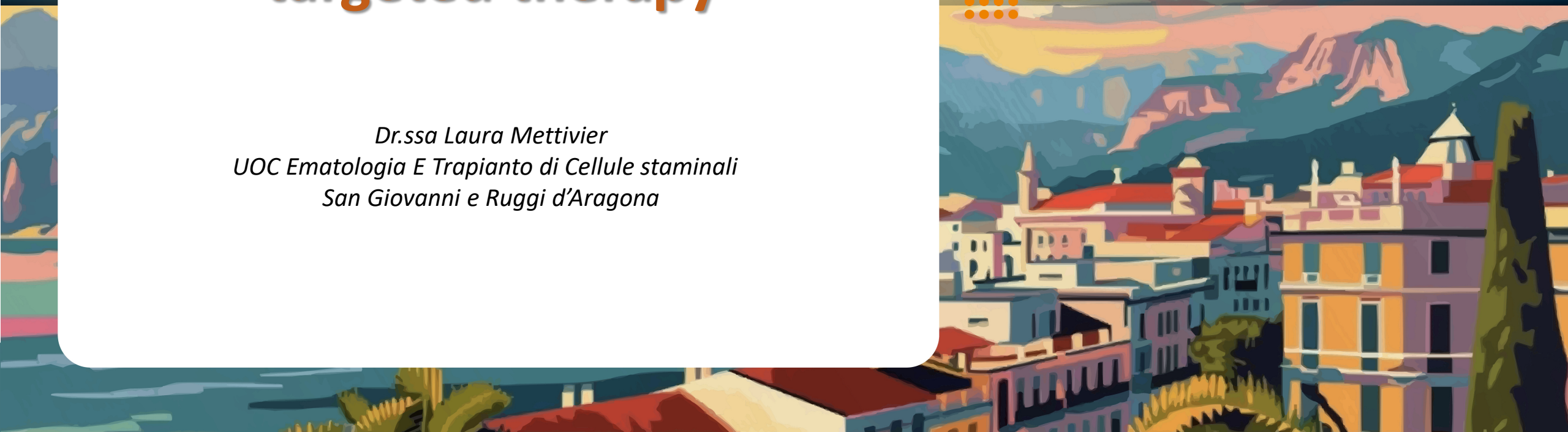
Management of long-term survivors in the era of targeted therapy

Dr.ssa Laura Mettivier
UOC Ematologia E Trapianto di Cellule staminali
San Giovanni e Ruggi d'Aragona

COACHES Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

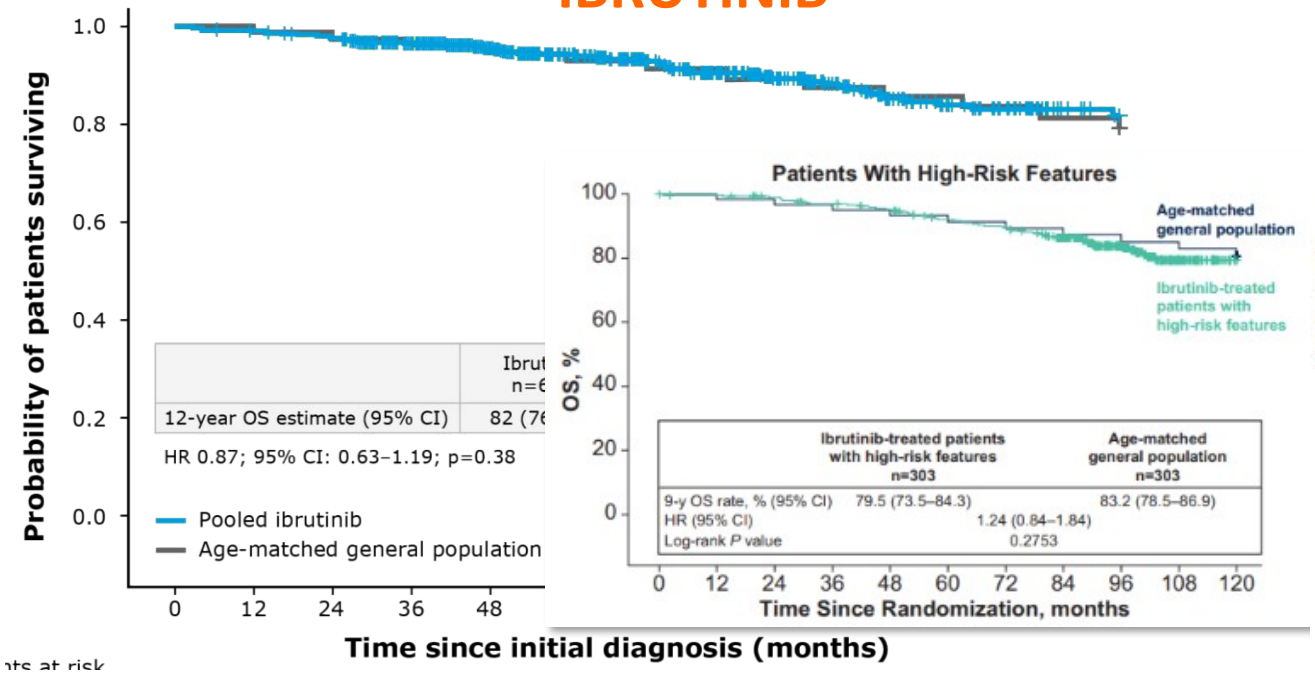


Disclosures of Name Surname

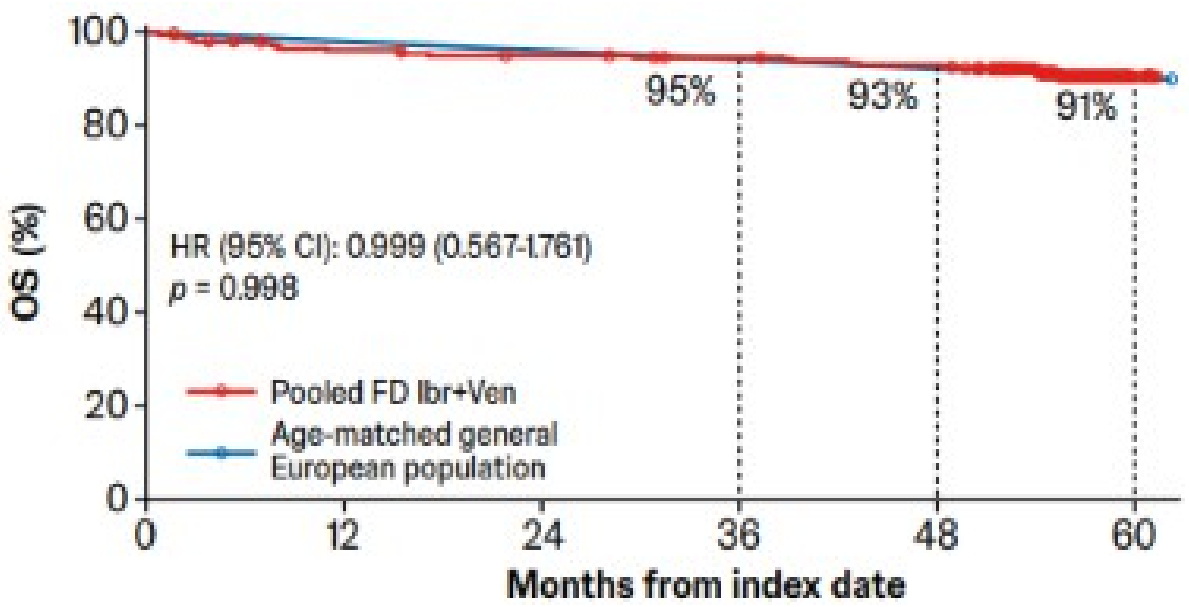
Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Jhonson&Jhonson						+	
Astrazeneca			+				

CLL: unprecedented responses using novel targeted therapies

IBRUTINIB



IBRUTINIB + VENETOCLAX



OS estimates in patients treated with ibrutinib are **SIMILAR** to **age-matched patients in the general US population**

OS estimates are **comparable** between the pooled Ibr+Ven–treated patients and the **age-matched general European population**

Ghia et al., Poster presented at the American Society of Hematology (ASH) 64th Annual Meeting & Exposition; December 10-13, 2022;l

Initiating First-Line Fixed-Duration Ibrutinib and Venetoclax in Patients With Chronic Lymphocytic Leukemia Improves Overall Survival Outcomes to Rates Approximating an Age-Matched General European Population

Conclusions:

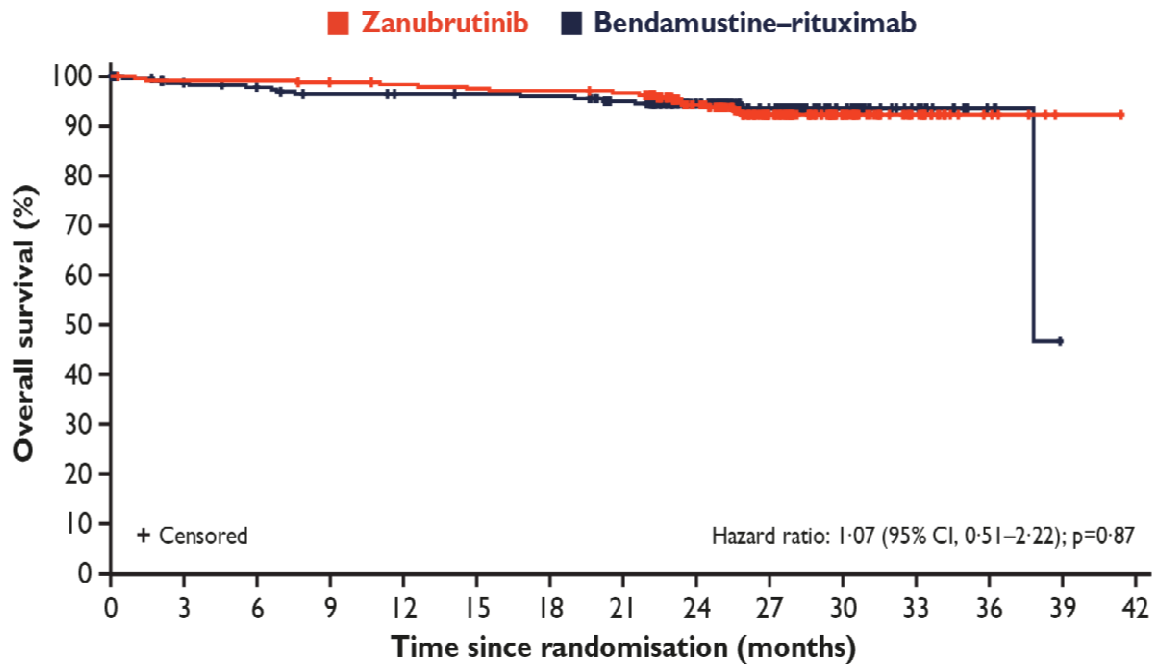
- This pooled analysis showed that **overall survival rates for patients with CLL treated with ibrutinib+venetoclax in the first-line setting were comparable to an age-matched general European population**
- Comparable overall survival rates versus the respective age-matched general European population were observed for subpopulation of patients **aged ≥ 65 years and < 65 years**
- Overall survival rates were also similar to the age-matched general European population, **regardless of IGHV mutation status**

Ghia, ASH 2024

CLL: unprecedented responses using novel zanubrutinib in high-risk patients

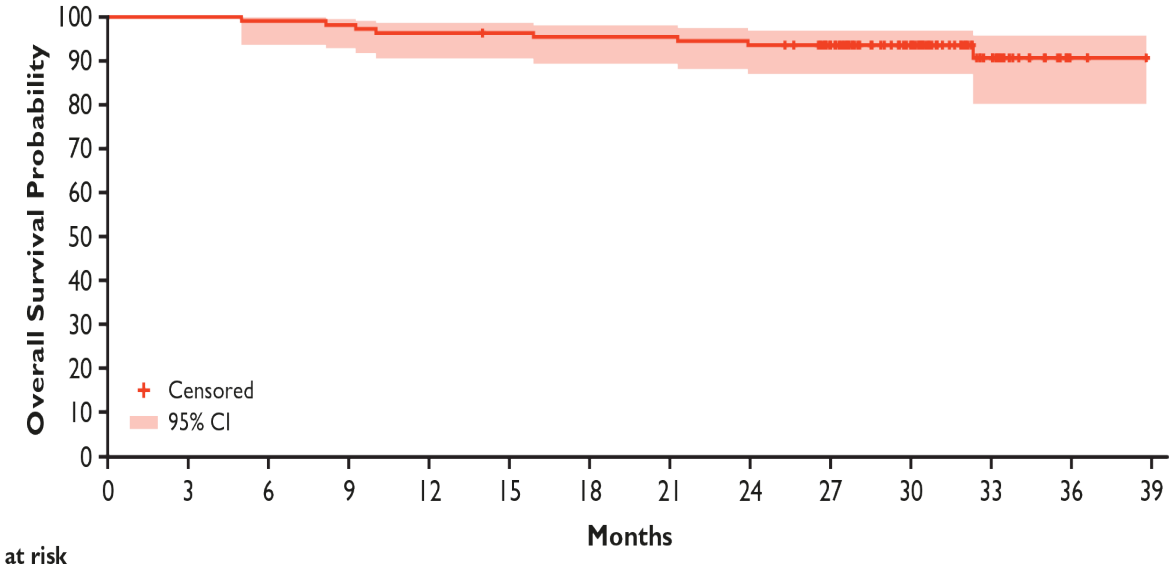
SEQUOIA: 5-year follow up

WITHOUT del(17p)



60-month **OS estimates 85.8%**

WITH del(17p)



