Andrea Visentin MD PhD
Università degli Studi di Padova

Il profilo di tollerabilità delle terapie target

LEUCEMIA LINFATICA CRONICA:
L'INNOVATIVITÀ TERAPEUTICA ED OLTRE...

28-29 MARZO 2023 BOLOGNA ROYAL HOTEL CARLTON

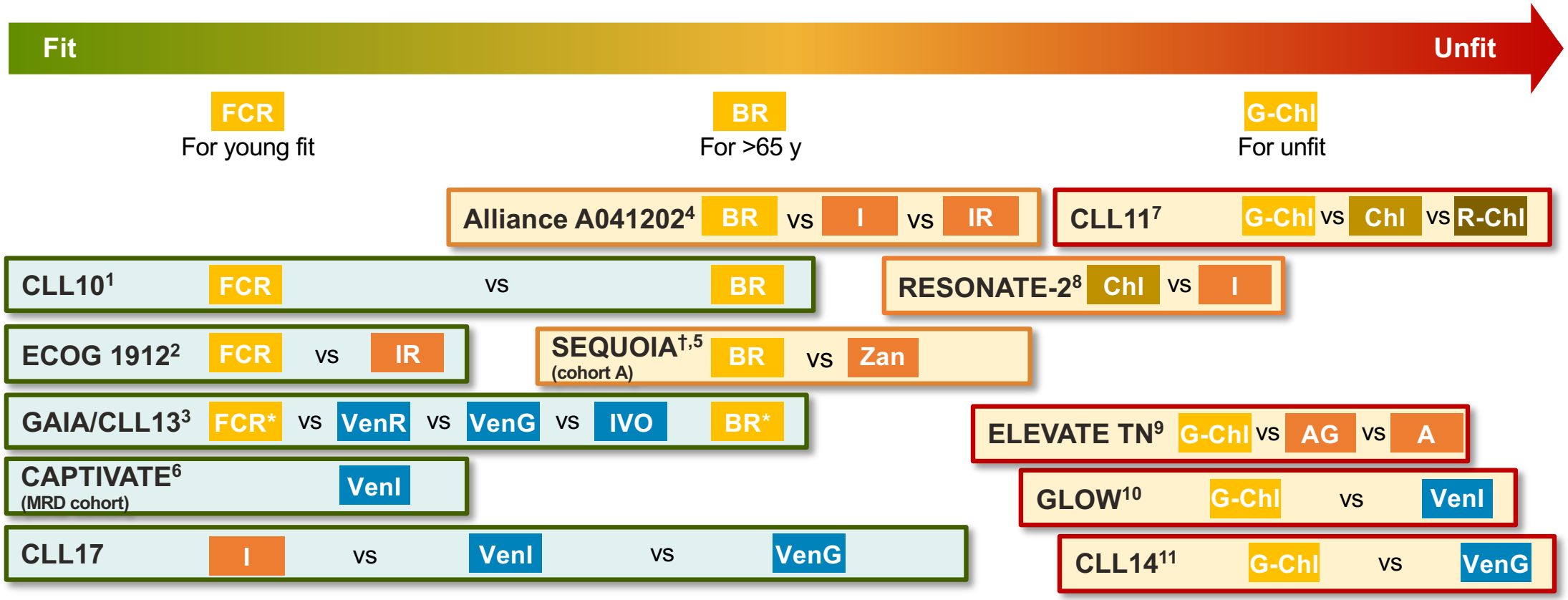
Considerations to optimize the selection of CLL treatment

- ★ Patient fitness/comorbidities
- ★ Fixed treatment duration vs continuous treatment
- ★ AE profiles
- Tolerability/discontinuation rates due to AEs
- Patient preference
- Cytogenetics: del(17p)/*TP53* mutated, IGHV mutational status ★
- Potential for deep responses (uMRD)
- Availability/accessibility, funding

IGHV, immunoglobulin heavy-chain variable region genes.

Brown J. *Hematology Am Soc Hematol Educ Program* 2018; **2018:**248–255;
Eichhorst B, *et al. Ann Oncol* 2021; **32:**23–33;
Wierda WG & Tambaro FP. *Blood* 2020; **135:**1421–1427.

Key phase 2/3 1L CLL clinical trials



IVO e VenI non autorizzate dall'Agenzia Regolatoria

1. Eichhorst, *Lancet Oncol* 2016; 2. Shanafelt, *Blood* 2022; 3. Eichhorst, EHA 2022; 4. Woyach, ASH 2021; 5. Tam, ASH 2021; 6. Wierda, *J Clin Oncol* 2021; 7. Goede, EHA 2018; 8. Barr, *Blood* 2022; 9. Sharman, EHA 2022; 10. Kater, *NEJM Evid* 2022; 11. Al-Sawaf, *J Clin Oncol* 2021.

