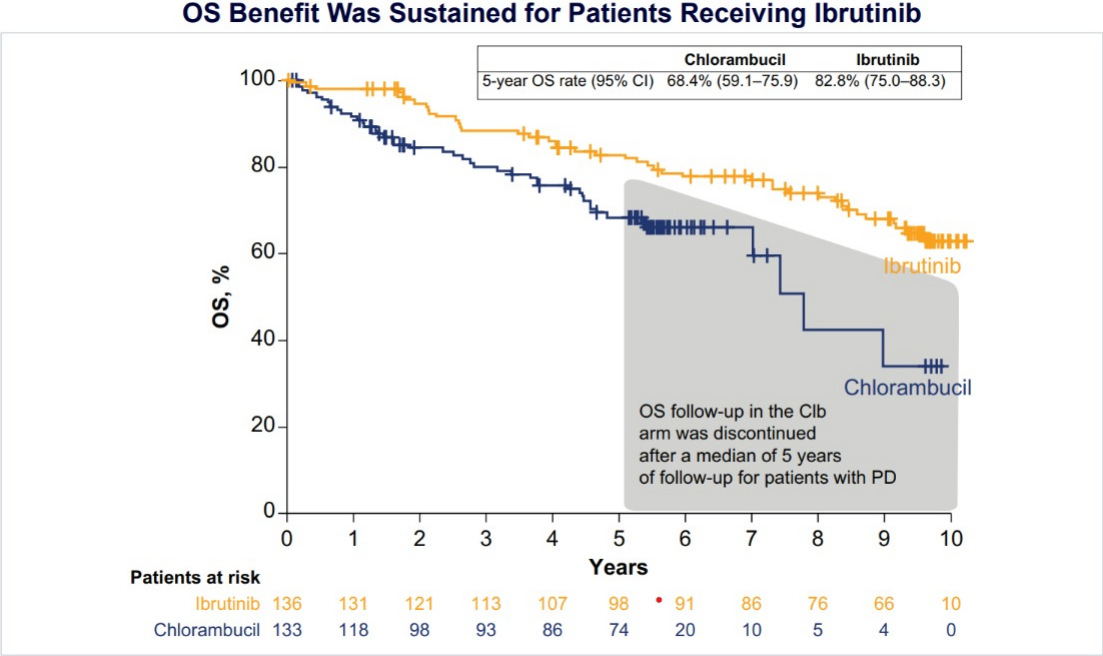
No. at risk											
IVen	106	99	92	90	88	83	80	75	68	55	11
OClb	105	101	95	61	50	43	33	24	20	15	2

Moreno, ASH 2023

Why CIT is unable in 2024 ?

- Efficacy of target therapies
- Better OS of target therapies

Final Analysis of the RESONATE-2 Study: Up to 10 Years of Follow-Up of First-Line Ibrutinib Treatment in Patients With CLL



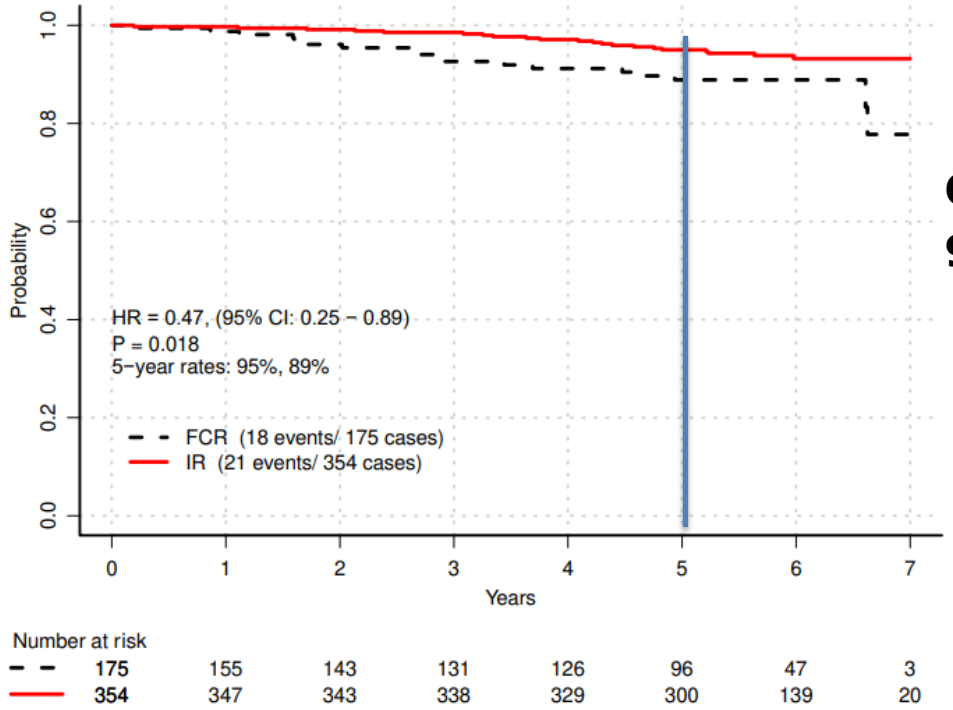
At 9 years, the OS rate was 68.0% (95% CI, 58.6–75.7) in the ibrutinib arm.

