MEET THE

EXPERT

in CLL

CREMONA, 30 GIUGNO 2025

Ospedale di Cremona

MARIA CRISTINA PASQUINI

Regione Lombardia

ASST CREMA

OSPEDALE MAGGIORE

Il sottoscritto Pasquini Maria Cristina

- *ai sensi dell'art. 3.3 sul Conflitto di Interessi, pag. 17 del Reg. Applicativo dell'Accordo Stato-Regione del 5 novembre 2009,*

dichiara

- *che negli ultimi due anni NON ha avuto rapporti diretti di finanziamento con soggetti portatori di interessi commerciali in campo sanitario*

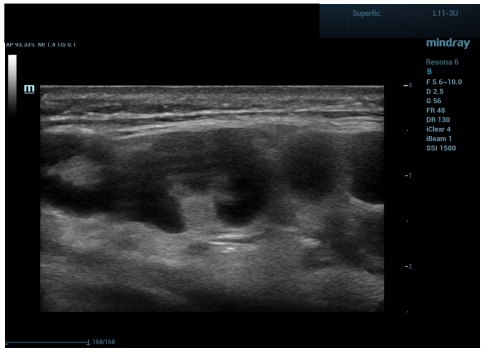
CASO CLINICO 3

Uomo di 68 anni

ambulatorio del MMG febbraio 20

- Autoriscontro di adenopatie collo

- Ecocollo: I linfonodi appaiono tutti con caratteristiche ecografiche di benignità, verosimilmente reattivi. Si consiglia inquadramento clinico specialistico ematologico. Ghiandole salivari maggiori nella norma con alcuni linfonodi intraparotidei bilateralmente reattivi.



- Emergenza COVID

H. San Donato (Medicina) febbraio21

- Ricovero per polmonite COVID, durante il ricovero necessità di NIV
- TC 2/21 alcuni LN mediastinici e ilari a destra, milza nei limiti, grossolane adenopatie confluenti nel tessuto adiposo mesenteriale in pacchetti 43 mm, LN inguinali bilaterali 24 mm a sn e lungo decorso iliaco-otturatorio max 3 cm
- Hb 15,5 g/dl GB 7690/mm3 L 2120/mm3 PLT 240.000/mm3 LDH nella norma
- Consulenza ematologica: indicata PET

PET (Casa di Cura Igea) maggio 21

- conferma adenopatie segnalate in TC

« a livello del collo plurime formazioni linfonodali in sede laterocervicale, retromandibolare, sottomandibolare e sovraclaveare bilaterale in parte non captanti, in parte debolmente e non significativamente SUV max 2,3 g/ml)»

..analoghi LN in sede mediastinica e addominale e inguinale.

Non significative captazioni degli addensamenti polmonari in esiti di polmonite.

I visita aprile

- Non sintomi B
- Non dolore , non disturbi nella deglutizione.
- Alla visita numerose adenopatie LC e sottomandibolari dx >sn fino a 4 cm, inguine sn 4 cm dx 2-3 cm, non splenomegalia palpabile

- Esami ematici
  - Hb 16,9 g/dl GB 11.600/mm3 L 5.280/mm3 PLT 129.000/mm3
  - funz renale ed epatica nella norma, LDH nella norma, sierologia CMV, EBV e HIV negative , Ig policlonali nella norma Beta2 4,4 mg/L
  - allo striscio: piccoli linfociti e rare ombre di Gumprecht

diagnosi

ESAME IMMUNOFENOTIPICO

Data 17/05/2022

Cognome **Nome**

Data di nascita *17/07/1952* **Reparto** *AMBMDH*

Materiale esaminato: *SANGUE PERIFERICO*

GB/µl: 12650 **CD34/µl:**

TIPIZZAZIONE IMMUNOLOGICA EFFETTUATA SU:

- CD8, LAMBDA, CD56, KAPPA, CD5, CD19, TCR, CD3, CD38, CD4, CD20, CD45
- CD23, CD10, CD79b, CD19, CD200, CD43, CD20, CD45

Conclusioni:

Esame eseguito con scattering linfocitario pari al 42%. Discreta compressione della popolazione T linfocitaria (39%) ed espansione della popolazione B linfocitaria pari a 47% con fenotipo CD5+++ CD38+, CD23+ CD10-, CD43+, CD200+, CD79b- Monoclonalità di superficie lambda.
Quadro compatibile con malattia linfoproliferativa CD5+