Key clinical trials on BTKi 1L

Study	Arms	Treatment duration (6m 1y to PD)	Grade 3–4 AEs* Neutropenia %	Infections, %	Febrile neutropenia %	TLS, %	Atrial fibrillation, %	Bleeding, %	Hypertension %	SPM, %	AE-related treatment d/c rates
RESONATE-2[1–3] *f/u: up to 8 y* *f/u OClb: 18.4 mo*	I Clb		13† 18†	–	2† 2†	–	5 –	7‡ 2‡	8§ 0†	–	24 23
ALLIANCE 202[4,5] *f/u: 38 mo*	IR I BR		22‖ 15‖ 40‖	19 19 13	1§ 2§ 7§	–	6§ 9 3§	3 2 0	34 29§ 15	8 4 3§	14 10
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1.Burger JA, *et al*. *N Engl J Med* 2015; **373:**2425–2437; 2. Burger JA, *et al*. *Leukemia* 2020; **34:**787–798; 3. Barr PM, *et al*. *Blood* 2022; ePub ahead of print (incl. suppl.); 4. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528; 5. Ruppert AS, *et al. J Clin Oncol* 2020; **38**(Suppl)**:**Abstract e20004; 6. Shanafelt TD, *et al. Blood* 2022; ePub ahead of print (incl. suppl.); 7. Sharman JP, *et al. Leukemia* 2022; **36:**1171–1175; 8. Tam CS, *et al.* ASH 2021. Abstract 396(Oral).

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Key clinical trials on BTKi 1L

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All-grade AEs for BTKi arms:[1–8]

- **Atrial fibrillation range: 3.3–17%**
- **Bleeding range: ~23–49.4%**
- **Hypertension range: 7.3–54%**

1.Burger JA, *et al*. *N Engl J Med* 2015; **373:**2425–2437; 2. Burger JA, *et al*. *Leukemia* 2020; **34:**787–798; 3. Barr PM, *et al*. *Blood* 2022; ePub ahead of print (incl. suppl.); 4. Woyach JA, *et al. N Engl J Med* 2018; **379:**2517–2528; 5. Ruppert AS, *et al. J Clin Oncol* 2020; **38**(Suppl)**:**Abstract e20004; 6. Shanafelt TD, *et al. Blood* 2022; ePub ahead of print (incl. suppl.); 7. Sharman JP, *et al. Leukemia* 2022; **36:**1171–1175; 8. Tam CS, *et al.* ASH 2021. Abstract 396(Oral).

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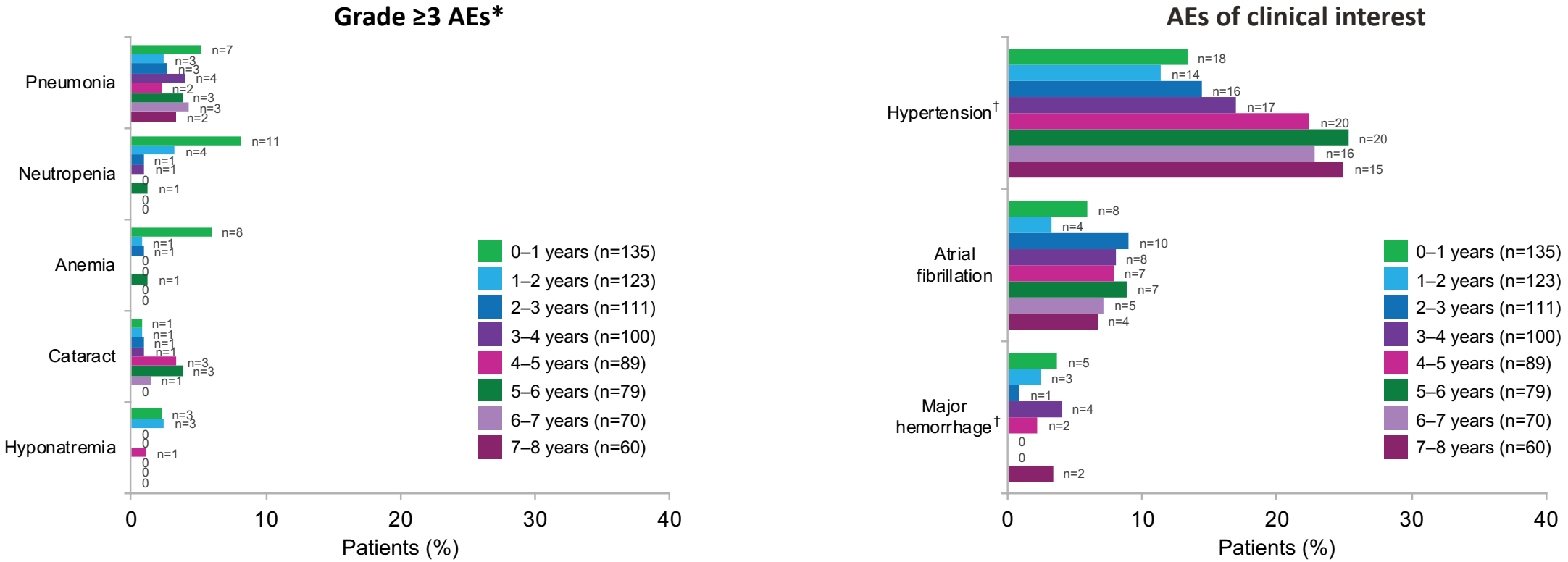
Adverse events over time with continuous ibrutinib therapy in 1L CLL

RESONATE-2: Median follow-up, 82.7 months; N=269



Barr PM, *et al. Blood* 2022; ePub ahead of print.