In patients with ≥1 high prognostic risk factors including mutated TP53/unmutated IGHV/del(11q), OS was significantly longer for patients treated with ibrutinib versus chlorambucil.

Burger, EHA 2024

ECOG1912 Results – Overall Survival

mFU: 70 mos



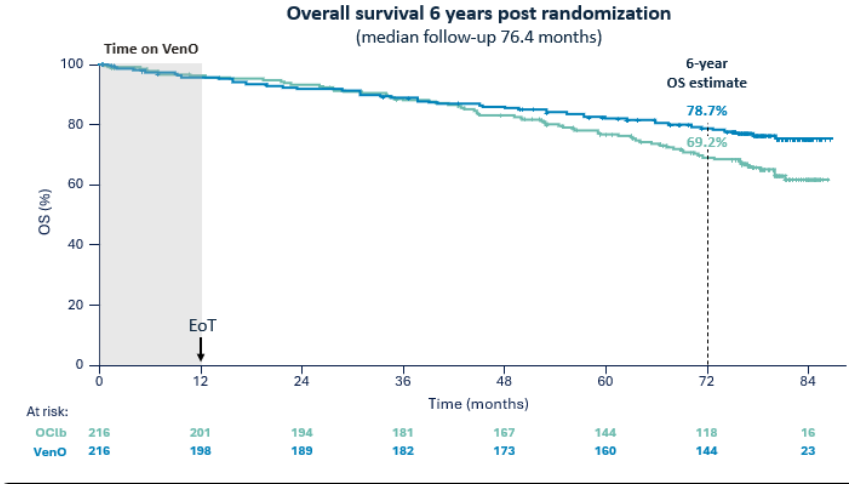
OS rates
95% IR vs 89% FCR

Sustained improvement in OS was observed for patients on the IR arm (HR=0.47; p=0.018)

T.D. Shanafelt et al., Blood 2021014960

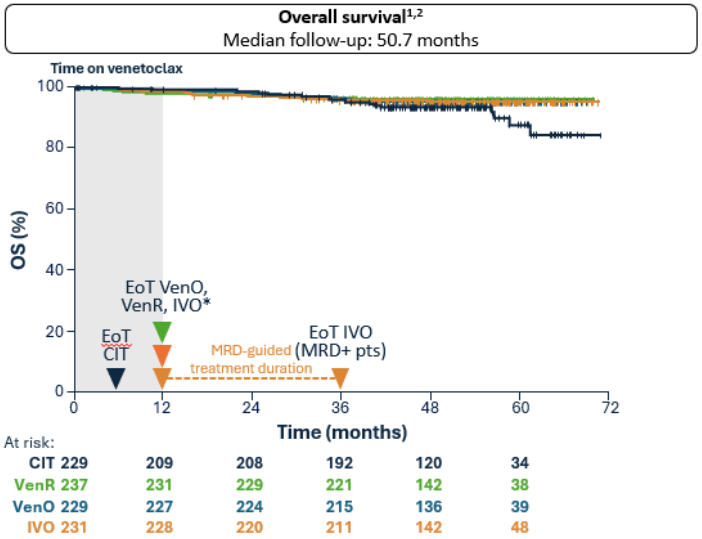
OS sustained benefit with venetoclax combinations

CLL14



	VenO	OClb
Events, n	48	70
Median OS, months	NR	NR
HR (95% CI), p-value	0.69 (0.48–1.01) p=0.052*	