Il Responsabile

caratterizzazione di malattia

LAB.analisi HSR

- FISH negativa per +12, 11q-, 17p-, 13q-
- TP53 (NGS) WT
- VHIg MUTATED

- CLL stadio I B
- CLL IPI score 4

Result summary: 2671_IgM_VH3a_IgM_sequence_exported_from_chromato	Productive IGH rearranged sequence (no stop codon and in-frame junction)		
V-GENE and allele	Homsap IGHV3-23*01 F, or Homsap IGHV3-23D*01 F	score = 1323	identity = 95.49% (275/288 nt)
J-GENE and allele	Homsap IGHJ4*02 F	score = 204	identity = 91.67% (44/48 nt)
D-GENE and allele by IMGT/JunctionAnalysis	Homsap IGHD3-3*02 F	D-REGION is in reading frame 3	
FR-IMGT lengths, CDR-IMGT lengths and AA JUNCTION	[25.17.38.11]	[8.8.14]	CAKDSISGPGGHFDYW
JUNCTION length (in nt) and decryption	48 nt = (11)0(0)-4(12)-15(11)-3(14)	(3'V)3'(N1)5'(D)3'(N2)5'(J)	

Stereotyped B-Cell Receptor

unassigned

Valori di riferimento

Genotipo mutato: Identità <98%; **Genotipo non mutato**: identità >=98%

Metodo

Amplificazione genica dei riarrangiamenti IGHV-IGHD-IGHJ con primers nella regione leader e sequenziamento Sanger bidirezionale
Analisi immunoinformatica: IMGT V-QUEST-ARResT/AssignSubset tool

Operatore Analisi Tecnica	Matteo Pisciali
Operatore Interpretazione Analisi	Silvia Rigamonti

Conclusione

Il risultato depone per un genotipo mutato.