24-month **OS estimates** are **93.6%**

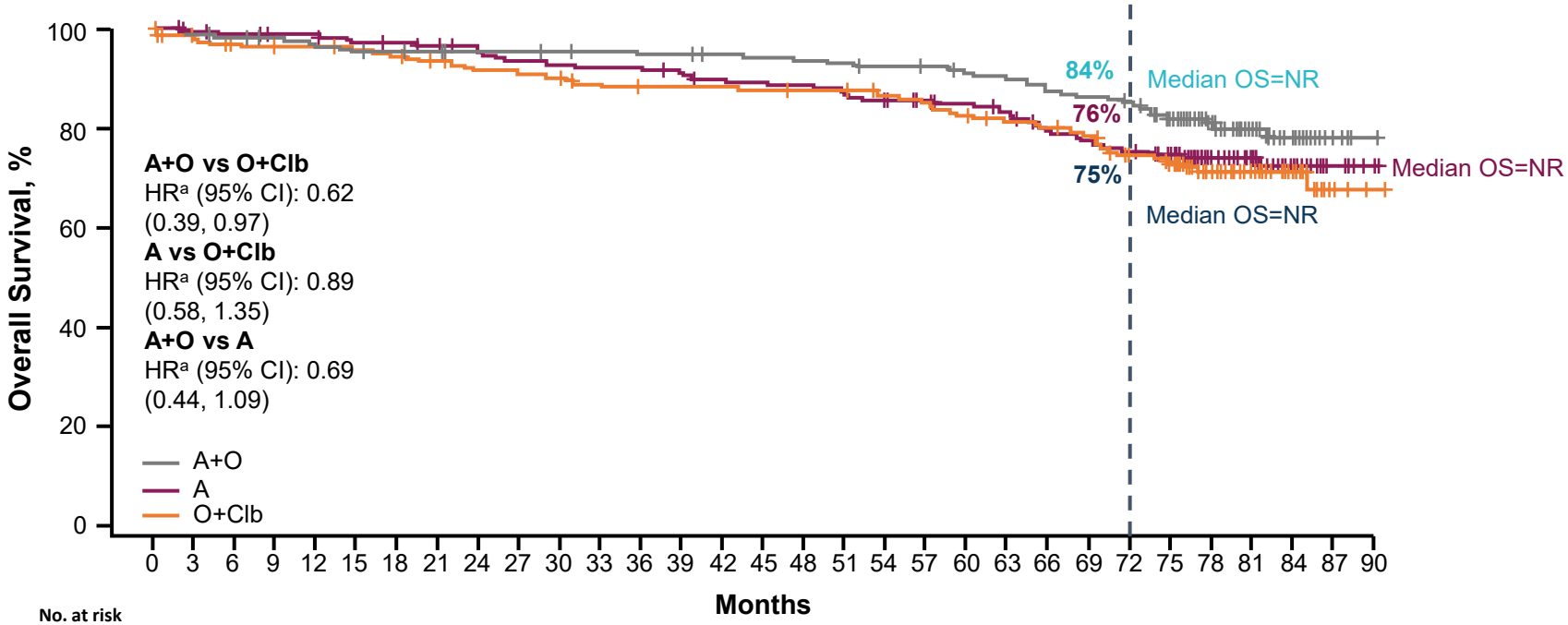
Conclusions:

SEQUOIA: 5-year follow up

- With a median study follow-up of 61.2 months, zanubrutinib has been shown to offer a sustained PFS benefit vs BR in treatment-naive patients with CLL/SLL, with a 71% reduction in risk of progression or death
- PFS benefit was consistent irrespective of IGHV status. Similarly, in prior reports, data from cohort 2 from SEQUOIA in patients with del(17p)/TP53 mutation showed an estimated 42-month rate of 79.4%, which was similar to PFS rates in those without this high-risk feature. This suggests that treatment with zanubrutinib may overcome negative prognostic factors such as IGHV and del(17p)/TP53.
- High CR/CRi rates in the zanubrutinib arm, 20.7% (95% CI: 15.8, 26.4), that increased over the course of the study are the highest reported with BTK inhibitor monotherapy
- Zanubrutinib was well tolerated over this extended treatment period, with low rates of atrial fibrillation/flutter, infections, and AEs that limit daily living activities such as GI toxicities
- The cumulative incidence of hypertension and atrial fibrillation/flutter remain low and are comparable to the background incidence in this patient population, which was observed in the BR arm
- The results of this extended follow-up in the SEQUOIA study support the use of Zanubrutinib as a standard first-line treatment option for patients regardless of disease risk status

ACALABRUTINIB TN

Overall Survival



No. at risk

A+O	179	178	175	173	170	168	167	165	164	164	163	162	161	161	159	158	157	155	154	153	148	147	142	141	133	105	63	41	21	4	0
A	179	175	173	171	169	167	166	163	159	157	156	155	154	151	148	147	146	143	140	135	134	128	122	119	116	91	61	42	19	5	0
O+Clb	177	166	162	160	160	158	156	152	148	147	144	141	140	140	140	139	138	137	134	130	126	124	121	114	107	87	53	38	18	3	0

- [a]Hazard ratio was based on unstratified Cox-Proportional-Hazards model.
- A = acalabrutinib; CI = confidence interval; Clb = chlorambucil; HR = hazard ratio; NR = not reached; O = obinutuzumab; OS = overall survival; vs = versus.
- Sharman JP et al. Oral Presentation Presented at: ASH; December 9-12, 2023; San Diego.

MURANO TRIAL

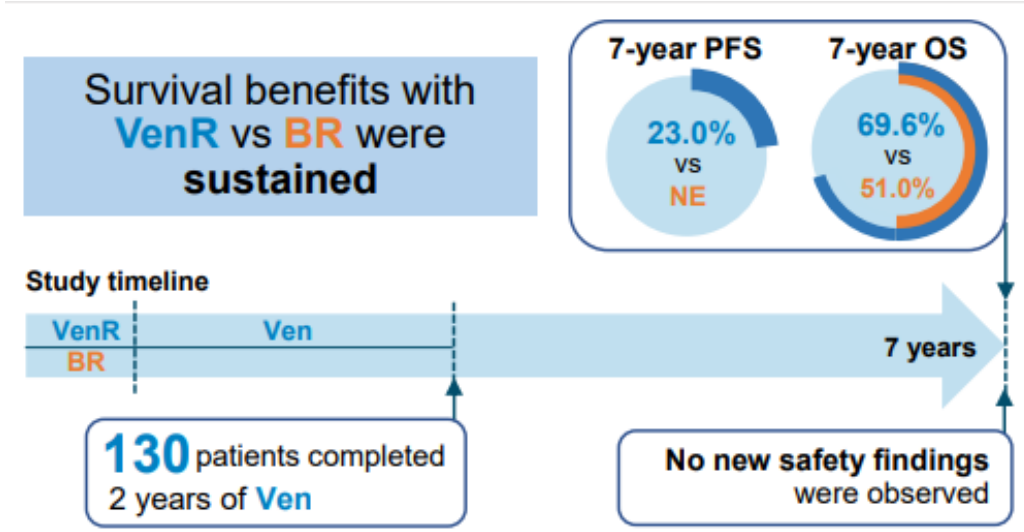
5-year OS rates were 82.1% vs 62.2% (PP<0.0001) Ven-R vs BR

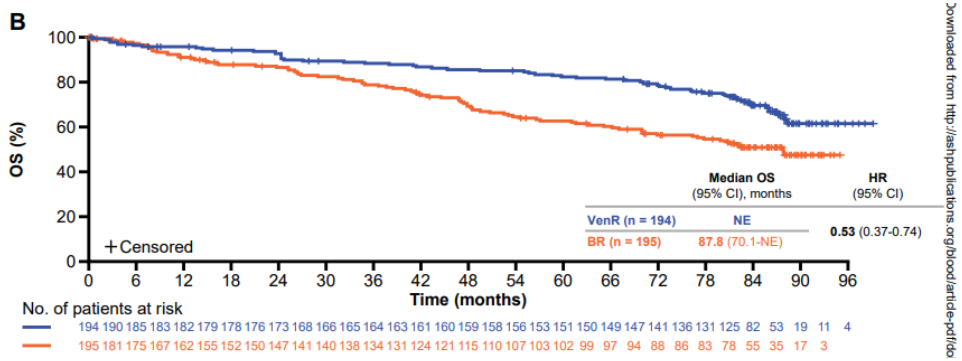
7-year OS rates (95% CI) were
69.6% with VenR and 51.0% with B (HR 0.53).

Median time to next treatment with VenR was 63.0 months vs 24.0 months with BR (HR 0.30)

37.1% of VenR-treated pts have not received subsequent anti-CLL

Substudy (progressive disease (PD) received VenR n=34), 25 pts received VenR re-treatment:
ORR was high (72%) and uMRD was still attainable in this high-risk population.





S201 FINAL 7-YEAR FOLLOW UP AND RETREATMENT SUBSTUDY ANALYSIS OF MURANO: VENETOCLAXRITUXIMAB (VENR)-TREATED PATIENTS WITH RELAPSED/REFRACTORY CHRONIC LYMPHOCYTIC LEUKEMIA (R/R CLL)

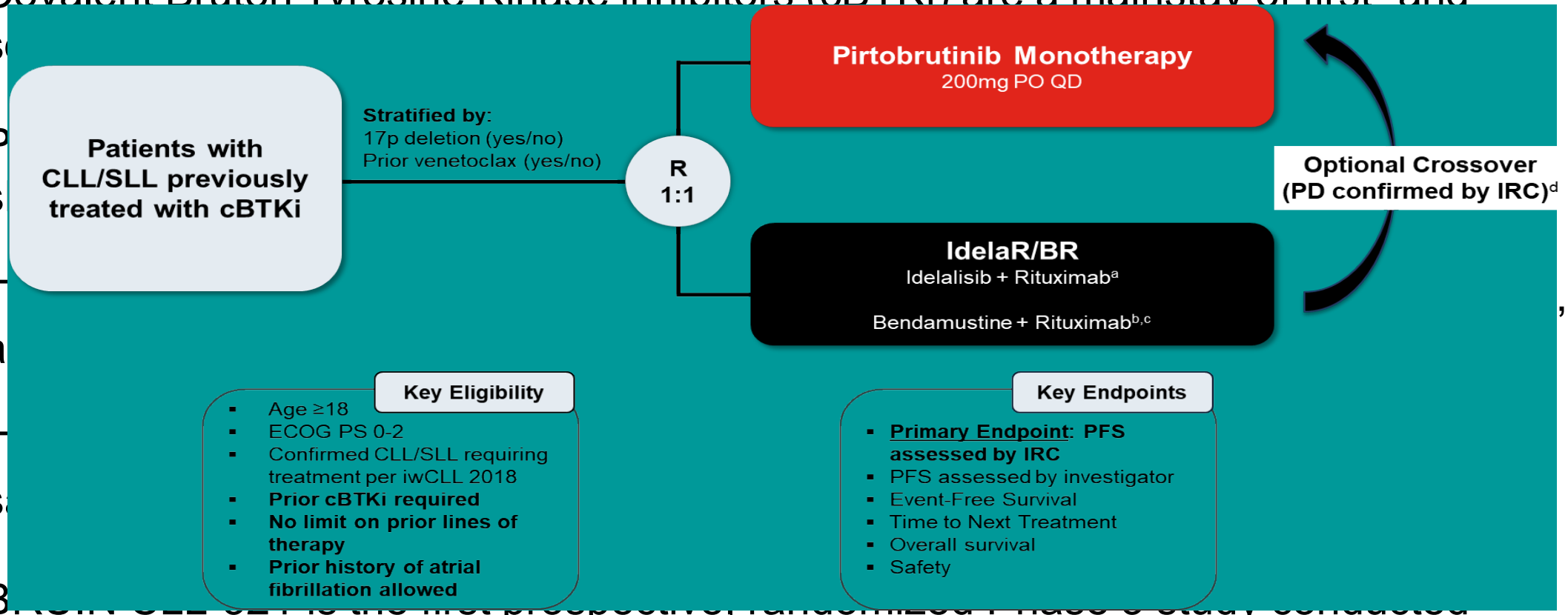
BRUIN CLL-321: Randomized Phase III Trial of Pirtobrutinib versus Idelalisib plus Rituximab (IdelaR) or Bendamustine plus Rituximab (BR) in BTK Inhibitor Pretreated Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Jeff P. Sharman[1], Talha Munir[2], Sebastian Grosicki[3], Lindsey E Roeker[4], John M Burke[5], Christine Chen[6], Norbert Grzasko[7], George Follows[8], Zoltán Mátrai[9], Alessandro Sanna[10], Shuhua Yi[11], Ru Feng[12], Vu Minh Hua[13], Jadwiga Holodja[14], Wojciech Jurczak[15], Matthias Ritgen[16], Lugui Qiu[11], Francesc Bosch[17], Catherine C Coombs[18], Katherine Bao[19], Vishalkumar Patel[19], Bin Liu[19], Livia Compte[19], Ananya Guntur[19], Denise Y. Wang[19], Marisa Hill[19], Ching Ching Leow[19], Paolo Ghia[20], Paul M Barr[21]

[1] Willamette Valley Cancer Institute and Research Center, US Oncology Research, Eugene, OR, USA, [2] Department of Haematology, St. James's University Hospital, Leeds, UK, [3] Department of Hematology &Cancer Prevention, Silesian Medical University, Katowice, Poland, [4] Department of Medicine, Memorial Sloan Kettering Cancer Center New York, NY, USA, [5] Sarah Cannon Research Institute, Rocky Mountain Cancer Centers, Aurora, CO, USA, [6] Division of Medical Oncology & Hematology, Princess Margaret Cancer Centre, Toronto, ON, Canada, [7] Department of Experimental Hematooncology, Medical University of Lublin, Lublin, Poland, [8] Department of Haematology, Addenbrooke's Hospital NHS Trust, Cambridge, UK, [9] Central Hospital of Southern Pest, National Institute for Haematology and Infectology, Budapest, Hungary, [10] Department of Hematology, AOU Careggi - University of Florence, Firenze, Italy, [11] Institute of Hematology & Blood Diseases Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, Tianjin 300020, China, [12] Department of Radiation Oncology, Nanfang Hospital, Southern Medical University, Guangzhou, Guangdong, China, [13] Haematology Department, Liverpool Hospital Sydney Australia, [14] Department of Hematology, City Hospital, Legnica, Poland, [15] Maria Sklodowska-Curie National Research Institute of Oncology, Krakow, Poland, [16] Universitätsklinik Schleswig-Holstein, Campus Kiel, Germany, [17] Department of Haematology, University Hospital Vall d'Hebron, Autonomous University, Barcelona, Spain, [18] University of California Irvine, Irvine, CA, USA, [19]Eli Lilly and Company, Indianapolis, IN, USA, [20] Università Vita-Salute San Raffaele and IRCCS Ospedale San Raffaele, Milano, Italy, [21] Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA.