CLL13

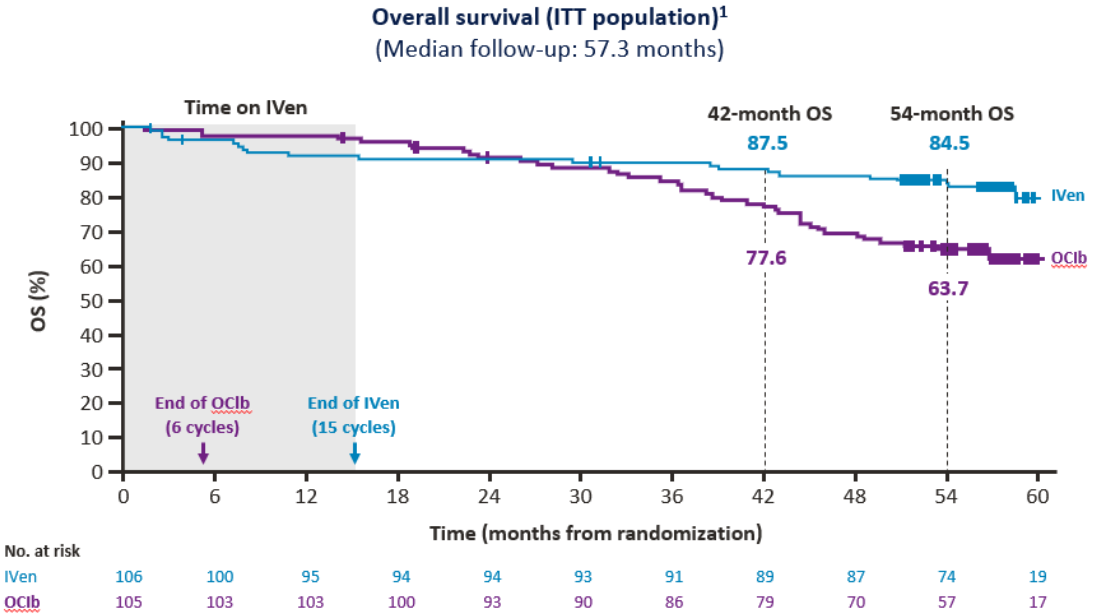


	CIT	VenR	VenO	IVO
HR vs CIT (97.5% CI) p-value[1,2]	–	0.46 (0.18–1.17) p=0.056	0.58 (0.24–1.38) p=0.15	0.58 (0.24–1.38) p=0.15
4-year OS, %[2]	93.5	96.2	95.1	95.0

- Al-Sawaf O, *et al. Blood* 2024; doi: 10.1182/blood.2024024631.

1. Fürstenau M, et al. Lancet Oncol 2024; 25:744–759 (incl. suppl.); 2. Fürstenau M, et al. ASH 2023. Abstract 635

GLOW Study: OS



	Iven (n=106)	Oclb (n=105)
HR (95% CI); p-value[1]	0.453 (0.261–0.785); p=0.0038*	

1. Moreno C, *et al*. ASH 2023. Abstract 634 (Oral);
2. Kater AP, *et al. NEJM Evid* 2022;

Why CIT is unable in 2024 ?

- Efficacy of target therapies
- Better OS of target therapies
- Secondary neoplasia