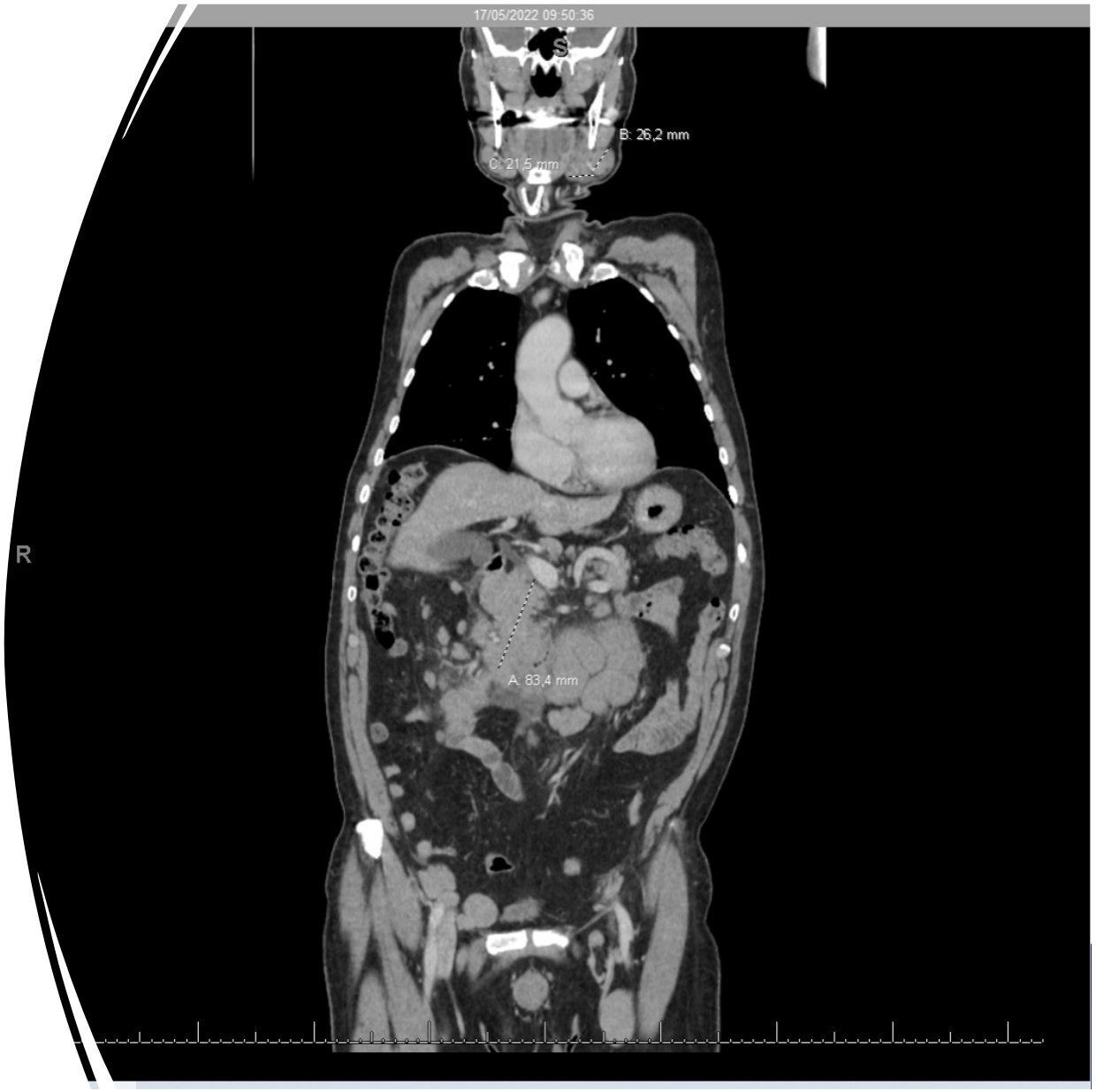
TC 5/22

- **Collo-Torace** :

Numerose adenopatie laterocervicali, ascellari, mediastiniche e delle catene. Aree di impegno parenchimale interstiziale a vetro smerigliato del medio, della lingula e dei lobi inferiori con area di addensamento di aspetto fibrotico dei segmenti basali del lobo inferiore sin.

- **Addome:**

Numerose adenopatie intra e retroperitoneali lungo la radice del mesentere ed i foglietti mesenteriali, intercavoaortici, periaortici, paracavale, del piccolo bacino e inguinali.
Minuta formazione rotondeggiante ipodensa di 5 mm in S4, non tipizzabile per le esigue dimensioni



Lo avreste avviato a terapia?

avviato a w.w giugno 22

- Asintomatico
- Esami Hb 16,4 g/dl PLT 122,000/mm3 GB 10320 L 4140/mm3
- Adenopatie < 10 cm

- Dispnea… post COVID

marzo 23

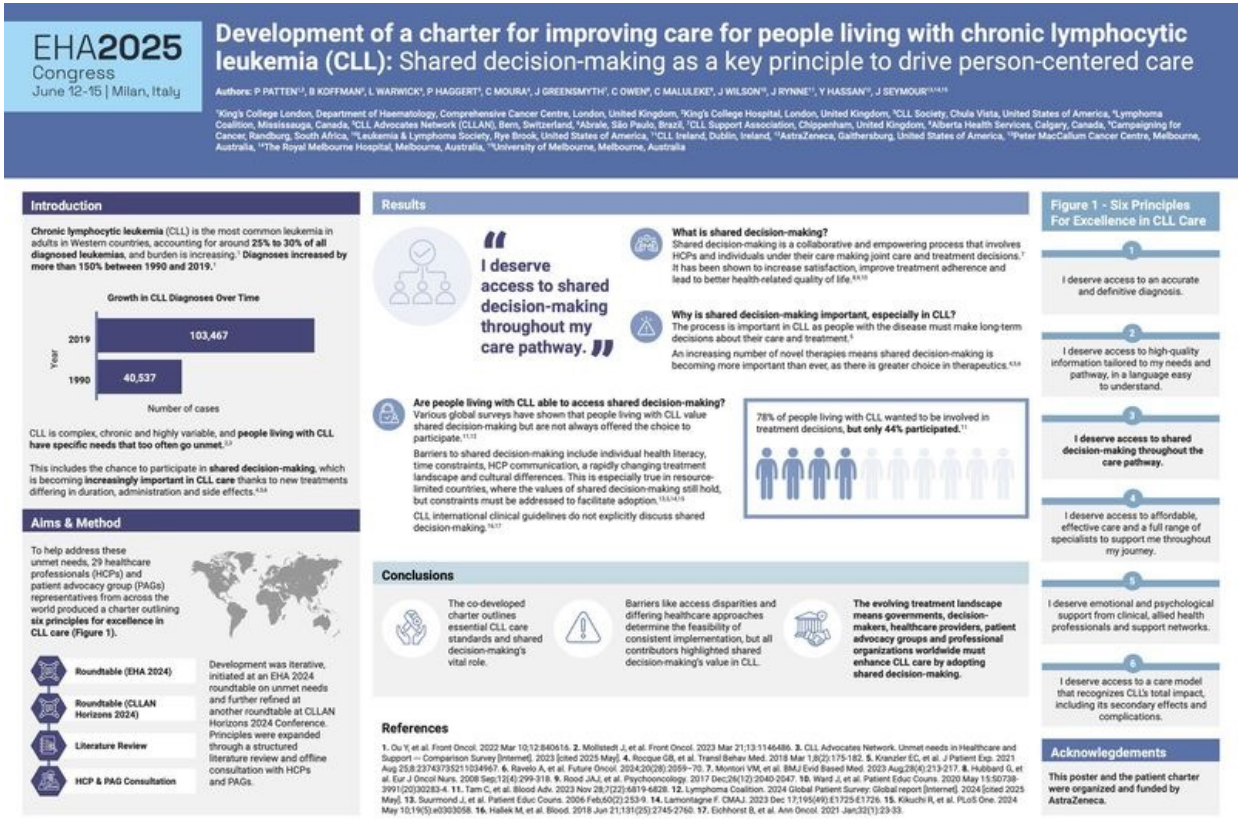
- Non sintomi B PC 96 Kg
- Hb 17,1 g/dl GB 16.280/mm3 L 9.000/mm3 PLT 130,000/mm3 LDH nella norma, eGFR 80 mL/min
- PD nodale : LN sottomentonieri a consistenza lignea, ridotte le adenopatie inguinali