Ibrutinib - hypertension

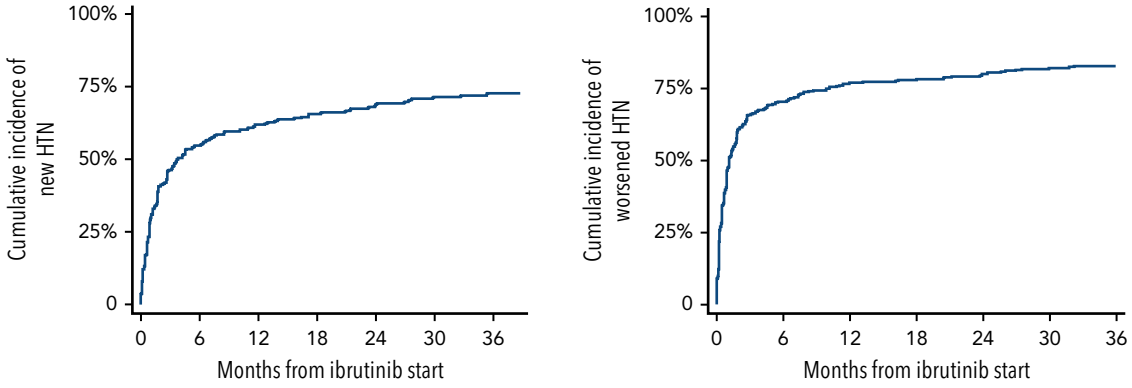
CLINICAL TRIALS AND OBSERVATIONS

Hypertension and incident cardiovascular events following ibrutinib initiation

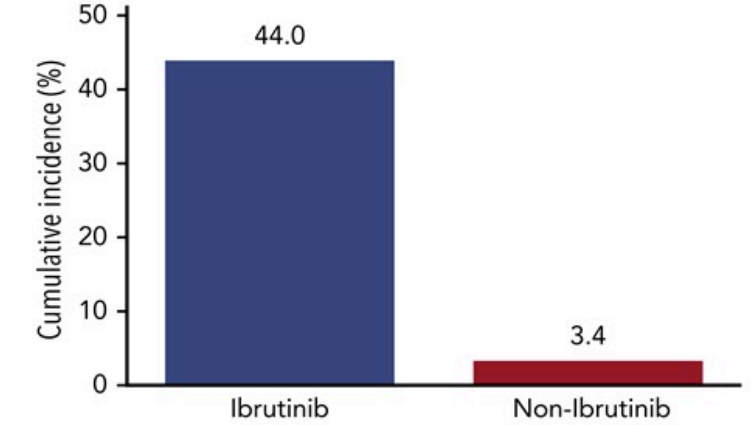
Blood (2019) 134 (22): 1919–1928.

Tyler Dickerson,[1] Tracy Wiczer,[1] Allyson Waller,[1] Jennifer Philippon,[1] Kyle Porter,[2] Devin Haddad,[3] Avirup Guha,[3] Kerry A. Rogers,[4] Seema Bhat,[4] John C. Byrd,[4] Jennifer A. Woyach,[4,*] Farrukh Awan,[4,*] and Daniel Addison[3,*]

Overall, 78.3% of ibrutinib users developed new or worsened HTN over a median of 30 months. New HTN developed in 71.6% of ibrutinib users, with a time to 50% cumulative incidence of 4.2 months.



In a multivariate model new or worsened HTN was associated with increased major adverse cardiovascular events (MACEs, including arrhythmia, myocardial infarction, stroke, heart failure, and cardio-vascular death) (HR, 2.17; 95% CI, 1.08-4.38). However, anti-hypertensive initiation was associated with a lower risk of a MACE (HR, 0.40; 95% CI, 0.24-0.66).



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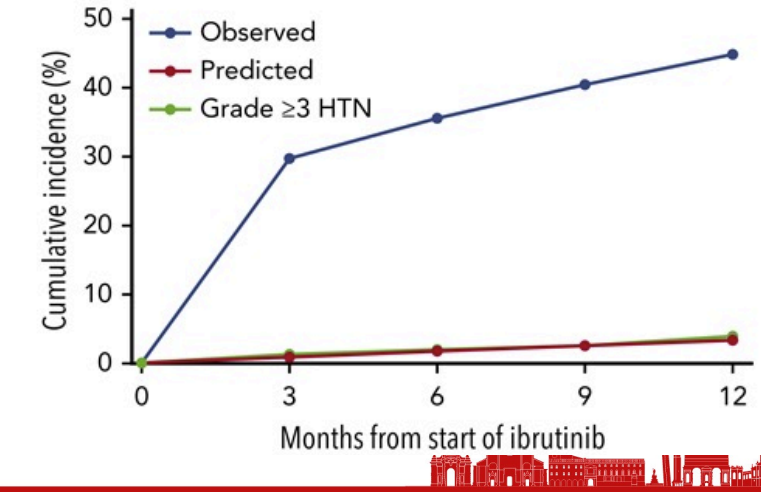
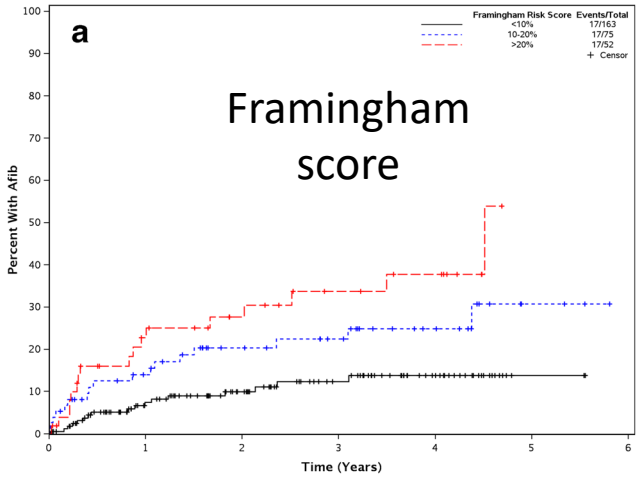
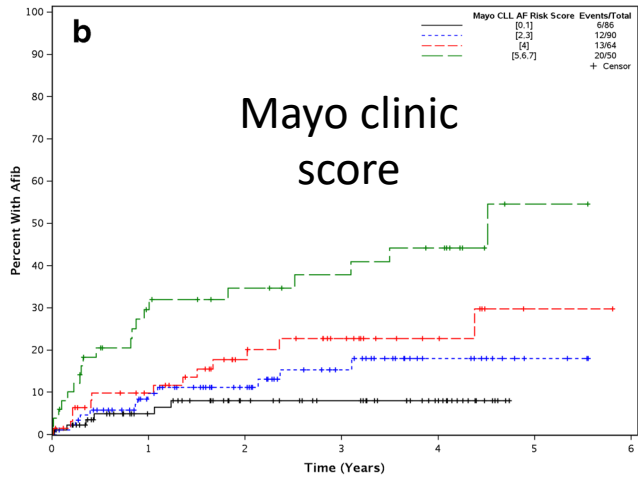