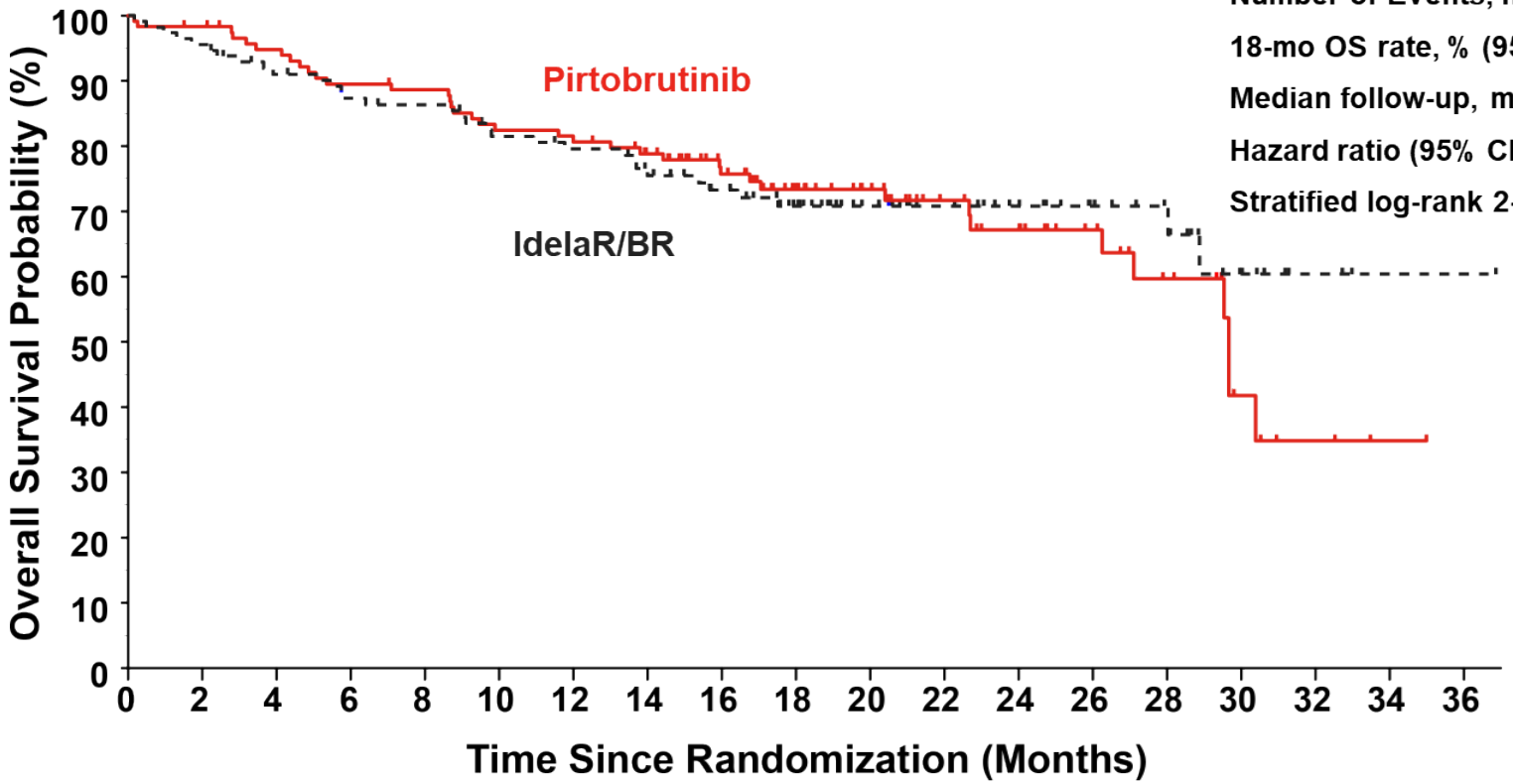
Background

- Covalent Bruton Tyrosine Kinase inhibitors (cBTKi) are a mainstay of first- and s
- P
  s
- T
  a
- T
  s
- B exclusively in a cBTKi-pretreated CLL/SLL population



[1]Mato et al. Clinical Lymphoma Myeloma and Leukemia. 2022; S2152-2650(22)01691-3. Abbreviations: cBTKi, covalent Bruton tyrosine kinase; CLL, chronic lymphocytic leukemia; CI, confidence interval; SLL, small lymphocytic lymphoma.

Overall Survival



Number at Risk

Pirtobrutinib	119	114	108	102	100	93	90	84	70	56	45	34	28	20	14	6	3	1	0
IdelaR/BR	119	107	99	93	91	83	80	71	64	54	40	32	27	21	16	8	3	1	1

	Pirtobrutinib n=119	IdelaR/BR n=119
Number of Events, n (%)	38 (32)	32 (27)
18-mo OS rate, % (95% CI)	**73.4** (63.9-80.7)	**70.8** (60.9-78.7)
Median follow-up, mo	20.4	19.2
Hazard ratio (95% CI)	**1.09 (0.68-1.75)**	
Stratified log-rank 2-sided p-value	0.7202	

Crossover Rate: 76% (50/66[a])

- IPCW crossover adjusted OS analysis: HR 0.87 (0.51-1.5)
- Two-stage AFT crossover adjusted OS analysis: HR 0.78 (0.48-1.26)

Overall survival follow-up limited and confounded by high rate of post-progression crossover

[a]Among patients whose event was INV PD and thus had the opportunity to crossover. Abbreviations: AFT, adjusted for treatment; BR, bendamustine + rituximab; CI, confidence interval; HR, hazard ratio; IdelaR, idelalisib + rituximab; IPCW, inverse-probability-of-censoring weighting; mo, months; NE, not estimable; NR, not reached; OS, overall survival.

CLINICAL TRIALS AND OBSERVATIONS

CME Article

MRD-guided zanubrutinib, venetoclax, and obinutuzumab in relapsed CLL: primary end point analysis from the CLL2-BZAG trial

Moritz Fürstenau,[1] Sandra Robrecht,[1] Christof Schneider,[2] Eugen Tausch,[2] Adam Giza,[1] Matthias Ritgen,[3] Jörg Bittenbring,[4] Holger Hebart,[5] Björn Schöttker,[6] Anna Lena Illert,[7] Ullrich Graeven,[8] Andrea Stoltefuß,[9] Bernhard Heinrich,[10] Robert Eckert,[11] Anna Fink,[1] Janina Stumpf,[1] Kirsten Fischer,[1] Othman Al-Sawaf,[1] Florian Simon,[1] Fanni Kleinert,[1] Jonathan Weiss,[1] Karl-Anton Kreuzer,[1] Anke Schilhabel,[3] Monika Brüggemann,[3] Petra Langerbeins,[1] Stephan Stilgenbauer,[2] Barbara Eichhorst,[1] Michael Hallek,[1] and Paula Cramer[1]

CME Article

MRD-guided zanubrutinib, venetoclax, and obinutuzumab in relapsed CLL: primary end point analysis from the CLL2-BZAG trial

Moritz Fürstenau,[1] Sandra Robrecht,[1] Christof Schneider,[2] Eugen Tausch,[2] Adam Giza,[1] Matthias Ritgen,[3] Jörg Bittenbring,[4] Holger Hebart,[5] Björn Schöttker,[6] Anna Lena Illert,[7] Ullrich Graeven,[8] Andrea Stoltefuß,[9] Bernhard Heinrich,[10] Robert Eckert,[11] Anna Fink,[1] Janina Stumpf,[1] Kirsten Fischer,[1] Othman Al-Sawaf,[1] Florian Simon,[1] Fanni Kleinert,[1] Jonathan Weiss,[1] Karl-Anton Kreuzer,[1] Anke Schilhabel,[3] Monika Brüggemann,[3] Petra Langerbeins,[1] Stephan Stilgenbauer,[2] Barbara Eichhorst,[1] Michael Hallek,[1] and Paula Cramer[1]

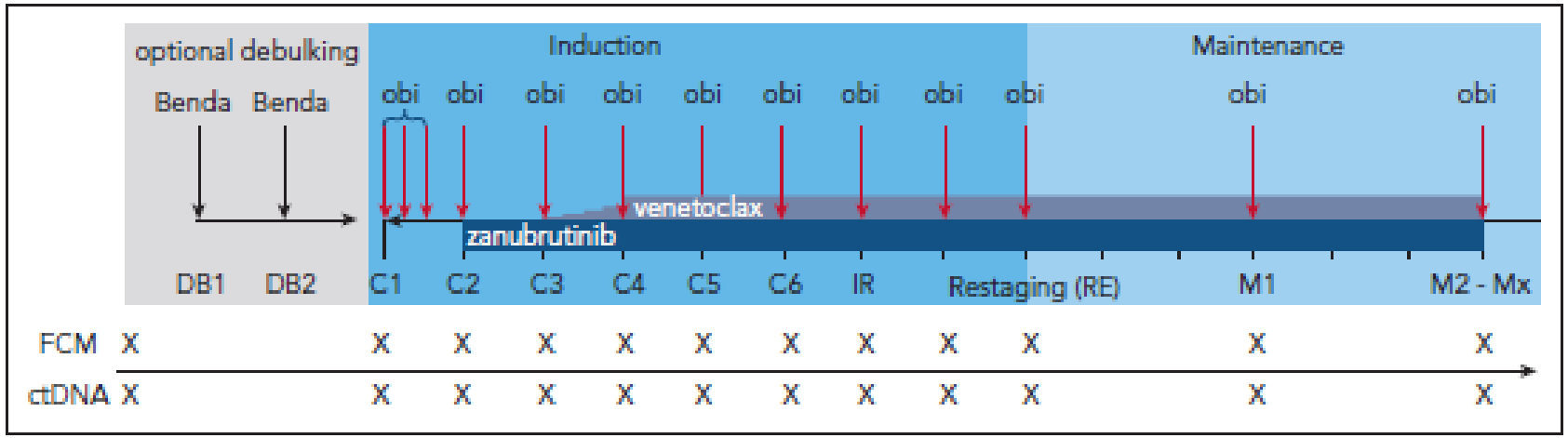


Figure 1. Treatment and sampling schedule. Every "X" on the sampling schedule represents an FCM and ctDNA sample. Benda, bendamustine; C1, cycle 1; C2, cycle 2; C3, cycle 3; C4, cycle 4; C5, cycle 5; C6, cycle 6; DB1, debulking cycle 1; DB2, debulking cycle 2; FCM, flow cytometry; IR, initial response assessment; M1, maintenance staging 1; M2, maintenance staging 2; Mx, maintenance stagings 3 to 8; obi, obinutuzumab; RE, final restaging.

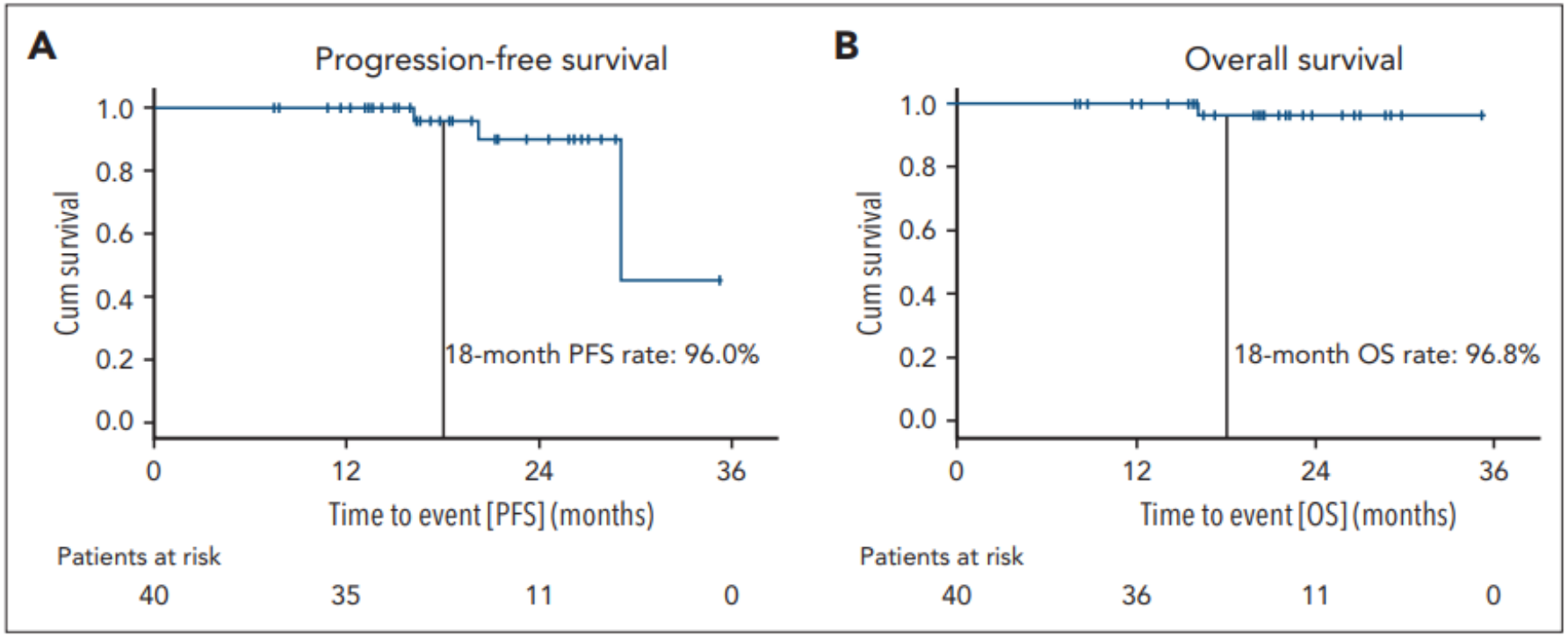


Figure 4. Progression-free and overall survival. PFS (A) and OS (B) are shown for the full analysis set; patients at risk at the respective time points are listed below the graphs.