« tutti quelli che mi vedono mi chiedono se sono malato»

supporto psico-oncologico

- esiste variabilità negli esiti psicologici e fisici dei pazienti con malattie croniche, anche tra quelli con la stessa malattia.
- il Modello di Autoregolamentazione di Leventhal (1980) propone che in risposta a una minaccia per la salute come un nuovo sintomo o segno fisico, gli individui costruiscono una rete interna di credenze (cioè percezioni di malattia) aventi contenuto cognitivo ed emotivo.
- la percezione della CLL da parte di un individuo è associata a stress specifico del cancro, sintomi depressivi e affaticamento

The Relation of Illness Perceptions to Stress, Depression, and Fatigue in Patients with Chronic Lymphocytic Leukemia. Travis D. Westbrook, et al. *Psychol Health. 2016 July ; 31(7): 891–902*
Individual differences moderate the relationship between physical symptom burden and psychological responses in individuals with Chronic Lymphocytic Leukemia. Eleshia J Morrison et. al. *Ann Hematol. 2016 Dec;95(12):1989-1997*



EHA2025 Congress
June 12-15 | Milan, Italy

Development of a charter for improving care for people living with chronic lymphocytic leukemia (CLL): Shared decision-making as a key principle to drive person-centered care

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Introduction

Chronic lymphocytic leukemia (CLL) is the most common leukemia in adults in Western countries, accounting for around **25% to 30% of all diagnosed leukemias**, and burden is increasing.[1] **Diagnoses increased by more than 150% between 1990 and 2019.**[1]

CLL is complex, chronic and highly variable, and **people living with CLL have specific needs that too often go unmet.**[2,3]

This includes the chance to participate in **shared decision-making**, which is becoming **increasingly important in CLL care** thanks to new treatments differing in duration, administration and side effects.[4,5,6]

Aims & Method

To help address these unmet needs, 29 healthcare professionals (HCPs) and patient advocacy group (PAGs) representatives from across the world produced a charter outlining **six principles for excellence in CLL care (Figure 1).**

- Roundtable (EHA 2024)
- Roundtable (CLLAN Horizons 2024)
- Literature Review
- HCP & PAG Consultation

Development was iterative, initiated at an EHA 2024 roundtable on unmet needs and further refined at another roundtable at CLLAN Horizons 2024 Conference. Principles were expanded through a structured literature review and offline consultation with HCPs and PAGs.

Results

> "I deserve access to shared decision-making throughout my care pathway."

What is shared decision-making?
Shared decision-making is a collaborative and empowering process that involves HCPs and individuals under their care making joint care and treatment decisions.[7] It has been shown to increase satisfaction, improve treatment adherence and lead to better health-related quality of life.[8,9,10]

Why is shared decision-making important, especially in CLL?
The process is important in CLL as people with the disease must make long-term decisions about their care and treatment.[5]

An increasing number of novel therapies means shared decision-making is becoming more important than ever, as there is greater choice in therapeutics.[4,5,6]

Are people living with CLL able to access shared decision-making?
Various global surveys have shown that people living with CLL value shared decision-making but are not always offered the choice to participate.[11,12]

Barriers to shared decision-making include individual health literacy, time constraints, HCP communication, a rapidly changing treatment landscape and cultural differences. This is especially true in resource-limited countries, where the values of shared decision-making still hold, but constraints must be addressed to facilitate adoption.[13,14,15]

CLL international clinical guidelines do not explicitly discuss shared decision-making.[16,17]

78% of people living with CLL wanted to be involved in treatment decisions, **but only 44% participated.**[11]

Conclusions

The co-developed charter outlines essential CLL care standards and shared decision-making's vital role.

Barriers like access disparities and differing healthcare approaches determine the feasibility of consistent implementation, but all contributors highlighted shared decision-making's value in CLL.

The evolving treatment landscape means governments, decision-makers, healthcare providers, patient advocacy groups and professional organizations worldwide must enhance CLL care by adopting shared decision-making.