IBRUTINIB – ATRIAL FIBRILLATION





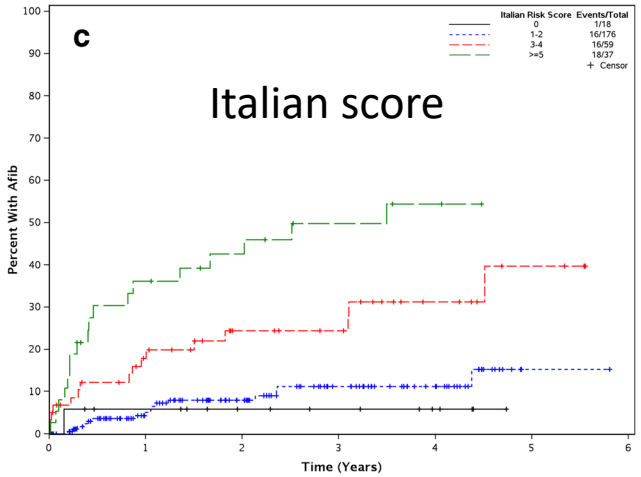


Table 4 Comparison of treatment-emergent AF risk prediction models (n = 290)

Model	N (%)	Hazard ratio (95% CI)	p value
Framingham risk*			
< 10%	163 (56)	Reference	
10–20%	75 (26)	2.2 (1.1–4.3)	*0.02*
> 20%	52 (18)	3.4 (1.7–6.5)	*0.0003*
Mayo CLL AF Score**			
0-1	86 (30)	Reference	
2–3	90 (31)	1.9 (0.7–5.1)	0.20
4	64 (22)	2.9 (1.1–7.7)	*0.03*
5–7	50 (17)	6.4 (2.6–16.0)	*< 0.0001*
Italian AF risk score***			
0	18 (6)	Reference	
1–2	176 (61)	1.7 (0.2–13.0)	0.64
3–4	59 (20)	5.2 (0.7–41.0)	0.12
> = 5	37 (13)	10.8 (1.4–85.3)	*0.02*

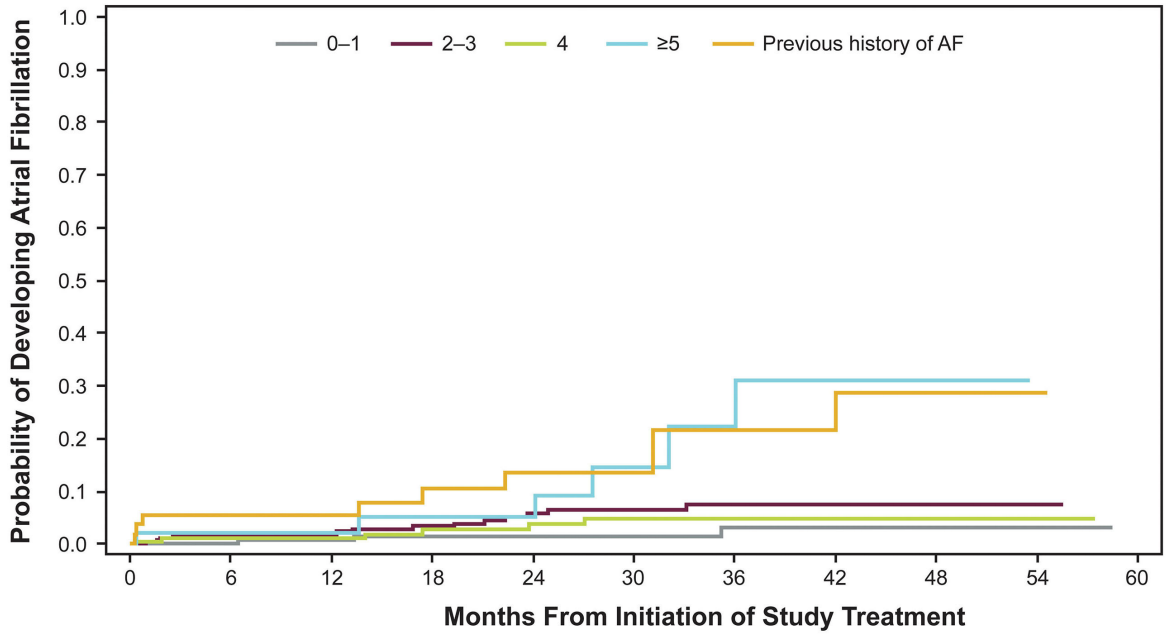
Based on lower Akaike information criteria (AIC), the Italian score (AIC = 513) was best able to predict risk of treatment-emergent AF versus the Mayo CLL risk score (AIC = 524) and the Framingham risk score (AIC = 530).