Received: 28 November 2023 | Accepted: 3 December 2023
DOI: 10.1002/ajh.27182

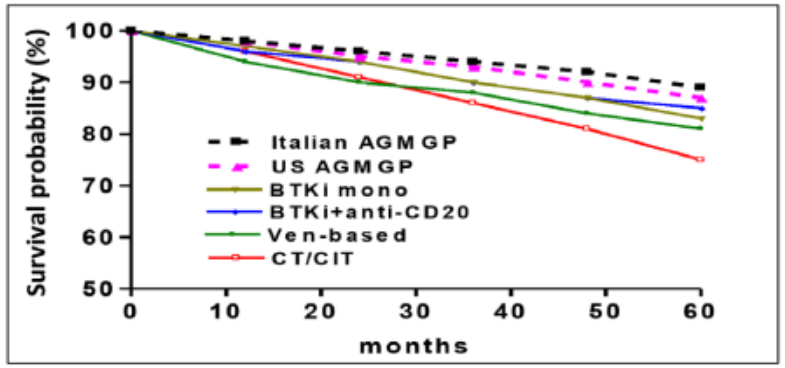
CORRESPONDENCE

AJH WILEY

Impact of targeted agents on survival of chronic lymphocytic leukemia patients age >65 relative to age- and sex-matched population

Impact of Targeted Agents on Survival of CLL Patients Age >65 Relative to Age and Sex-Matched Population

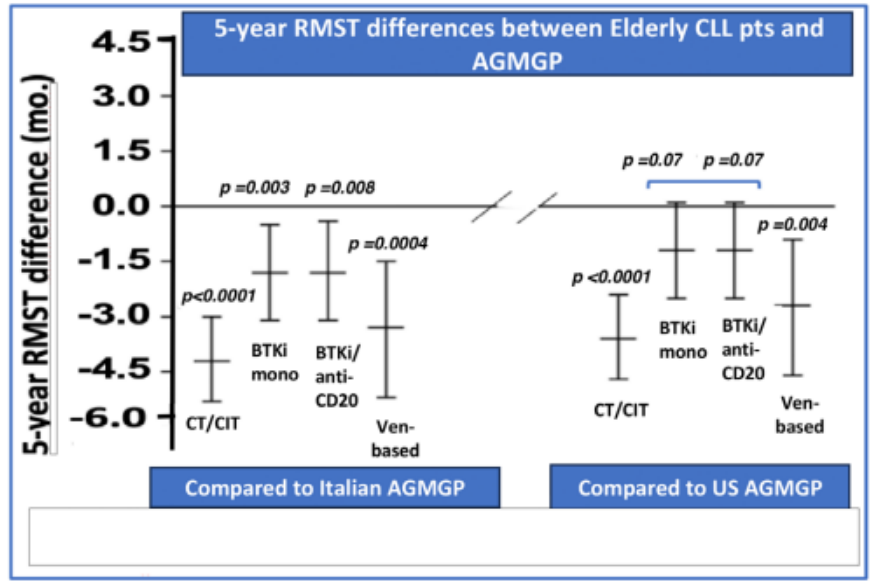
(A)



(B)

	5-year RMST in mo. (95% CI)	Rank
AGM Italian population	56.9	
AGM US population	56.3	
BTKi monotherapy	55.1 (53.8-56.4)	1
BTKi +anti-CD20	55.1 (53.8-56.5)	1
Ven-based therapy	53.6 (51.7-55.4)	2
CT/CIT	52.7 (51.6-53.9)	3

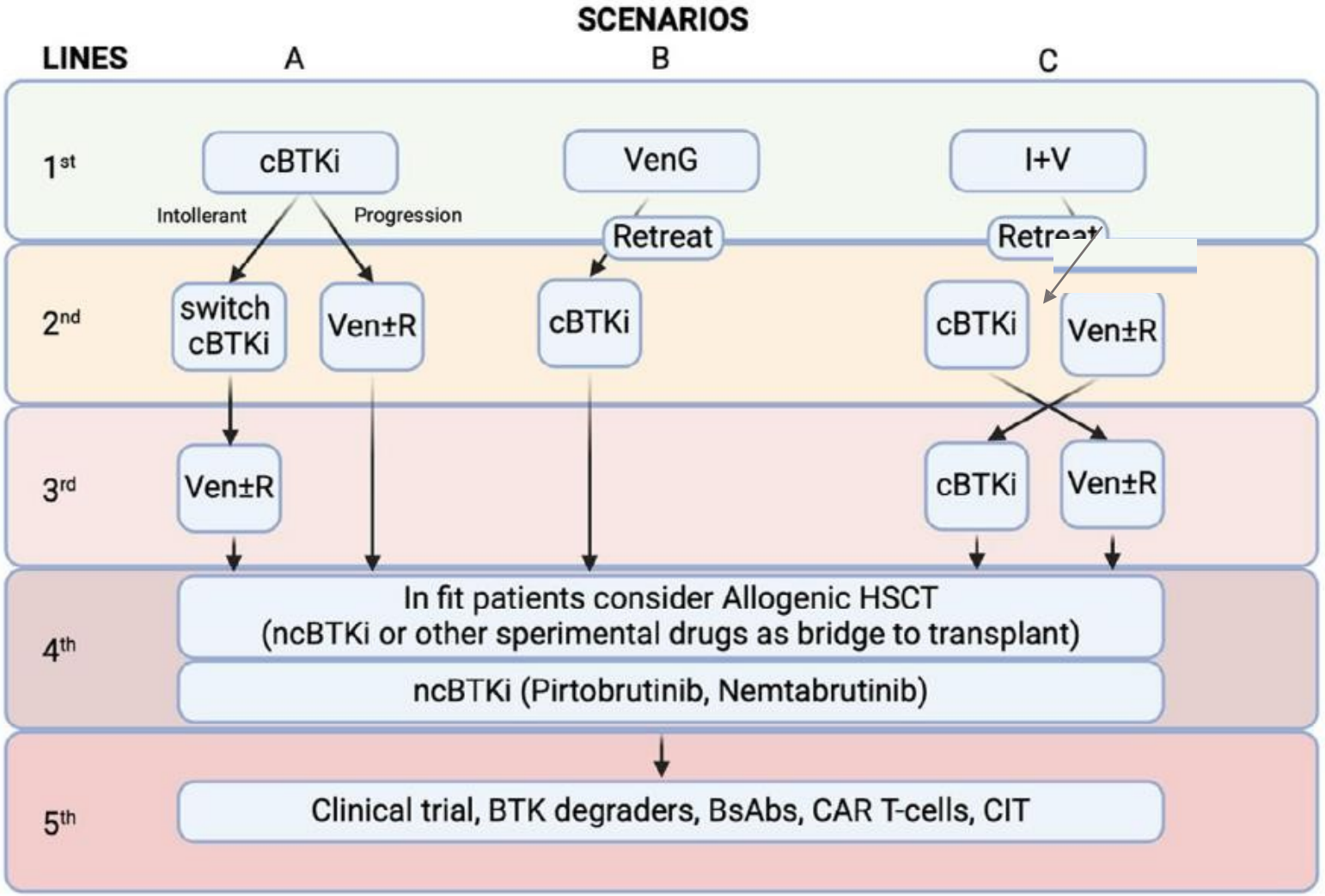
(C)

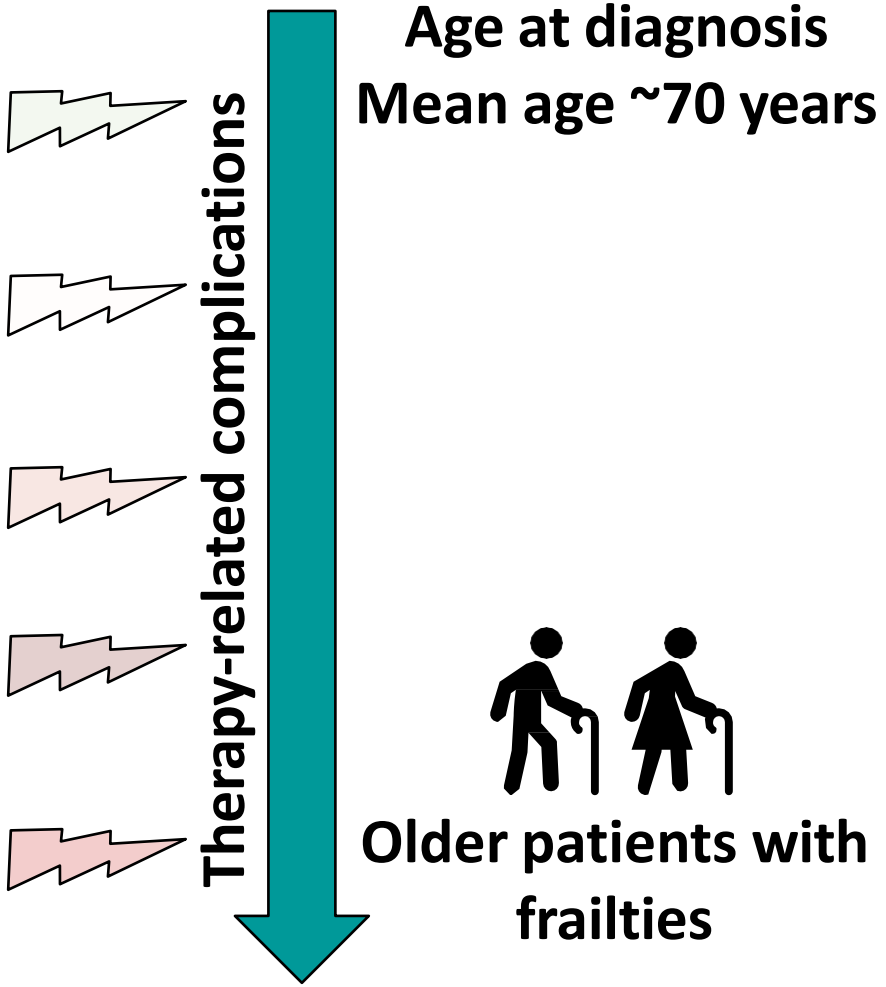


RMST, Restricted Mean Survival Time
AGMGP, Age Gender-Matched General Population

FIGURE 1 Overall survival (OS) comparison of elderly (≥65 years)/unfit chronic lymphocytic leukemia (CLL) patients included in phase 3 clinical trials (RESONATE2, ALLIANCE, ELEVATE-TN, ILLUMINATE, GLOW, and CLL14) to Italian, and US age- and gender-matched general population (AGMGP): (A) OS Kaplan–Meier curves comparing CLL patients enrolled in experimental or control arms of the trials to US AGMGP and Italian AGMGP. (B) Five-year restricted mean survival time (RMST) ranking of CLL patients, Italian AGMGP, and US AGMGP. (C) Five-year RMST difference comparing CLL patients, to Italian AGMGP and US AGMGP. In these analyses (A–C) CLL patients were grouped into one of four treatment categories: (i) BTKi-monotherapy, (ii) BTKi + anti-CD20, (iii) fixed-duration Ven-based combinations, and (iv) CT or CIT. The 95% confidence interval (CI) crossing zero indicates that the *p* value will be higher than .05. [Color figure can be viewed at wileyonlinelibrary.com]

CLL: a chronic disease with long-term complications





Serafin et al. Br J Haematol 2025; 00:1–10

Consequence of improved outcomes and long-term CLL survivors in T.A. era

Emergent challenges :

1. risk of infections
2. cardiovascular complications
3. secondary malignancies

Chronic Lymphocytic Leukemia—Time to Care for the Survivors

Pasquale L. Fedele, MBBS (Hons), PhD, FRACP, FRCPA[1] and Stephen Opat, MBBS (Hons), FRACP, FRCPA[1]

DOI https://doi.org/10.1200/JCO.23.02738

While progressive CLL or treatment-related complications were previously the predominant cause of death, most patients diagnosed in the current era will die from non–CLL-related causes, including second cancers, vascular disease, and infection. A study of 1,274 patients from 2000 to 2019 at the Mayo clinic identified the cause of death as CLL progression in 35%, infection in 6%, second malignancy in 16%, and other unrelated conditions, including cardiovascular disease (CVD), stroke, dementia, lung disease, and renal disease, in 21%.[7] Many of these conditions and their risk factors can be identified with routine screening and are therefore potentially preventable. Thus, it is likely that further improvement in outcome for our patients with CLL will not come from improvements in CLL-directed therapy, rather from addressing competing causes of death.

RISK OF INFECTIONS

DISEAS

10.3389/fphar.2022.989830

SFUNCTION

TABLE 1 Pooled cumulative incidence of severe infections.