FCR vs Target Therapies

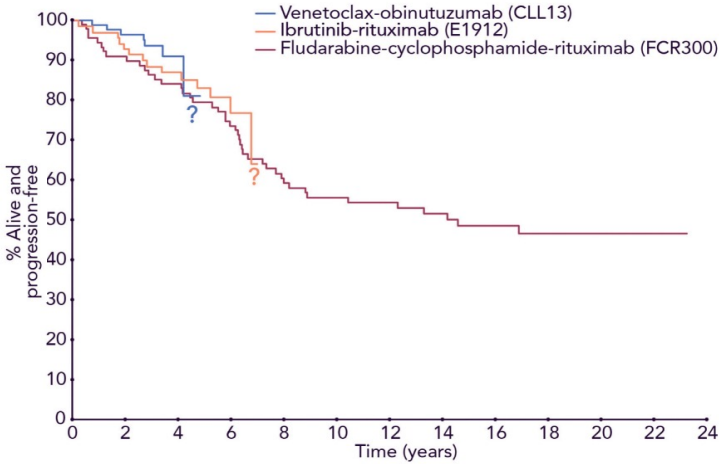
CLINICAL TRIALS AND OBSERVATIONS

Comment on Thompson et al, page 1784

Functional cure reported in CLL

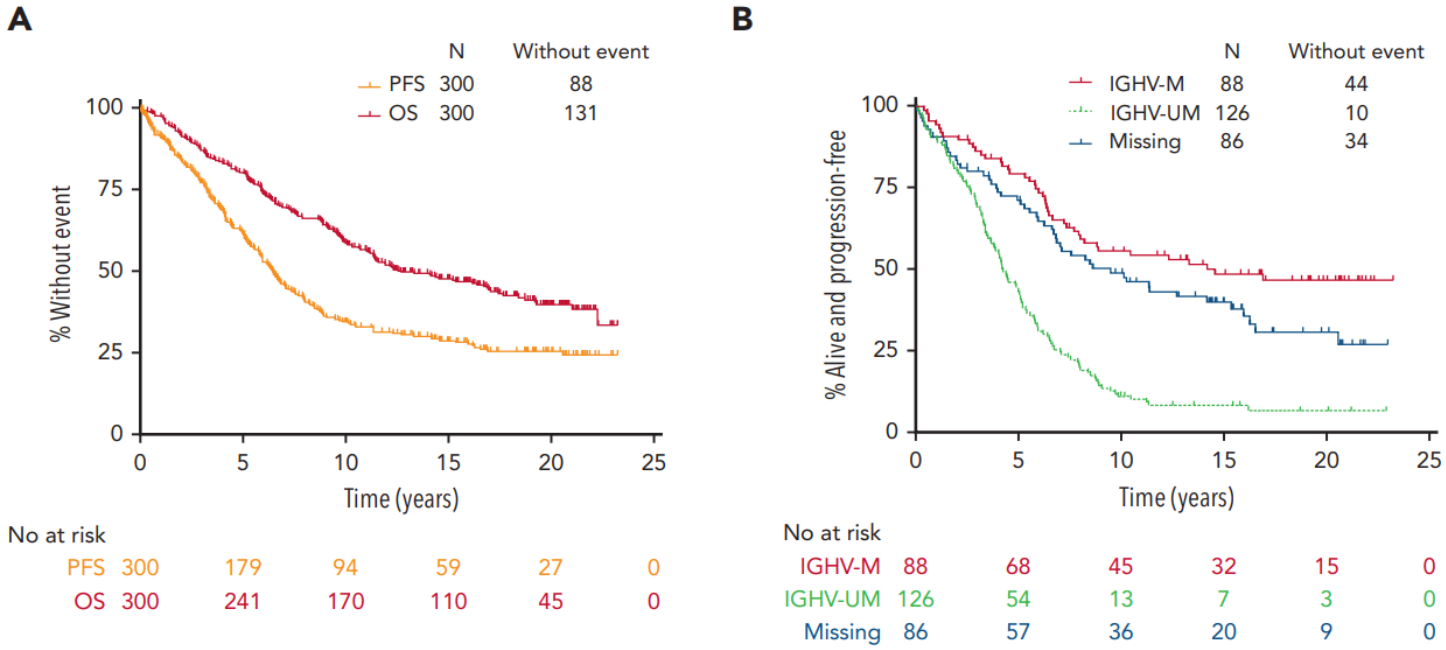
Matthew S. Davids | Dana-Farber Cancer Institute

"So now when I sit with a young patient with CLL and he or she asks what I would choose for frontline therapy […] FCR remains a reasonable choice […] But given the **risks of secondary MDS/ AML, prolonged myelosuppression, and infectious complications**, my usual answer now is that I would choose a targeted therapy regimen and hope that we will continue to develop new approaches to add to the impressive array of novel therapies we already have available for patients with CLL."