Archibald W, Annals of Hematoly 2020

ACALABRUTINIB – ATRIAL FIBRILLATION

Study name	Study description	Number of patients[a]
ACE-CL-001 (NCT02029443)	Ph I/II study of acalabrutinib in patients with CLL	301; TN/RR: 112/189
ACE-CL-007 (NCT02475681; ELEVATE-TN)[b]	Ph III study of acalabrutinib ± O *vs* C+O in TN CLL	224; all TN
ACE-CL-309 (NCT02970318; ASCEND)	Ph III study of acalabrutinib *vs* IdR or BR in RR CLL	189; all RR
15-H-0016 (NCT02337829)	Ph II study of acalabrutinib in patients with RR or TN with del(17p) CLL	48; TN/RR: 16/32

762 patients
median age 67yy (32-89)
BMI 26,7kg7m2 (16-49)



Number of Patients at Risk

Shanafelt risk score	0–1	171	142	132	99	85	74	60	41	13	3
	2–3	297	236	222	173	153	113	81	55	26	2
	4	190	162	145	109	95	66	43	30	10	3
	≥5	48	36	32	29	23	12	9	4	2	0
Previous history of AF		56	43	40	32	29	23	16	11	5	1

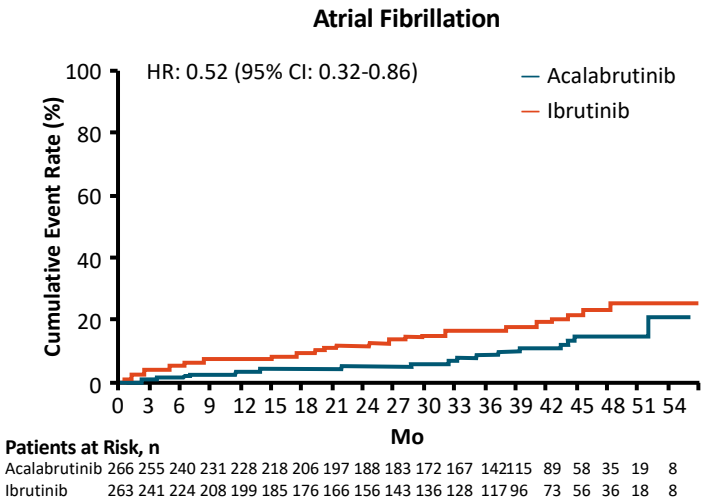
Brown J, Haematologicaa 2022

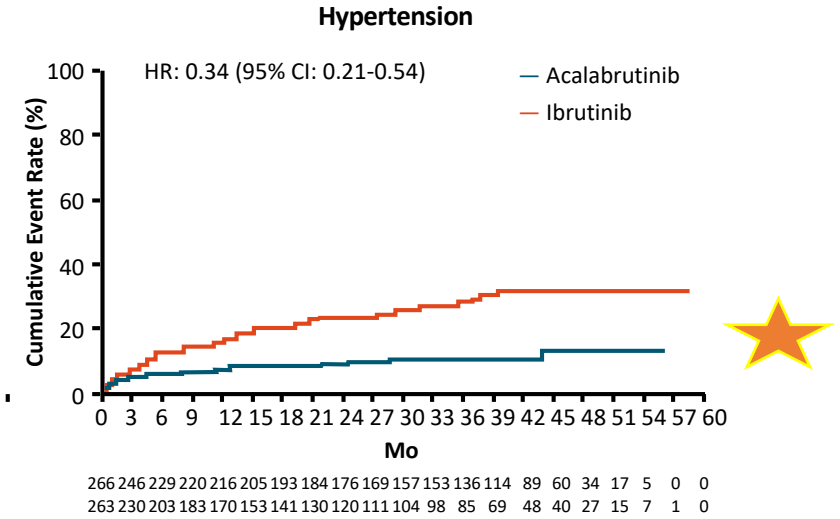
1st vs 2nd generation BTKi R/R

atrial fibrillation

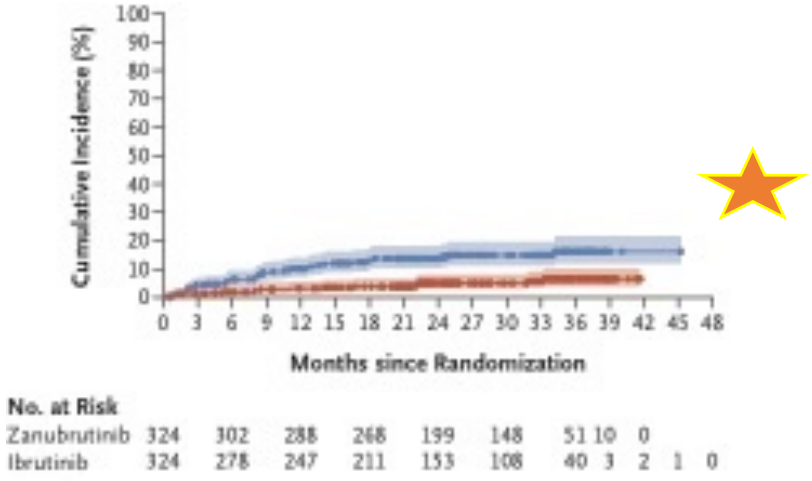
hypertension

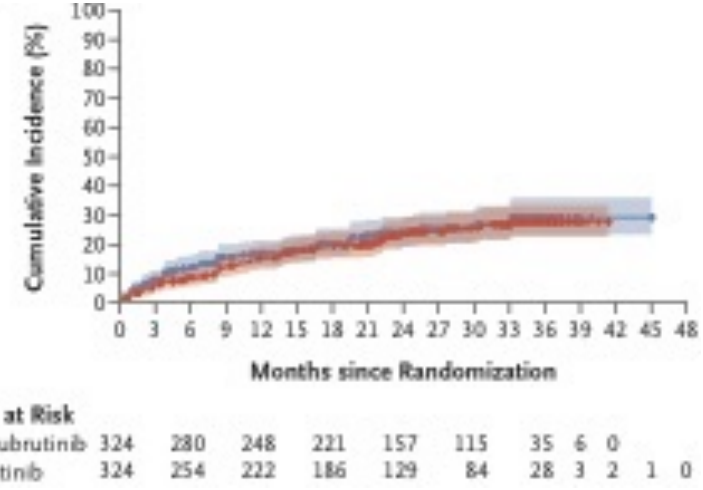
ACALABRUTINIB





ZANUBRUTINIB





Byrd J, JCO 2021; Brown J, NEJM 2022

Key phase 2/3 clinical trials on BCL-2i 1L

Study	Arm	Treatment duration (6 12 15 24 to PD)	Grade 3–4 AEs*							SPM, %	AE-related treatment D/C rates