Drug Class	Pooled cumulative incidence (%)	95% CI
BTKi	19.86	16.03–23.98%
PI3Ki	30.89	24.33–37.85%
2nd generation anti-CD20	13.46	10.52–16.70%
Rituximab	19.85	16.06–23.94%
Anti-BCL2	17.49	13.92–21.36%
Lenalidomide	13.33	7.83–19.90%
anti-CD52	45.09	7.46–86.25%

BCL2, B-cell lymphoma-2, protein; BTKi, Bruton tyrosine kinase inhibitor; CI, confidence interval, PI3Ki, Phosphoinositide 3-kinase inhibitor.
Drug names list: Anti-BCL2: venetoclax, anti-CD52: alemtuzumab, anti-CD20: obinutuzumab, ofatumumab, rituximab BTKi: acalabrutinib, ibrutinib, PI3Ki: idelalisib.

RISK OF INFECTIONS

DISEASE-INDUCED IMMUNE DYSREGULATION

SECONDARY HYPOGAMMAGLOBULINEMIA

IMPAIRED CELL-MEDIATED IMMUNITY DUE TO T-CELL DYSFUNCTION

IMMUNIZZATION WITH VACCINE

IMMUNOGLOBULIN REPLACEMENT

PROPHYLACTIC ANTIMICROBIALS AGENT

The Role of Vaccination

Despite impaired responses, the **benefits of vaccinations** outweigh the risks.

Vaccinated CLL patients for COVID-19 showed **lower hospitalization** rates and improved overall survival.

ECIL Strong Recommendations (Class 1, inactivated vaccines):

Annual influenza
Pneumococcal
Herpes zoster
COVID-19
Varicella herpes zoster

Temporary BTKi interruption may enhance vaccine antibody responses.

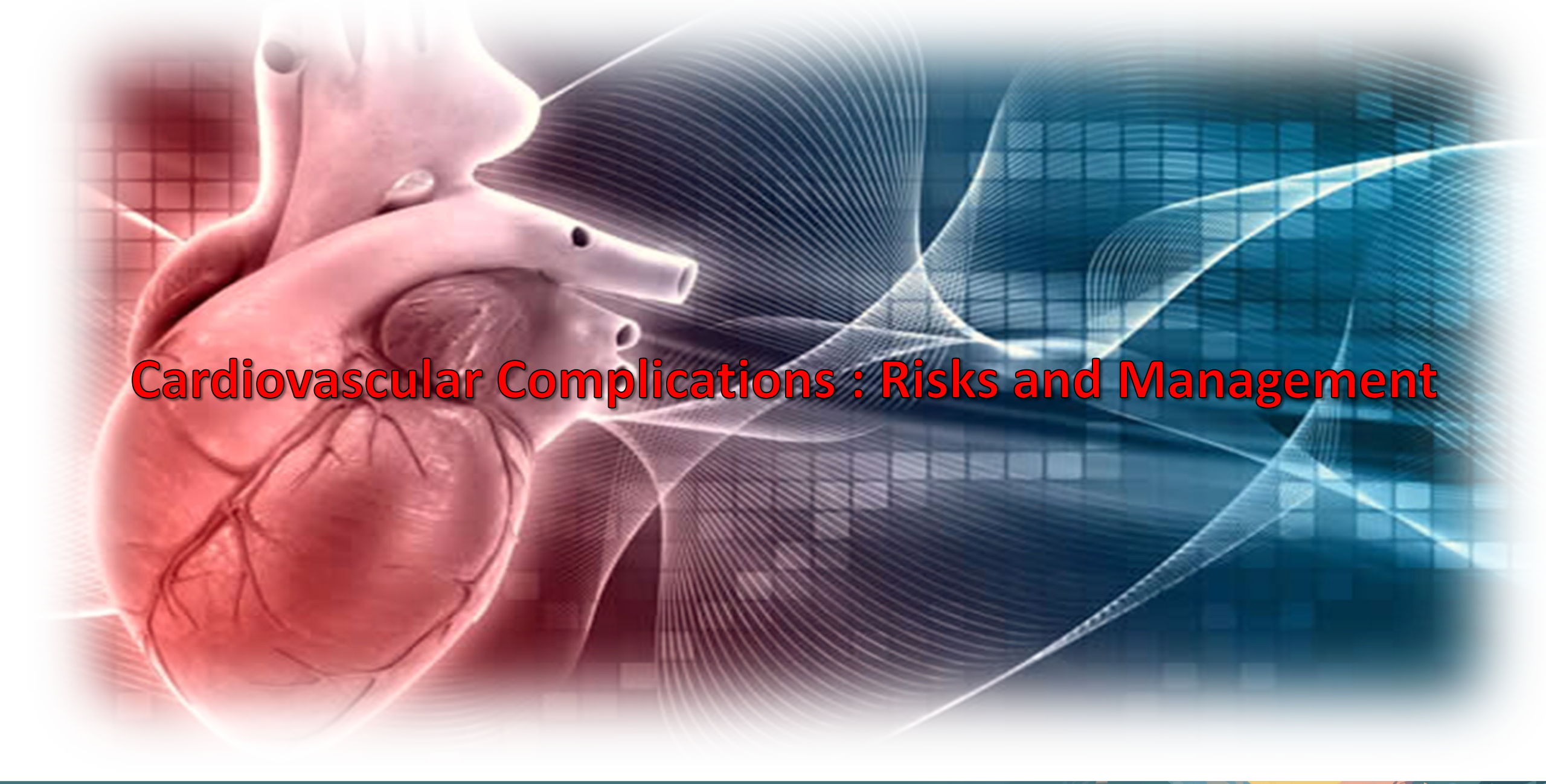
	Drugs	COVID-19	Varicella zoster	Seasonal influenza	Pneumococcus	Hepatitis B
BTKi	Ibrutinib, Acalabrutinib	↓ ↓	↓ ↓	↓ ↓	↓	☑ ↓
BCL-2i	Venetoclax	↓	⊗	⊗	↓	⊗
Anti-CD20	Rituximab, Obinutuzumab	☑ ↓	⊗	☑ ↓	↓	⊗

Humoral response Cellular response ⊗ No data

Francis ER, Vu J, Perez CO, Sun C. Semin Hematol. 2024 Apr;61(2):131-138.

TABLE 1. Key Health Domains and Survivorship Recommendations in CLL

Domain	Recommendations	Strength of Recommendation[a]	Level of Evidence[a]
Immunity and infections	Vaccinations as per consensus guidelines (eg, [37,38]), preferably before treatment or during maintenance. (although poor vaccine responses are well described in CLL)		
	Annual inactivated influenza vaccine	1	B-NR
	Pneumococcal vaccine (pneumococcal conjugate vaccine, followed by pneumococcal polysaccharide 23-valent vaccine ≥2 months later)	1	B-NR
	COVID-19 vaccination as per local guidelines	1	B-NR
	Recombinant Varicella Zoster Virus vaccine[39]	1	B-NR
	Consider other inactive vaccines (including Respiratory Syncytial Virus, Haemophilus Influenzae B, Human Papilloma Virus, and Hepatitis B vaccine) as per age, comorbidities, and local recommendations, 3-6 months following treatment	1	B-NR
	Avoidance of live vaccines	1	C-LD
	Consideration of IVIg/SCIg in patients with hypogammaglobulinemia and severe/recurrent bacterial infection	2a	B-R
Cardiovascular disease	Modifiable risk factors		
	Regular physical activity and advice regarding nutrition and diet as per international cardiovascular primary prevention guidelines[40]	2a	C-LD
	Optimal control of modifiable cardiac risk factors such as hypertension, dyslipidemia, and diabetes mellitus	2a	C-LD
	BTK inhibitors[41]	2a	C-LD
	Cardiovascular assessment (including BP measurement and pulse-taking [or ECG rhythm strip]) should be conducted at every visit	2a	C-LD
	Weekly home BP monitoring for 3 months, followed by monthly monitoring should be considered	2b	C-EO
	Transthoracic echocardiogram recommended in all high-risk patients at baseline and in all patients who develop AF	2a	C-EO
	Early referral to a cardiologist/cardio-oncology service	2b	C-EO



Cardiovascular Complications : Risks and Management

Review

Applied Cardio-Oncology in Hematological Malignancies: A Narrative Review

Evdokia Mandala [1], Kyranna Lafara [1], Dimitrios Kokkinovasilis [1], Ioannis Kalafatis [2], Vasiliki Koukoulitsa [2], Eirini Katodritou [3] and Christos Lafaras [2,*]

[1] Division of Hematology, Forth Department of Medicine, School of Medicine, Aristotle University of Thessaloniki, 54642 Thessaloniki, Greece; eudokiamandala@gmail.com (E.M.); kyralafa@gmail.com (K.L.); dkokkinovasilis@gmail.com (D.K.)
[2] Cardiology-Oncology Unit, Theagenion Cancer Hospital, 54639 Thessaloniki, Greece; jkal71@gmail.com (I.K.); vkoukoul@yahoo.gr (V.K.)
[3] Department of Hematology, Theagenion Cancer Hospital, 54639 Thessaloniki, Greece; eirinikatodritou@gmail.com
* Correspondence: lafarasc@gmail.com

Abstract: Applied cardio-oncology in hematological malignancies refers to the integration of cardiovascular care and management for patients with blood cancer, particularly leukemia, lymphoma, and multiple myeloma. Hematological cancer therapy-related cardiotoxicity deals with the most common cardiovascular complications of conventional chemotherapy, targeted therapy, immunotherapy, chimeric antigen receptor T (CAR-T) cell and tumor-infiltrating lymphocyte therapies, bispecific antibodies, and hematopoietic stem cell transplantation. This narrative review focuses on hematological cancer-therapy-related cardiotoxicity's definition, risk stratification, multimodality imaging, and use of cardiac biomarkers to detect clinical and/or subclinical myocardial dysfunction and electrical instability. Moreover, the most common cardiotoxic profiles of the main drugs and/or therapeutic interventions in patients with hematological malignancies are described thoroughly.

Patients with hematological malignancies are vulnerable to cardiovascular complications due to the type and stage

A disease-specific approach to risk stratification for hematological cancer therapy-related cardiotoxicity aligns with the principles of precision medicine.

(EHA); the European Society for Therapeutic Radiology and Oncology (ESTRO); and the International Cardio-Oncology Society (IC-OS) developed by the task force on cardio-oncology of the European Society of Cardiology.

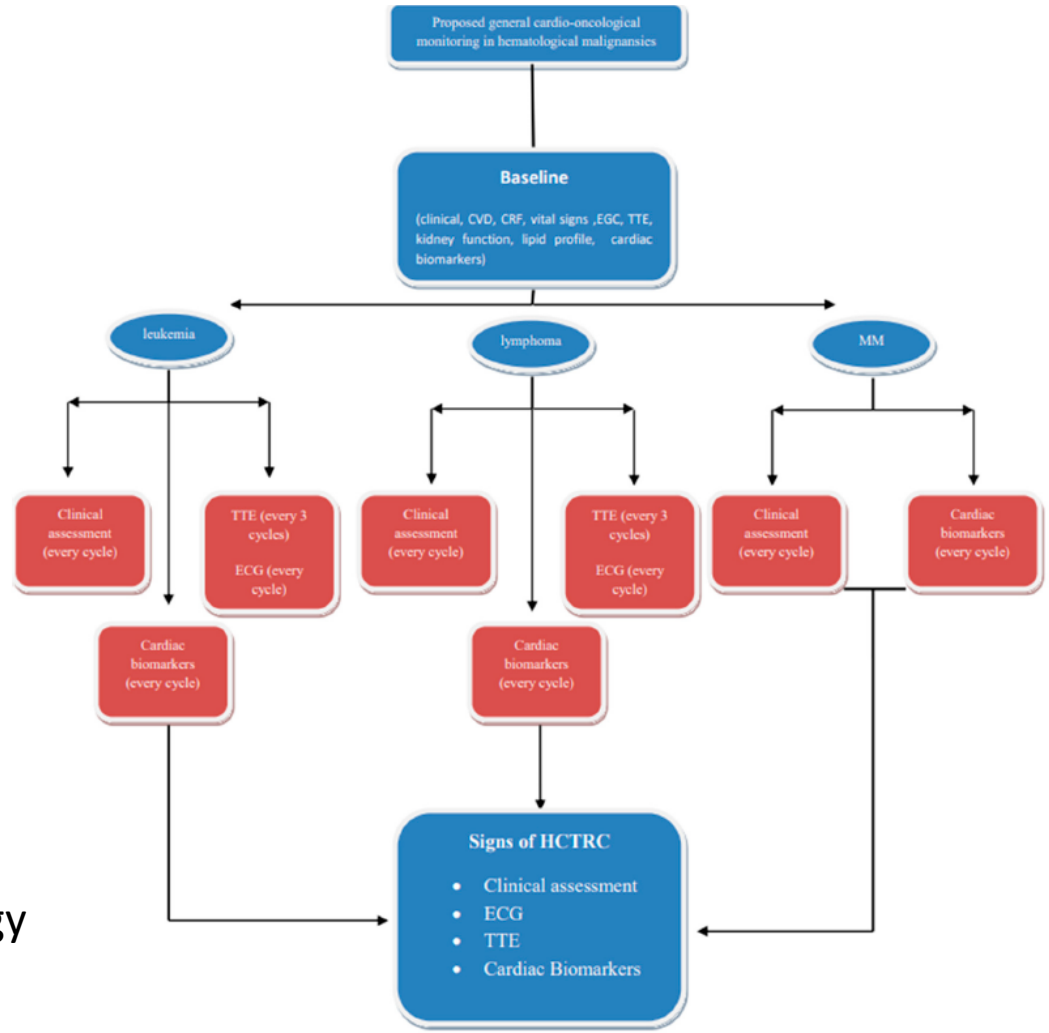
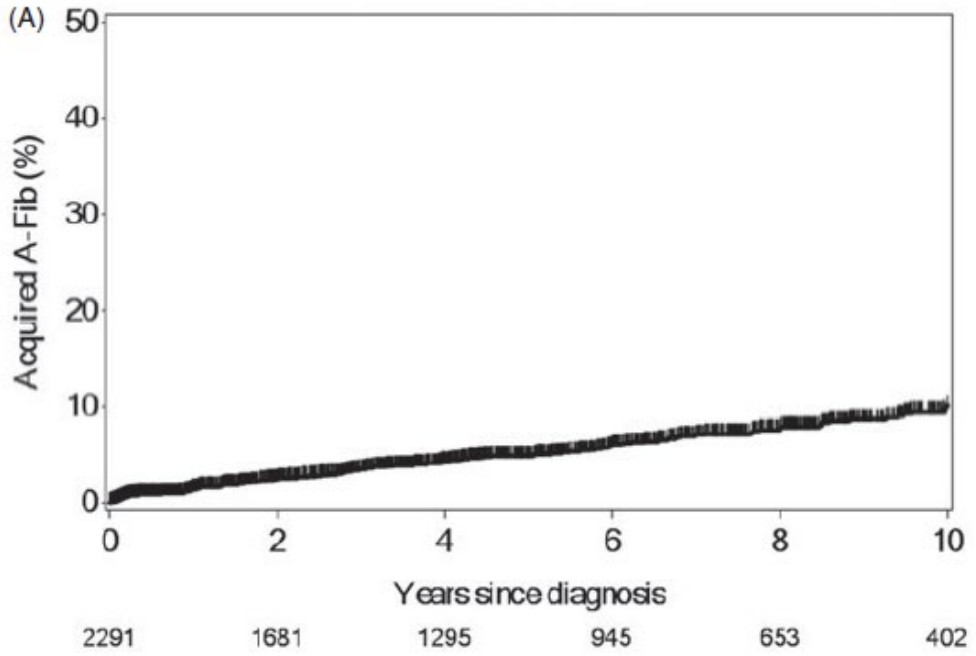