Davids M.S. et al., blood 2023

Sustained remission after FCR (19y-LTFU) but…



32% of patients develop secondary malignancies, 6% MDS/AML

Thompson P.A. et al., blood 2023

CLL8

Complications of FCR therapy

- Treatment- related myeloid neoplasms (tMNs)
  - 1 % to 5 % of patients
  - DNA damage created by alkylating agents
  - median time to onset of 40 months
- Prolonged Neutropenia
  - More severe in reduced renal function
- Infection
  - older patients are prone to neutropenia (85 % with grade ≥ 3) and infections (38 % with grade ≥ 3)

CLL13: SPMs and RT

AE, n	CIT (n=216)	VenR (n=237)	VenO (n=228)	IVO (n=231)
Second primary malignancies*	**56**	**30**	**31**	**37**
Solid tumors	19	13	15	18
Hematologic malignancies	4	2	0	8
Non-melanoma skin cancer	33	15	16	11
Richter transformation	**6**	**5**	**7**	**3**

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

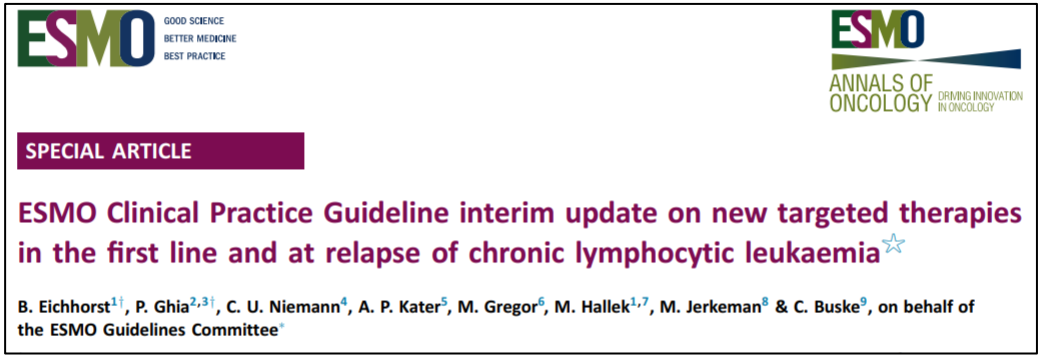
Median follow-up: 50.7 months.
* Overall cases of secondary primary malignancies does not include benign tumors and Richter transformation; SPMs counted as cases, not as patients affected.
CIT, chemoimmunotherapy; IVO, ibrutinib + venetoclax + obinutuzumab; O, obinutuzumab; R, rituximab; Ven, venetoclax.

Fürstenau M, *et al. Lancet Oncol* 2024; **25**:744–759 (incl. suppl.).

Why CIT is unable in 2024 ?

- Efficacy of target therapies
- Better OS of target therapies
- Secondary neoplasia
- EVEN IF……

Chemoimmunoterapia: ESMO guidelines 2024



ESMO GOOD SCIENCE BETTER MEDICINE BEST PRACTICE

ESMO ANNALS OF ONCOLOGY DRIVING INNOVATION IN ONCOLOGY

SPECIAL ARTICLE

ESMO Clinical Practice Guideline interim update on new targeted therapies in the first line and at relapse of chronic lymphocytic leukaemia ☆

B. Eichhorst[1†], P. Ghia[2,3†], C. U. Niemann[4], A. P. Kater[5], M. Gregor[6], M. Hallek[1,7], M. Jerkeman[8] & C. Buske[9], on behalf of the ESMO Guidelines Committee*

Time-limited chemoimmunotherapy (CIT) such as fludarabine-cyclophosphamide-rituximab (FCR) **should only be considered** for patients with a **good genetic risk profile** [defined as mutated immunoglobulin heavy chain variable (IGHV) status and no TP53 aberrations] and, in addition, a non-complex karyotype (defined by less than five aberrations if complex karyotype was evaluated) **and if targeted therapies are not reimbursed**. Progression-free survival (PFS) of other CIT regimens (bendamustine-rituximab, chlorambucile-obinutuzumab or chlorambucile-rituximab) is shorter when compared with time-limited targeted agents; but this has not yet been shown for OS in most studies.

eUpdate ESMO Guidelines Commitee Ann Oncol 2024

National Comprehensive Cancer Network®

- Conditioning regimen for ALLO-TMO in HR patients (TP53 o del17p) with available donor in second line
- Chemo as linfodepletive therapy before CAR-T approved in March 2024 FDA
- Palliative therapies as CHL or CTX

Khouri et al., Blood 2014
Khouri et al., BMT 2017
Geyer MB et al., JCI Insight. 2019

EBMT registry data 2008:

Allo-HSCT total: 10782

Allo-HSCT CLL: 366 (3,4%)

EBMT registry data 2017:

Allo-HSCT total: 18281

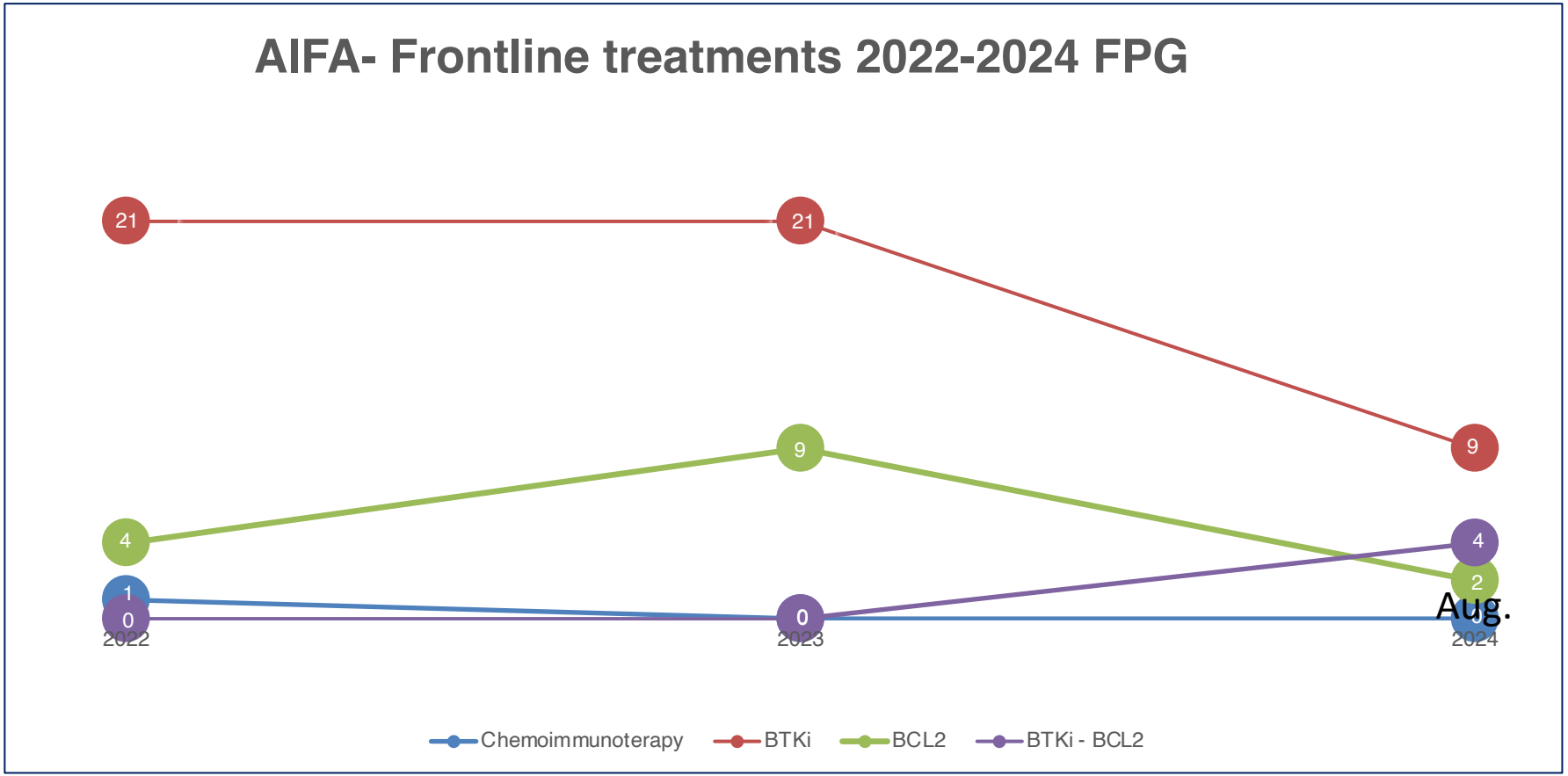
Allo-HSCT CLL: 230 (1,2%)

EBMT registry data 2022:

Allo-HSCT total: 19011

Allo-HSCT CLL: 157 (0,8%)

Gratwohl et al, BMT 2010
Passweg et al, BMT 2019
Passweg et al, BMT 2024


AIFA- Frontline treatments 2022-2024 FPG
21
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2022
2023
2024
Aug.
Chemoimmunoterapy
BTKi
BCL2
BTKi - BCL2

Grazie per l'attenzione

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