			Neutropenia %	Infections, %	Febrile neutropenia %	TLS, %	Atrial fibrillation, %	Bleeding, %	Hypertension %		
CLL14[1] *f/u: 28.1 mo*	VenG G-Chl		53 48	18 15	5 4	1† 2†	–	–	–	14‡ 10‡	16 15
CLL13[2] *f/u: 27.9 mo*	IVO VenG VenR FCR/BR	**	49 56 46 52	22 14 11 20	8 3 4 11	7§, ¶ 9§, ¶ 10§, ¶ 4§, ¶	3 0 1 1	2 1 1 1	–	2‖ – 2‖ –	12 6 6 15
GLOW[3] *f/u: 27.7 mo*	VenI G-Chl	††	35 50	15 11	2¶ 3¶	0 6	7 0	–	8 2	–	10 2
CAPTIVATE[4] (MRD cohort) *f/u: 31.3 mo*	VenI	VenI uMRD unconfirmed I mono ††	31¶ 35¶	16¶ 19¶	–	0	3¶ 3¶	3¶ 0¶	6¶ 10¶	–	4 6
CAPTIVATE[5] (FD cohort) *f/u: . 27.9mo*	VenI	††	33	8	0.6	0	1	1	6	-	5

† Any grade laboratory TLS; ‡ All grade, most frequently reported were basal cell carcinoma and squamous cell carcinoma; ‖ Secondary neoplasia during therapy until d84 after EoT, mostly nonmelanoma skin cancer; ¶ Grade ≥3 AEs; ** Continuation of ibrutinib up to C36 allowed if MRD still detectable;†† 3-month Ibr lead-in followed by 12 cycles of combination.

1. Fischer K, *et al*. *N Engl J Med* 2019; 380:2225–2236 (incl. appendix); 2. Eichhorst B, *et al*. ASH 2021. Abstract 71 (Oral); 3. Kater AP, *et al*. *N Engl J Med* 2022; ePub ahead of print; 4. Wierda WG, *et al*. *J Clin Oncol* 2021; 39:3853–3865. 5 Tam C, Blood 2022, 22 (139: 3278-3289

IVO e VenI non autorizzate dall'Agenzia Regolatoria

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CLL14: Grade 3/4 neutropenia