Figure 2. Proposed simplified cardio-oncological monitoring/surveillance algorithm in hematological malignancies. This protocol should be modified according the possible HCTRC effects of therapeutic regimens. Abbreviations: CVD, cardiovascular disease; CRF, cardiac risk factors; ECG, electrocardiogram; HCTRC, hematological cancer therapy-related cardiotoxicity; MM, multiple myeloma; TTE, transthoracic echocardiogram.

Pevalence of AF is substantial, estimated at 2.3% in individuals older than 40 years and 5.9% in those older than 65 years in the general population

A large cohort of patients **with CLL** (n 2,444, median age 65 years) seen within 12 months of diagnosis at Mayo Clinic in Rochester, Minnesota, **the prevalence of AF was approximately 6%.**

Among patients who did not have AF at the time of CLL diagnosis, **the risk of incident AF over time was approximately 1% per year.**



Second-generation BTKi: better responses better heart?

Phase 3 Trials Comparing Ibrutinib to Acalabrutinib and Zanubrutinib:

- Both acalabrutinib and zanubrutinib showed a 2- to 4-fold reduction in AF risk compared to ibrutinib.
- Acalabrutinib associated with significantly lower rates of hypertension (9% vs. 23% with ibrutinib).
- Zanubrutinib showed quantitatively lower hypertension rates in the ASPEN trial (Waldenström macroglobulinemia).
- Lower mean changes in systolic blood pressure observed with zanubrutinib in the ALPINE trial.
- Antihypertensive medication use linked to decreased major adverse cardiovascular events.

Cardiac Risk Profile in BTKi Selection Clinical Implications

Crucial, especially for patients with pre-existing CVD.

Proactive Management and Monitoring: Essential for all patients on BTKi therapy.

Transition to More Selective BTKis: May refine treatment decisions.

Avoid BTKis in High-Risk Patients: History of heart failure, ventricular arrhythmias, or uncontrolled hypertension (?)

Venetoclax and Cardiotoxicity: Rare in CLL, but reported in AML with HMAs; monitoring recommended for CLL patients with cardiac comorbidities.

JACC: CARDIOONCOLOGY VOL. 6, NO. 2, 2024

ORIGINAL RESEARCH

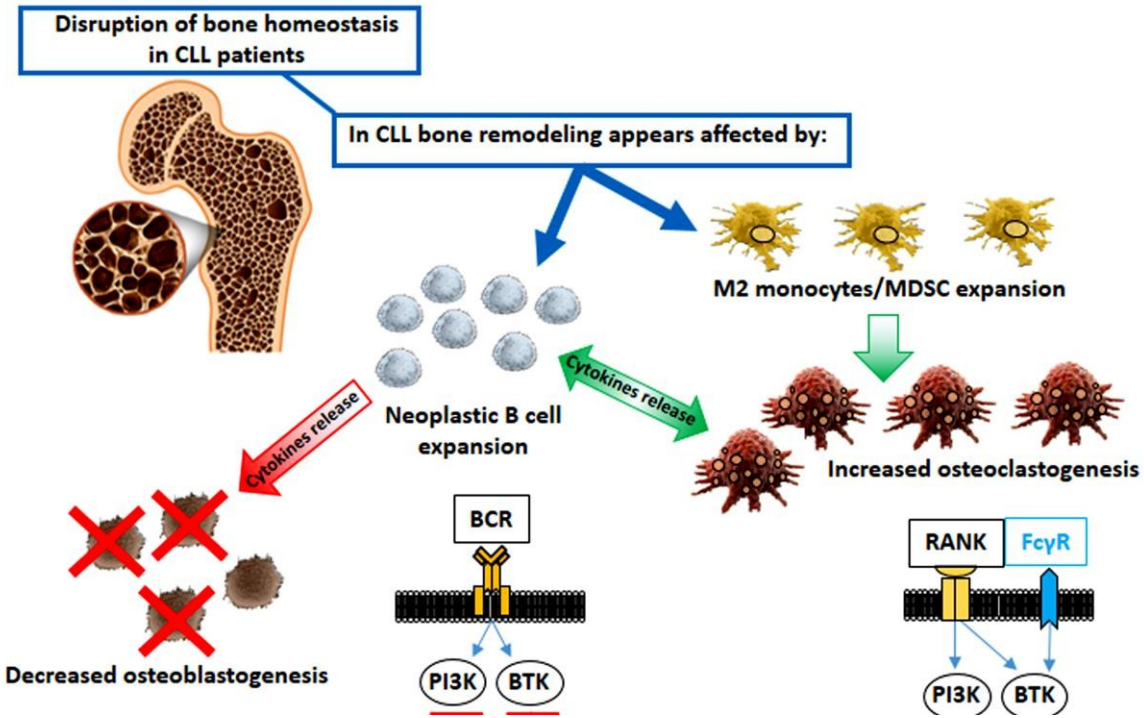
Artificial Intelligence Electrocardiography to Predict Atrial Fibrillation in Patients With Chronic Lymphocytic Leukemia

Georgios Christopoulos, MD,[a] Zachi I. Attia, PhD,[a] Sara J. Achenbach, MS,[b] Kari G. Rabe, MS,[b] Timothy G. Call, MD,[c] Wei Ding, MD, PhD,[c] Jose F. Leis, MD, PhD,[d] Eli Muchtar, MD,[c] Saad S. Kenderian, MD,[c] Yucai Wang, MD, PhD,[c] Paul J. Hampel, MD,[c] Amber B. Koehler, PA-C,[c] Neil E. Kay, MD,[c] Prashant Kapoor, MD,[c] Susan L. Slager, PhD,[b,c] Tait D. Shanafelt, MD,[e] Peter A. Noseworthy, MD,[a] Paul A. Friedman, MD,[a] Joerg Herrmann, MD,[a,*] Sameer A. Parikh, MD[c,*]

Clinical Approach to Bone Abnormalities and Fracture Risk in CLL

↑ Higher inflammatory cytokines (e.g., TNF-α, IL-6)
Increased RANKL expression
Increased risk of Axial Fragility Fractures

↓ vitamin D deficiency



- 13% incidence of fractures (increased axial fracture risk)
- Vitamin D deficiency in approximately 30% of cases
- Increased risk of progression

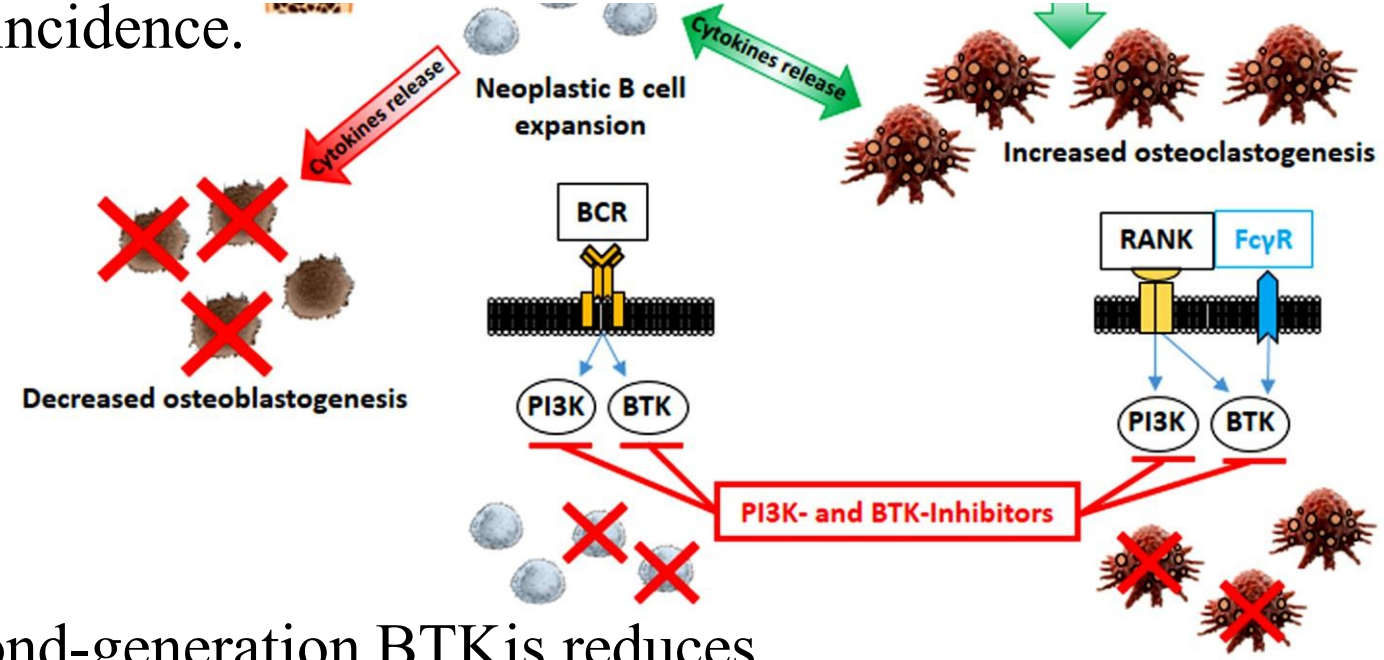
Osteoporosis prevention strategies:

- Calcium and vitamin D supplementation
- Regular exercise
- Monitoring bone mineral density in both asymptomatic and symptomatic patients
- Early initiation of antiresorptive therapy for patients with osteoporosis on bone densitometry

Impact of BTK Inhibitors on Bone Health

Ibrutinib and Vertebral Fractures: higher incidence.

Second-Generation BTK Inhibitors (Acalabrutinib, Tirabrutinib): Inhibit RANKL-induced osteoclast differentiation in preclinical studies, potentially preventing bone loss.



Potential for Reduced Fracture Risk: second-generation BTKis reduces fracture risk in CLL patients.

Fixed-Duration Combinations: Venetoclax-ibrutinib may lower fracture risk by shortening ibrutinib exposure.

Second Primary Malignancies

Solid tumors developed at a median of 4.4 years (interquartile range, 2.0–7.6 years) after CLL diagnosis, with non-melanoma skin and prostate cancers being the most common, followed by colorectal (1.9%) and breast cancers (1.7%)

Secondary AML and MDS were associated with the poorest survival outcomes.