References

1. Ou Y, et al. Front Oncol. 2022 Mar 10;12:840616. 2. Mollistedt J, et al. Front Oncol. 2023 Mar 21;13:1146486. 3. CLL Advocates Network. Unmet needs in Healthcare and Support — Comparison Survey [Internet]. 2023 [cited 2025 May]. 4. Rocque GB, et al. Transl Behav Med. 2018 Mar 1;8(2):175-182. 5. Kranzler EC, et al. J Patient Exp. 2021 Aug 25;8:23743735211034967. 6. Ravelo A, et al. Future Oncol. 2024;20(28):2059–70. 7. Montori VM, et al. BMJ Evid Based Med. 2023 Aug;28(4):213-217. 8. Hubbard G, et al. Eur J Oncol Nurs. 2008 Sep;12(4):299-318. 9. Rood JAJ, et al. Psychooncology. 2017 Dec;26(12):2040-2047. 10. Ward J, et al. Patient Educ Couns. 2020 May 15:S0738-3991(20)30283-4. 11. Tam C, et al. Blood Adv. 2023 Nov 28;7(22):6819-6828. 12. Lymphoma Coalition. 2024 Global Patient Survey: Global report [Internet]. 2024 [cited 2025 May]. 13. Saurmond J, et al. Patient Educ Couns. 2006 Feb;60(2):253-9. 14. Lamontagne F. CMAJ. 2023 Dec 17;195(49):E1725-E1726. 15. Kikuchi R, et al. PLoS One. 2024 May 10;19(5):e0303058. 16. Hallek M, et al. Blood. 2018 Jun 21;131(25):2745-2760. 17. Eichhorst B, et al. Ann Oncol. 2021 Jan;32(1):23-33.

Figure 1 - Six Principles For Excellence in CLL Care

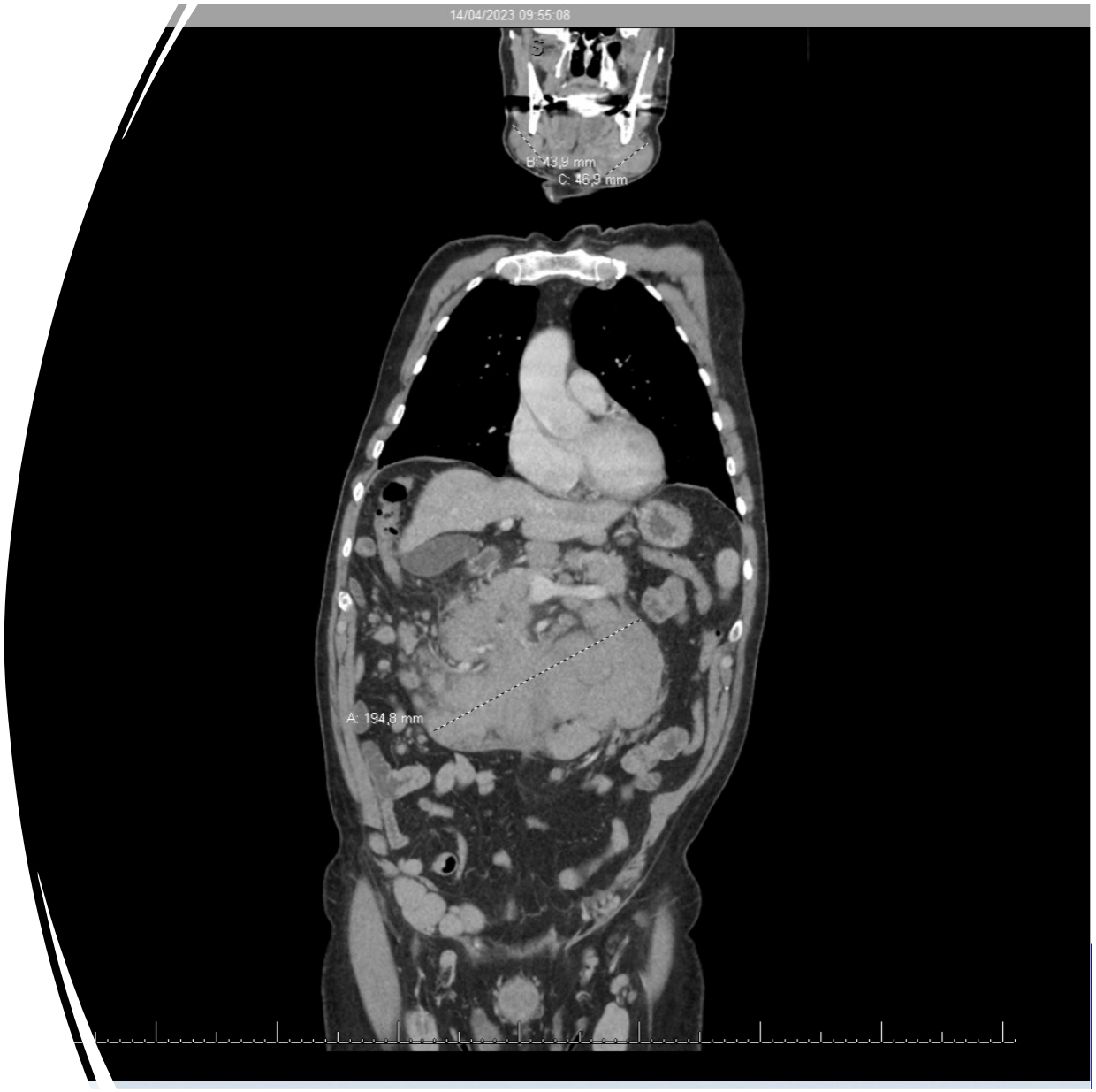
1. I deserve access to an accurate and definitive diagnosis.
2. I deserve access to high-quality information tailored to my needs and pathway, in a language easy to understand.
3. **I deserve access to shared decision-making throughout the care pathway.**
4. I deserve access to affordable, effective care and a full range of specialists to support me throughout my journey.
5. I deserve emotional and psychological support from clinical, allied health professionals and support networks.
6. I deserve access to a care model that recognizes CLL's total impact, including its secondary effects and complications.