13% IB
8-yy FU

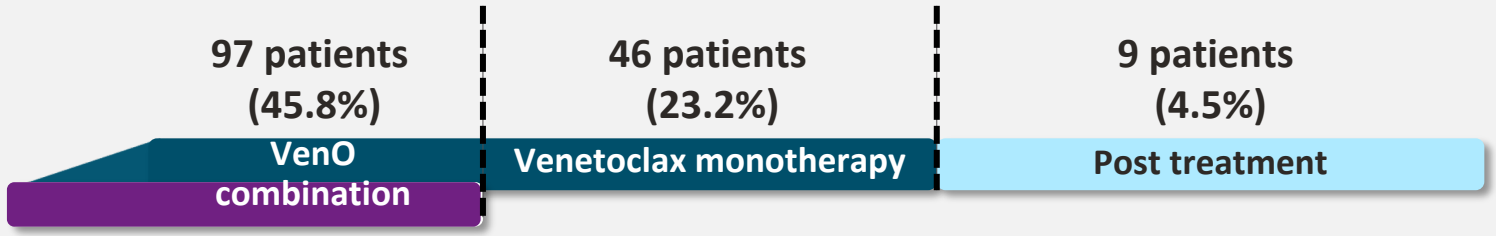
11% ACAL
4-yy FU

Select Grade 3/4 AEs[1]	VenO (N=212*)	OClb (N=214)
Neutropenia, n (%)	112 (52.8)	103 (48.1)
Febrile neutropenia, n (%)	11 (5.2)	8 (3.7)

Median (range) duration of Grade 3 and 4 neutropenia[†,2]

VenO arm	OClb arm
22 days (2–363)	22 days (2–456)

In the VenO arm, most Grade 3 and 4 neutropenia occurred during the combination period[3]



The rates of neutropenia and febrile neutropenia were comparable across treatment arms;[1] median duration of neutropenia[†] was similar between arms (22 days);[2] G-CSF was administered in 43.5% and 45.8% of patients in the VenO and OClb arms, respectively[1]

Key phase 2/3 clinical trials on BCL-2i 1L

Study	Arm	Treatment duration (6 12 15 24 to PD)	Grade 3–4 AEs*								
			Neutropenia %	Infections, %	Febrile neutropenia %	TLS, %	Atrial fibrillation, %	Bleeding, %	Hypertension %	SPM, %	AE-related treatment D/C rates
CLL14[1] *f/u: 28.1 mo*	VenG G-Chl		53 48	18 15	5 4	1† 2†	0	0	0	14‡ 10‡	16 15
CLL13[2] *f/u: 27.9 mo*	IVO VenG VenR FCR/BR	**	49 56 46 52	22 14 11 20	8 3 4 11	7§, ¶ 9§, ¶ 10§, ¶ 4§, ¶	3 0 1 1	2 1 1 1	0	2‖ – 2‖ –	12 6 6 15
GLOW[3] *f/u: 27.7 mo*	VenI G-Chl	††	35 50	15 11	2¶ 3¶	0 6	7 0	–	8 2	–	10 2
CAPTIVATE[4] (MRD cohort) *f/u: 31.3 mo*	VenI	VenI uMRD unconfirmed I mono ††	31¶ 35¶	16¶ 19¶	0	0	3¶ 3¶	3¶ 0¶	6¶ 10¶	–	4 6
CAPTIVATE[5] (FD cohort) *f/u: . 27.9mo*	VenI	††	33	8	0.6	0	1	1	6	-	5

† Any grade laboratory TLS; ‡ All grade, most frequently reported were basal cell carcinoma and squamous cell carcinoma; ‖ Secondary neoplasia during therapy until d84 after EoT, mostly nonmelanoma skin cancer; ¶ Grade ≥3 AEs; ** Continuation of ibrutinib up to C36 allowed if MRD still detectable;†† 3-month Ibr lead-in followed by 12 cycles of combination.

1. Fischer K, *et al*. *N Engl J Med* 2019; 380:2225–2236 (incl. appendix); 2. Eichhorst B, *et al*. ASH 2021. Abstract 71 (Oral); 3. Kater AP, *et al*. *N Engl J Med* 2022; ePub ahead of print; 4. Wierda WG, *et al*. *J Clin Oncol* 2021; 39:3853–3865. 5 Tam C, Blood 2022, 22 (139: 3278-3289

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TLS mitigation measures implemented in 1L and R/R CLL clinical studies, successfully mitigate the risk of TLS with venetoclax

AbbVie clinical trials assessment

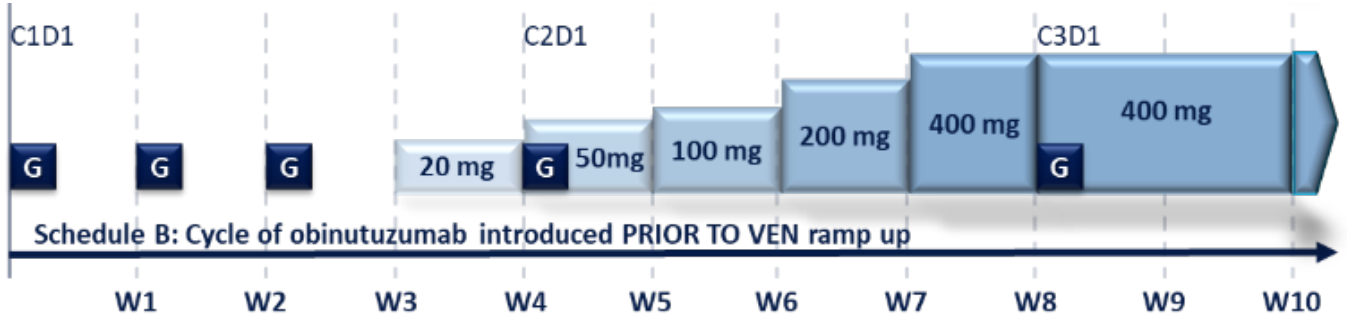
	TLS Risk			Total
	Low	Medium	High	
Treatment-naive CLL, n	**206**	**81**	**17**	**304**
TLS (any AE), n (%)	1 (0.5)	0	1 (5.9)	2 (0.7)
Clinical TLS*	1 (0.5)	0	0	1 (0.3)
Labs meeting Howard criteria†, n (%)	7 (3.4)	3 (3.7)	3 (17.6)	13 (4.3)
R/R CLL, n	**215**	**382**	**203**	**834‡**
Any AE of TLS, n (%)	0	8 (2.1)	10 (4.9)	18 (2.2)
Clinical TLS*	0	3 (0.8)	1 (0.5)	4 (0.5)
Labs meeting Howard criteria†, n (%)	2 (0.9)	12 (3.1)	22 (10.8)	37 (4.4)
Total patients, n	**421**	**463**	**220**	**1,138‡**
Any AE of TLS, n (%)	1 (0.2)	8 (1.7)	11 (5.0)	20 (1.8)
Clinical TLS*	1 (0.2)	3 (0.6)	1 (0.5)	5 (0.4)
Labs meeting Howard criteria†, n (%)	9 (2.1)	15 (3.2)	25 (11.4)	50 (4.4)