The FCR regimen was associated with an increased risk of AML and MDS (GCLLSG)

Whereas patients treated exclusively with newer agents such as BTKi or venetoclax were not noted to develop these disorders

Second Primary Malignancies

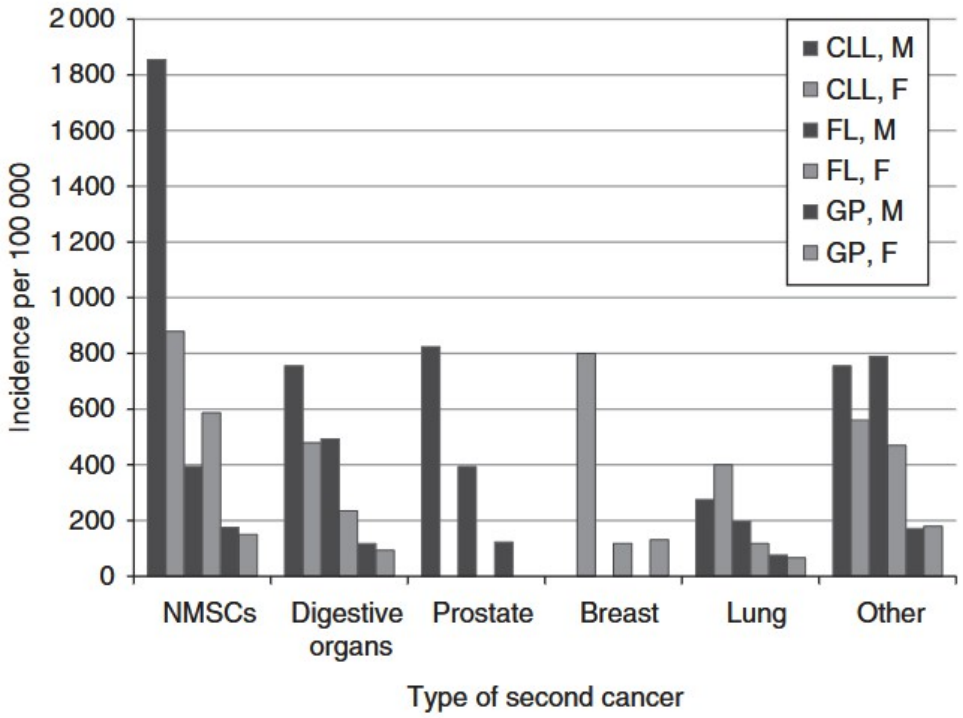


Table 2. Increased rates of second cancers in treated CLL and FL patients, and in untreated CLL patients compared with untreated FL patients

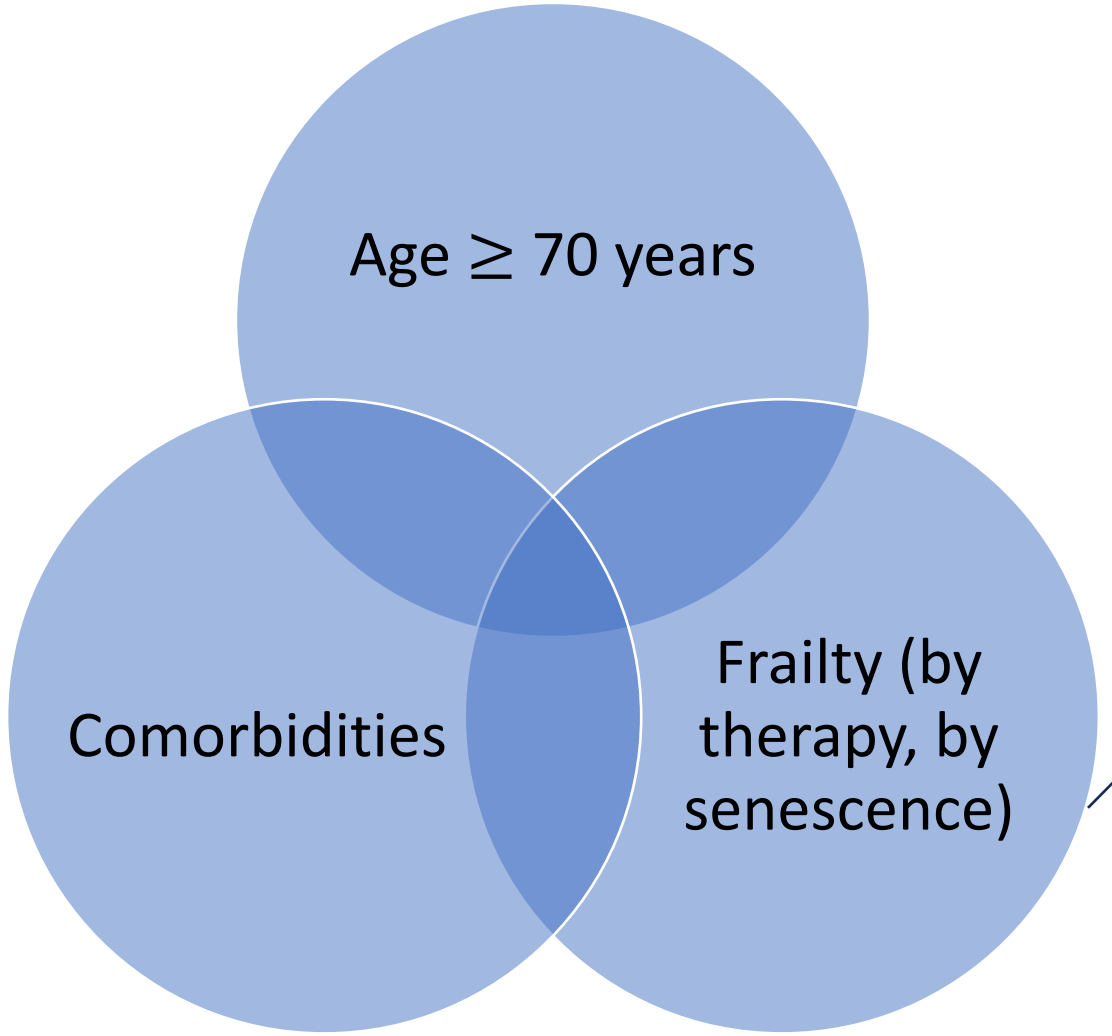
	CLL	FL
Treated (%)	141 (30)	202 (66)
Median TTFT (range)	5.3 mth (0–9.6 yr)	1.4 mth (0–9.0 yr)
Second cancer after treatment (%)	32 (23)	25 (12)
Median time from treatment to second cancer diagnosis (range)	3.1 yr (6.4 mth–11.2 yr)	4.0 yr (6.3 mth–11.2 yr)
Treated *vs* untreated SHR (95% CI)	Tx 1.81 (1.18–2.78) Age 3.80 (1.57–9.18)	Tx 2.47 (1.05–5.80) Age 2.52 (1.08–5.85)
Untreated CLL *vs* untreated FL SIR	2.05 (1.38–3.05)	

- 63% higher risk of developing a SPM compared to general population.
- Solid tumors and hematological malignancies.
- Highest incidence after more than five years from diagnosis.
- Squamous cell carcinoma of the skin, melanoma, lung, colorectal, soft-tissue sarcoma, AML, and thyroid cancers.

Beiggi S, et al. Br J Cancer. 2013 Sep 3;109(5):1287-90.

	Early referral to a cardiologist/cardio-oncology service	2b	C-EO
Secondary malignancy	Preventative measures		
	Cessation of smoking,[42] avoidance of excessive alcohol consumption, adherence to sun protection guidelines	1	A
	Age-based screening programs guided by personal and family history, radiation exposure, and other risk factors		
	Skin cancer surveillance[43]	1	C-LD
	Fecal occult blood testing (or colonoscopy in high-risk patients)	1	A
	Breast cancer screening program (mammography)	1	A
	Cervical screening (Pap-smears)	1	A
	Prostate cancer screening (PSA) as per local guidelines (not universally recommended in asymptomatic men)	2b	C-EO
Bone disease	Optimization of vitamin D and calcium status	2a	C-LD
	Weight bearing exercise	2a	C-LD
	Bone densitometry screening in patients with high corticosteroid exposure or other risk factors	2a	C-LD
	Early referral to metabolic bone clinic/commencement of antiresorptive therapy	2b	C-LD
Frailty	Treatment of underlying CLL[44]	1	B-R
	A geriatric assessment (eg, PGA) should be performed on all patients >65 years old and updated at key milestones[45]	1	B-R
	Motivate patients to maintain regular exercise, including aerobic exercise and resistance exercise for all major muscle groups	2a	C-LD
	Consider exercise physiology referral	2b	C-EO
	Occupational therapy and physiotherapy referral as required	2b	C-EO

Comorbidity and frailty are closely related to age



Rate of multimorbidity in the Italian population (65-74 yrs: 44%
(ISTAT 2019)

The prevalence of frailty in community-dwelling adults aged 70 is around 15-30%
(JAMA Netw Open 2019)

Targeted Therapies and Frailty

Frailty in CLL is often associated with reduced mobility, cognitive impairment, and psychological disorders as well as age-related comorbidities increase the risk of treatment toxicity.

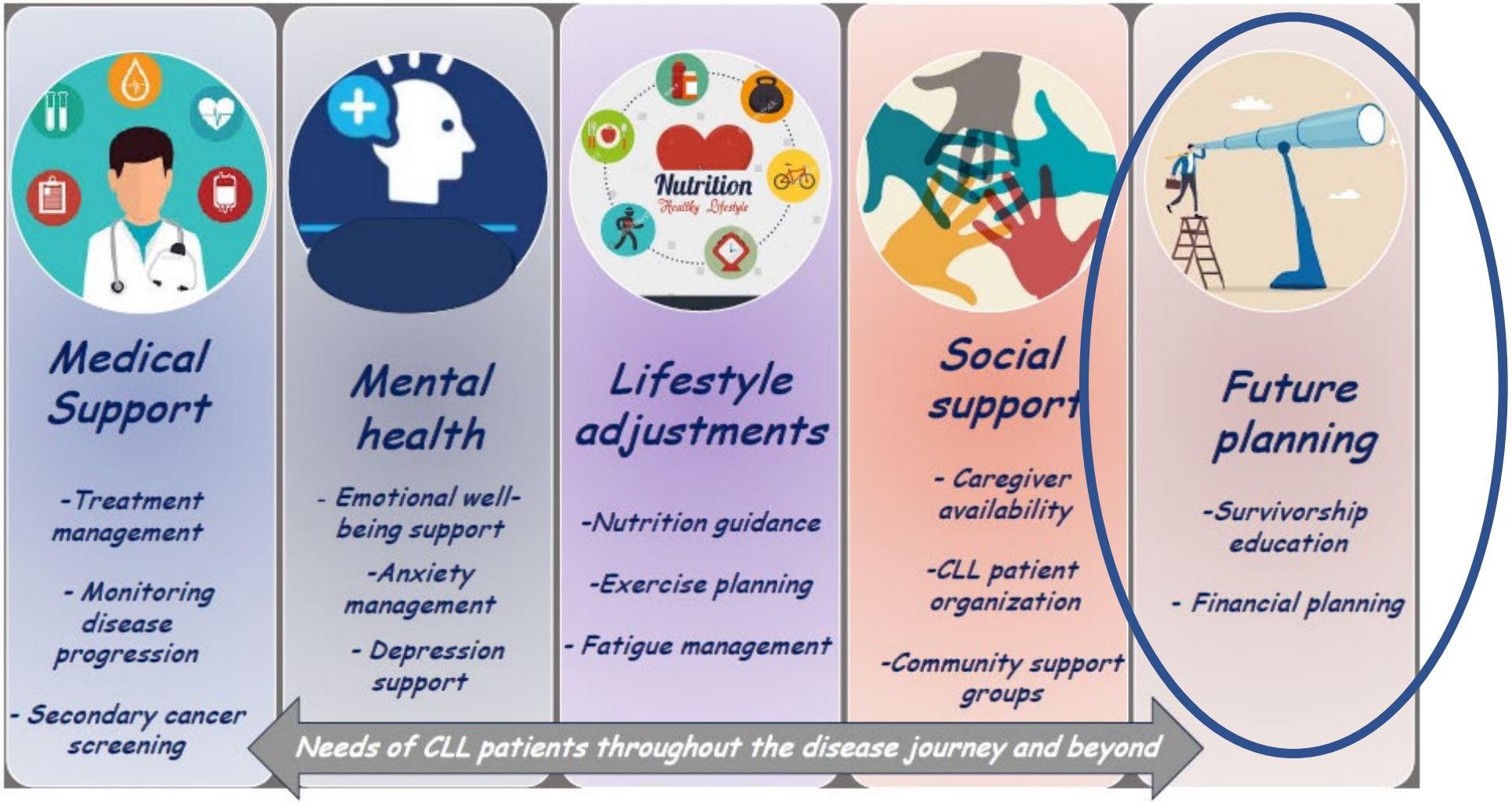
Prospective Frailty Evaluation Recommended To identify patients at higher risk.

Targeted therapies can improve frailty in older adults:
HOVON139/GiVe Trial (Venetoclax-Obinutuzumab): Showed a significant reduction in geriatric impairments during treatment in frail patients.

Improved Health-Related Quality of Life (HRQoL): Clinically meaningful improvements observed in specific subscales.

Ibrutinib in Very Elderly Patients (>80 years): Demonstrated median PFS of 42.5 months and OS of 51.8 months, with a cardiovascular event rate of 22.8%.

CLL-Frail Trial (Acalabrutinib Monotherapy in Frail/Elderly): Interim analysis showed no unexpected safety signals, with most patients remaining on therapy.



Chronic Lymphocytic Leukemia Care and Beyond: Navigating the Needs of Long-Term Survivors
Molica S., David Allsup
Cancers ***2025****, 17, 119*

Figure 2. A conceptual graph illustrating the needs of CLL patients throughout their disease journey and beyond, with a particular emphasis on long-term survivors.

Integrating Geriatric Assessments in CLL Management

Key Priority for Clinical Trials: Incorporate Geriatric Assessments (GA) at baseline.