Acknowledgements

This poster and the patient charter were organized and funded by AstraZeneca.

TC 4/4/23

- **Collo-torace**
  Al controllo attuale incremento volumetrico delle adenopatie in sede latero-cervicale bilateralmente, a tutti i livelli, la maggiore in sede sottomandibolare sinistra, del diametro trasverso massimo di 55 mm (VS 29 mm).
  Incremento volumetrico delle adenopatie in sede ascellare bilateralmente, la maggiore a destra, del diametro trasverso massimo di 34 mm (VS 22 mm). Sostanzialmente invariate per numero e dimensioni le adenopatie in sede ilo-mediastinica.
  Riduzione in compattezza delle aree di alterazione interstizio-alveolare a vetro smerigliato precedentemente segnalate bilateralmente.
  Addome
  Milza del diametro bipolare di 14,6 cm, rilievo invariato.
  Incremento volumetrico delle adenopatie confluenti lungo il ventaglio mesenterico con diametro complessivo massimo del di circa 18 cm.
  Incremento numerico e volumetrico delle adenopatie in sede interaorto-cavale e para-aortica sinistra, la maggiore del diametro trasverso massimo di circa 44 mm, e lungo le catene iliache esterne bilateralmente, la maggiore a sinistra del diametro trasverso massimo di 78 mm.
  Adenopatie in sede inguinale bilaterale, la maggiore a sinistra del diametro trasverso massimo di 36 mm.
  Non versamento libero in addome.
  Sostanzialmente invariati i restanti rilievi.