* Clinical TLS was defined per Howard criteria. † Includes both labs meeting Howard criteria without a reported AE and with reported AEs. These were compiled by AbbVie. ‡ TLS risk was calculated for studies M15-550 and M15-889 based on ALC and LN sizes as a result of differences in the specification of TLS risk categories in the eCRFs for these studies compared with the other studies included in this summary. Risk for some patients could not be determined, so the sum of the Ns across risk categories is less than the total N in this summary. ALC, absolute lymphocyte count; eCRF electronic case report form; LN, lymph node; TLS, tumor lysis syndrome.

Seymour J, *et al*. ASH 2020. Abstract 2231 (Poster).

Obinutuzumab infusion related reactions (IRRs)

IRR	G-CHL	FCR/BR	RVe	GVe	GIVe
CLL11 any grade G3 or higher	 221 (66%) **67 (20%)**	 -	 -	 **-**	 -
CLL14 any grade G3 or higher	 107 (55%) 22 (11%)	 -	 -	 96 (44%) **19 (9%)**	 -
CLL13 any grade G3 or higher	 -	 70 (32.4%) 12 (5.6%)	 82 (34.6%) 18 (7.6%)	 119 (52.2%) **10 (4.3%)**	 53 (22.9%) 10 (4.3%)



Flinn IW, *et al. Blood* 2019;

Eichhorst B, abstract 71, ASH 2021

Prophylaxis for obinutuzumab-related IRRs

Oral acetaminophen and antihistamine	30–60 min before first and subsequent infusions
Corticosteroids*	60 min before first C1D1/2 infusion(s) At subsequent infusions, administer if prior Grade 3 IRR or if ALC >25×10^9/L or at investigator's discretion

The first dose is infused at a reduced rate of 25 mg/hour over 4 hours (escalated in increments of 50 mg/hour every 30 minutes to 400 mg/hour†) and can be split over 2 days (100/900 mg)

If IRR develops, infusion should be temporarily interrupted/slowed down and concomitant medication administered as appropriate. Upon resolution, the infusion will resume at half of the previous rate

* Prednisolone or equivalent such as dexamethasone or methylprednisolone. Hydrocortisone should not be used;
† In the absence of IRRs/sensitivity; ‡ ALC ≥25×109/L or bulky lymphadenopathy.
ALC, absolute lymphocyte count; IRR, infusion-related reaction

Fischer K, et al. N Engl J Med 2019; 380:2225–2236 (Ind. appendix).

Key phase 2/3 clinical trials on BCL-2i 1L

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CLL14[1] *f/u: 28.1 mo*	VenG		53	18	5	1†	0	0	0	14‡	16
	G-Chl		48	15	4	2†				10‡	15
CLL13[2] *f/u: 27.9 mo*	IVO	**	49	22	8	7§, ¶	3	2	0	2‖	12
	VenG		56	14	3	9§, ¶	0	1		–	6
	VenR		46	11	4	10§, ¶	1	1		2‖	6
	FCR/BR		52	20	11	4§, ¶	1	1		–	15
GLOW[3] *f/u: 27.7 mo*	VenI	††	35	15	2¶	0	7	–	8	–	10
	G-Chl		50	11	3¶	6	0		2		2
CAPTIVATE[4] (MRD cohort) *f/u: 31.3 mo*	VenI	VenI; uMRD unconfirmed; I mono; ††	31¶	16¶	0	0	3¶	3¶	6¶	–	4
			35¶	19¶			3¶	0¶	10¶		6
CAPTIVATE[5] (FD cohort) *f/u: . 27.9mo*	VenI	††	33	8	0.6	0	1	1	6	-	5

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CONCLUSIONs

- The knowledge of the safety profile of targeted drugs plays a pivotal role in the clinical practice;
- Integration of the safety profile with the biological markers allow to personalized the treatment;
- The optimal strategies to prevent AEs (such as TLS and IRR) decrease the rate of discontinuation, allow full-therapy exposure and, likely, to reach a better outcome.

Thank you for the attention!