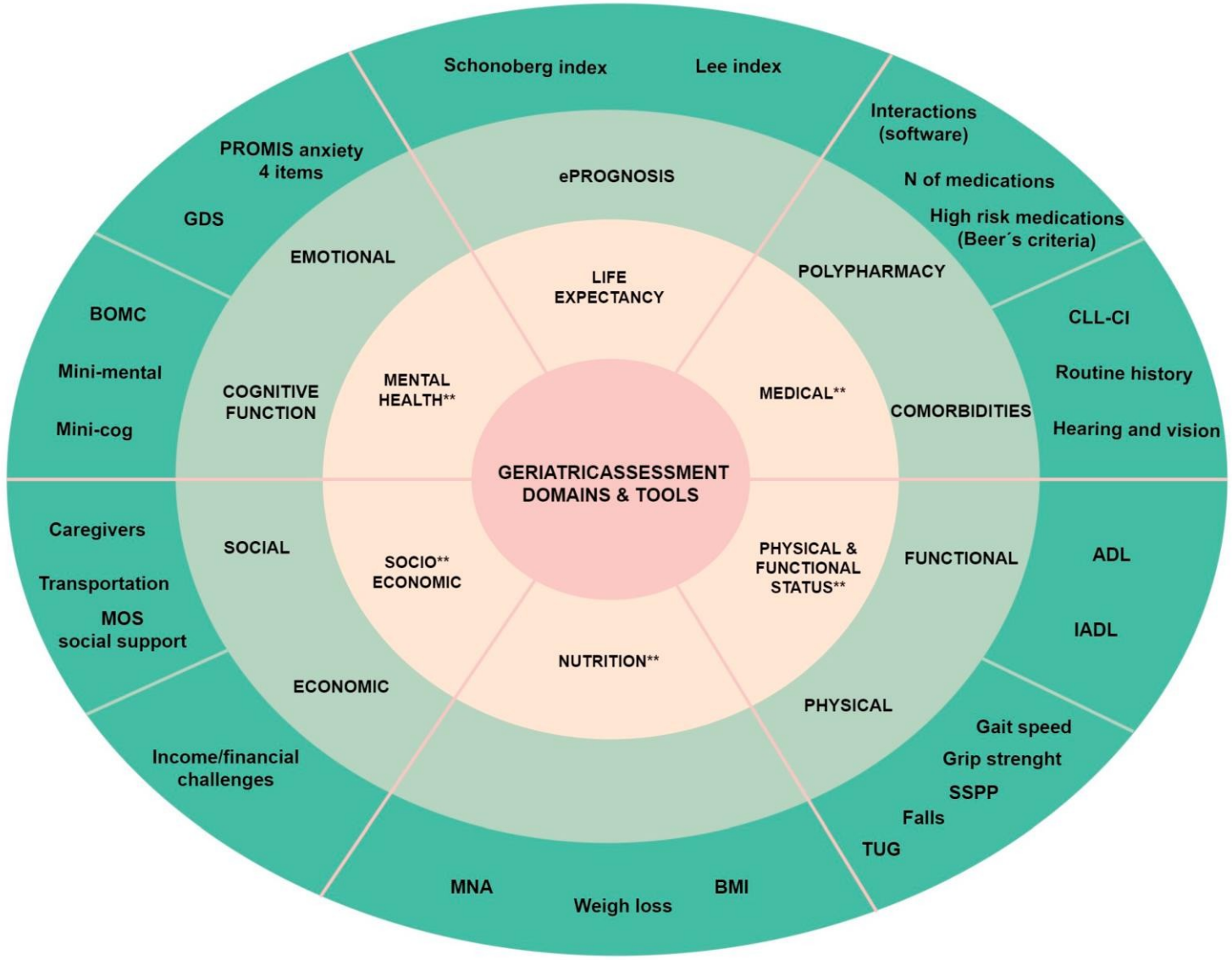
Multi-Dimensional Evaluation.

Provides a Clearer Picture: of an older patient's health status and therapy suitability.

Track Frailty and QoL Outcomes.

Holistic Understanding of Treatment Impact: On overall well-being and functionality.

Regular Frailty Assessment: Changes can be as important as hematologic outcomes.



González-Gascón-Y-Marín I, et al. Cancers (Basel). 2023 Sep 2;15(17):

OUR EXPERIENCE

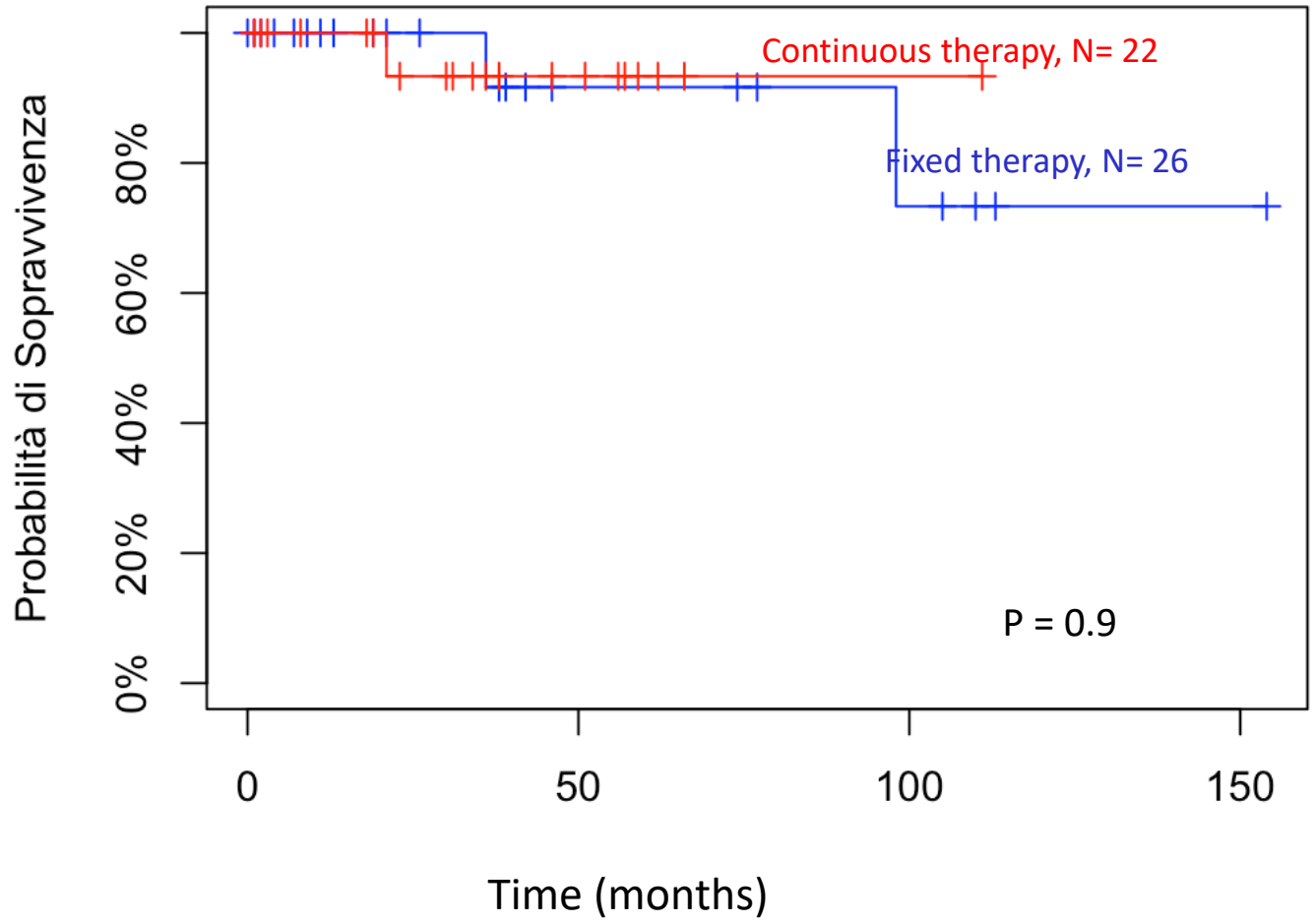
COACHES

Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno

Survival probability



	Infectious events	No infectious events
Fixed therapy	15	11
Continuos therapy	13	9

P=0.89

Take Home Message:

The goal in CLL: prolong the quality of life and overall survival while offering the least possible toxicity

Adopt all therapeutic and non-therapeutic strategies
to ensure the best quality of life

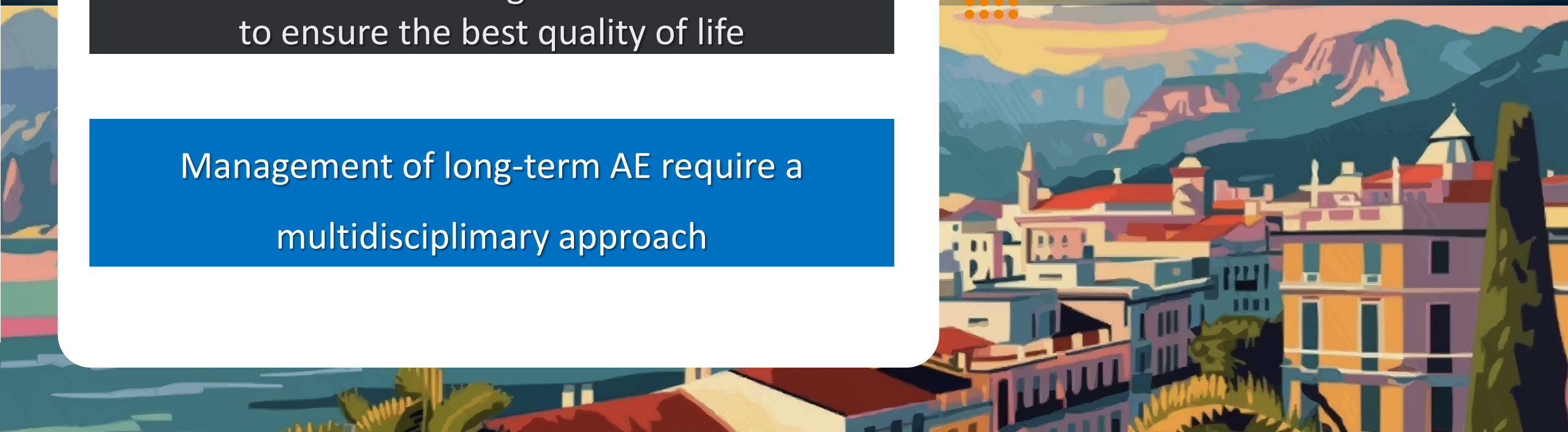
Management of long-term AE require a multidisciplimary approach

COACHES

Current Opinions, Advances, Controversies in HEmatology in Salerno

Updates in **Chronic Lymphocytic Leukemia** and **Lymphomas**

Salerno | **14 aprile 2025** | Grand Hotel Salerno



Special thanks to

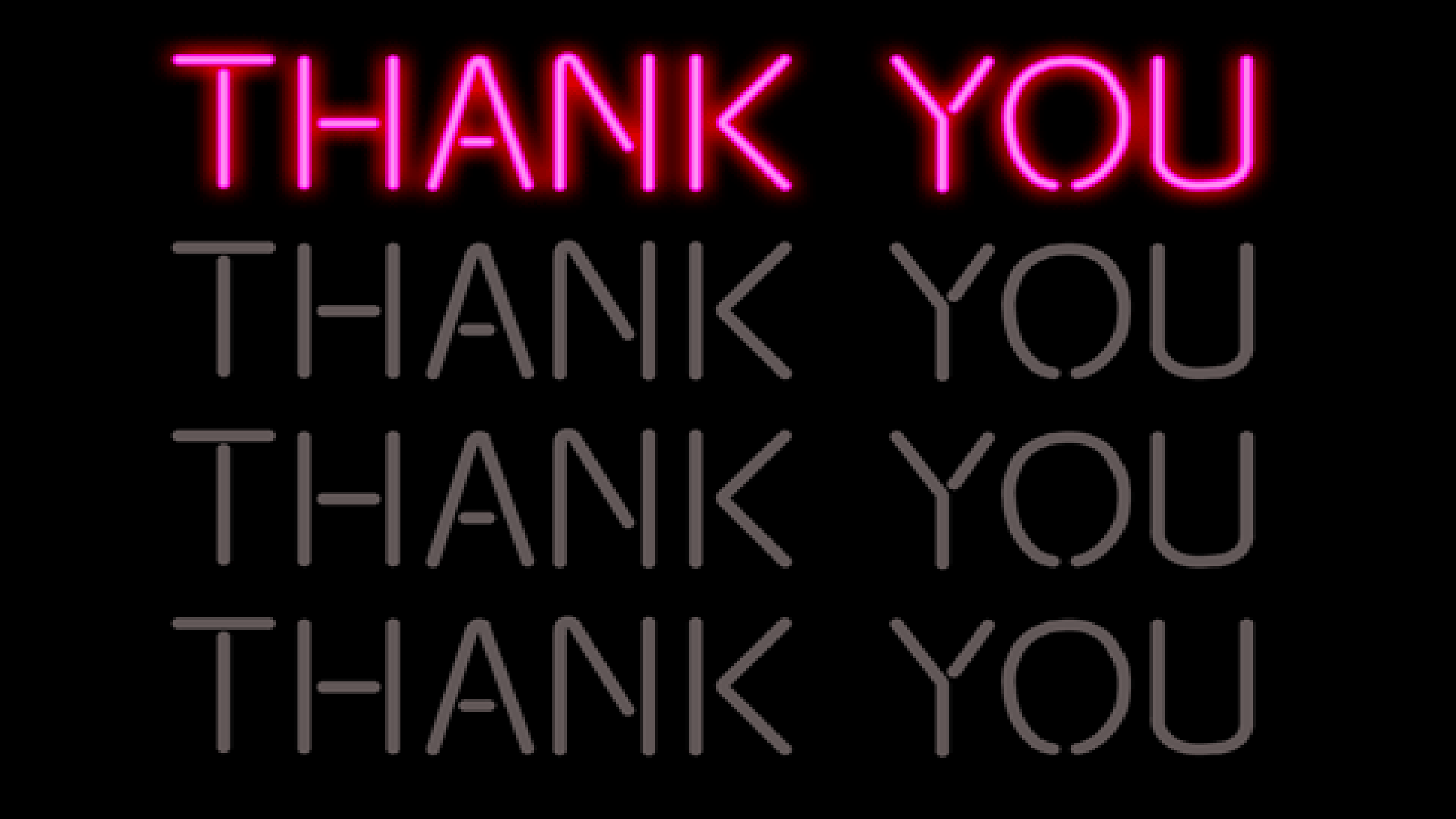
TEAM: HEMATOLOGY UNIT
Chief Prof. Carmine Selleri

FLOW CITOMETRY LAB

CLINICAL TRIAL UNIT

BONE MARROW TRANSPLANT LAB

And all of you for your attention!


THANK YOU
THANK YOU
THANK YOU
THANK YOU