Valutazioni pre terapia

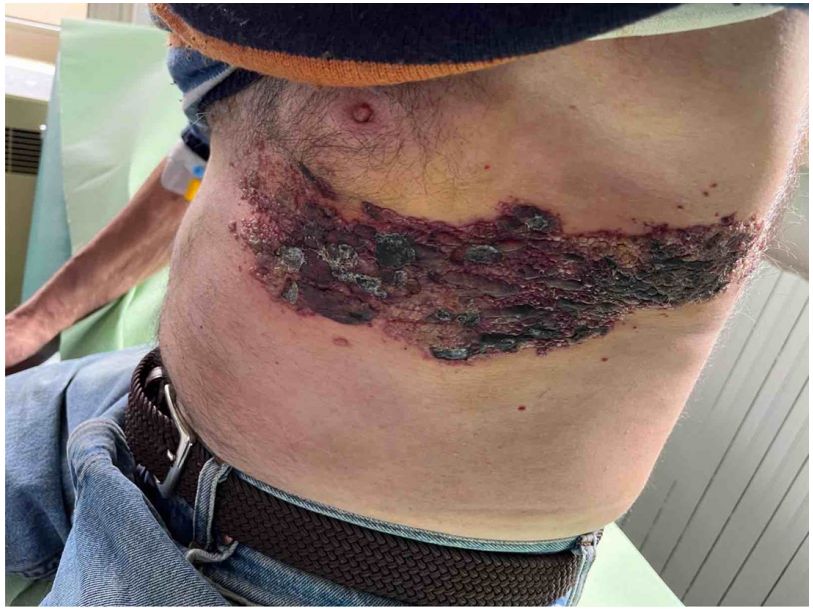
Valutazioni pre terapia
VACCINAZIONI

ECIL 7

	Inactivated influenza vaccine	Pneumococcal vaccines	Other inactivated vaccines	Comments
Multiple myeloma	Yearly vaccination (one dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised	One dose of PCV13 followed by one dose of PPSV23, at least 8 weeks later, is recommended (B II u), preferably before treatment or during maintenance	Other inactive vaccines should be considered 3–6 months after the end of treatment, according to age, comorbidities, and country recommendations	LAVs are contra-indicated until at least 3 months after the end of chemotherapy (D III)
Lymphoma	Yearly vaccination (one dose) is strongly recommended (A II u) as long as the patient is considered immunocompromised, except in patients receiving intensive chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months	One dose of PCV13 followed by one dose of PPSV23, at least 8 weeks later, is recommended (B II t), preferably before treatment or during maintenance, except in patients who are receiving high-dose chemotherapy or who are receiving or have received anti-CD20 antibodies in the previous 6 months	Human papillomavirus vaccine is recommended in healthy adolescents and young adults according to country recommendations for age after the end of treatment (B II t). Other inactive vaccines should be considered 3–6 months after the end of treatment, according to age, comorbidities, and country recommendations	In patients who are receiving or have received anti-CD20 antibodies in the previous 6 months, any inactivated vaccine should be delayed for at least 6 months after the last dose (B II u for IIV). LAVs are contra-indicated until at least 3 months after the end of chemotherapy (D III)
Chronic lymphocytic leukaemia	Same recommendation as for lymphoma patients	One dose of PCV13 followed by one dose of PPSV23, at least 8 weeks later, are recommended (B II u), preferably before treatment	Same recommendation as for lymphoma patients	Same recommendation as for lymphoma patients. Novel drugs might significantly impair the vaccination response

All the recommendations are based on laboratory endpoint—serological response, mainly seroconversion rate. ECIL 7=2017 European Conference on Infections in Leukaemia. LAVs=live-attenuated vaccines. PCV13=pneumococcal conjugate 13-valent vaccine. PPSV23=pneumococcal polysaccharide 23-valent vaccine. For the evidence-based medicine grading system (A II u, B II u, B II t, D III) see appendix.

Table 3: ECIL 7 recommendations for vaccination of patients with lymphoproliferative diseases



Vaccination of patients with haematological malignancies who did not have transplantations: guidelines from the2017 European Conference on Infections in Leukaemia (ECIL 7) *Malgorzata Mikulska et al. Lancet Infect Dis* 2019;19: e188–99

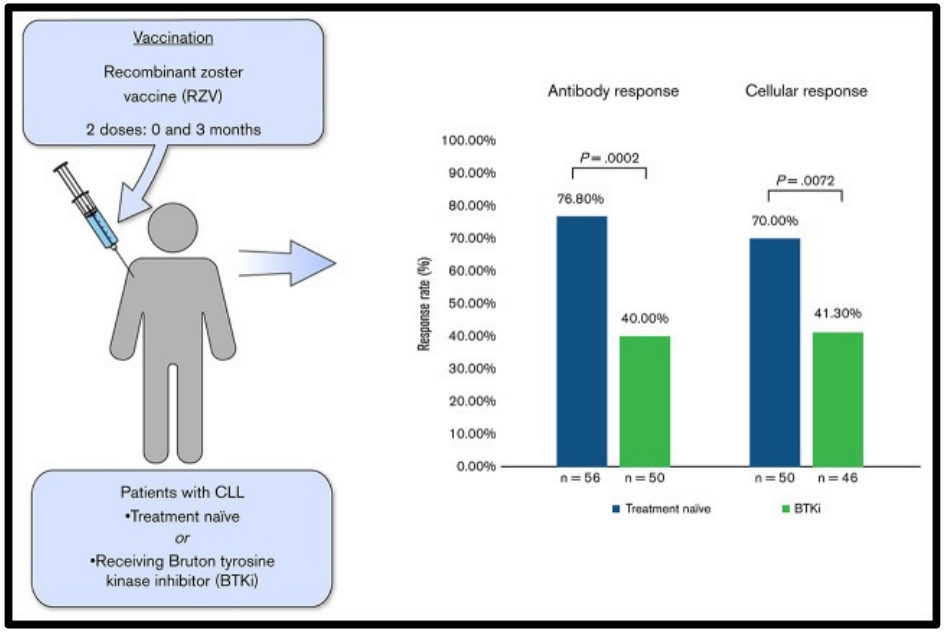
HZ: profilassi e vaccino

- HZ reactivation is frequently observed in patients with lymphoma or chronic lymphocytic leukemia, but is distributed over a prolonged risk period, even years after treatment discontinuation.
- In **CLL pts treated with ibrutinib the incidence of HZ was 5%** during a long-term follow-up while 2.9 cases per 1,000 patient-years in those treated with various regimens in the pre-ibrutinib era. There is no clear evidence that HZ risk is greatly increased after rituximab and other anti-CD20 treatments
- The expert panel agreed that aRZV is highly recommended, possibly at the onset of the disease while planning hematologic treatment, and particularly in elderly patients, although low immunogenicity after anti-CD20 treatment is expected.
- In patients treated with fludarabine or bendamustine, antiviral prophylaxis is indicated until at least 1 month after the second dose of vaccine.
- Anti varicella zoster virus (VZV) or herpes simplex virus (HSV)prophylaxis is not recommended during ibrutinib or idelalisib treatment; however, a suppressive therapy with acyclovir or valacyclovir should be considered in patients with a history of recurrent VZV or HSV disease in the last 12 months

Towards personalized prevention of Herpes zoster infection in patients with hematologic diseases orhematopoietic stem cell transplant recipients: a position paper from an ad hoc Italian expert panel
Corrado Girmenia, Fabio Ciceri, Paolo Corradini, Antonio Cuneo, Fortunato D'Ancona,Pellegrino Musto, Antonio Maria Risitano, Maria Teresa Voso, Adriano Venditti. and Giovanni Barosi. Haematologica 109 November 2024

Infection control in patients treated for chronic lymphocytic leukemia with ibrutinib or idelalisib: recommendations from Italian society of hematology. *Pier Luigi Zinzani, Alessandro Rambaldi, Gianluca Gaidano, Corrado Girmenia,Monia Marchetti, Fabrizio Pane, Sante Tura, Giovanni Barosi*. Leukemia Research 81 (2019) 88–94

CLL: risposta immune al vaccino adiuvato ricombinante per HZ

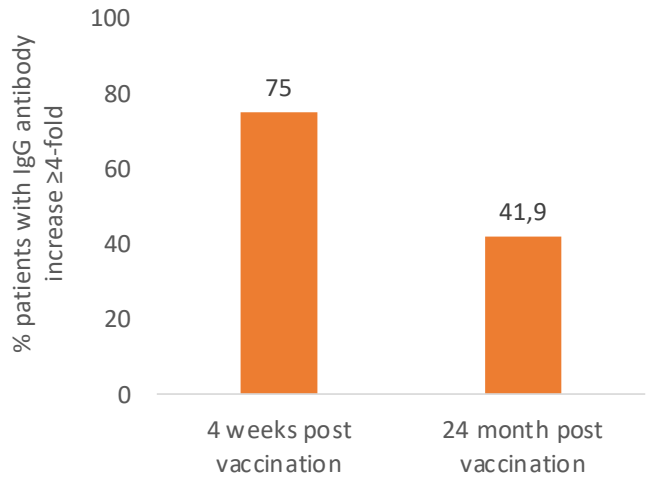


- BTKis interfere with B-cell receptor signaling and may suppress antibody immune responses.
- CLL receiving the BNT162b2 messenger RNA) COVID-19 vaccine, 32 of 58 (55%) treatment-naïve (TN) patients achieved a humoral response, compared with only 8 of 50 (16%) patients treated with a BTKi.

BTK inhibitors impair humoral and cellular responses to recombinant zoster vaccine in CLL. *Christopher Pleyer et al.Blood* Advance. 22 MARCH 2022 • VOLUME 6

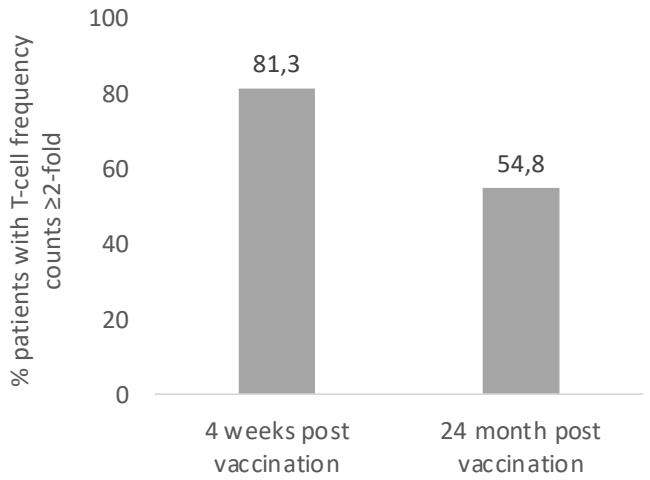
RZV elicits and maintains durable humoral and T-cell responses for 24 months in leukemia patients receiving BTKi therapy

% of patients meeting or sustaining humoral immunogenicity threshold after vaccination



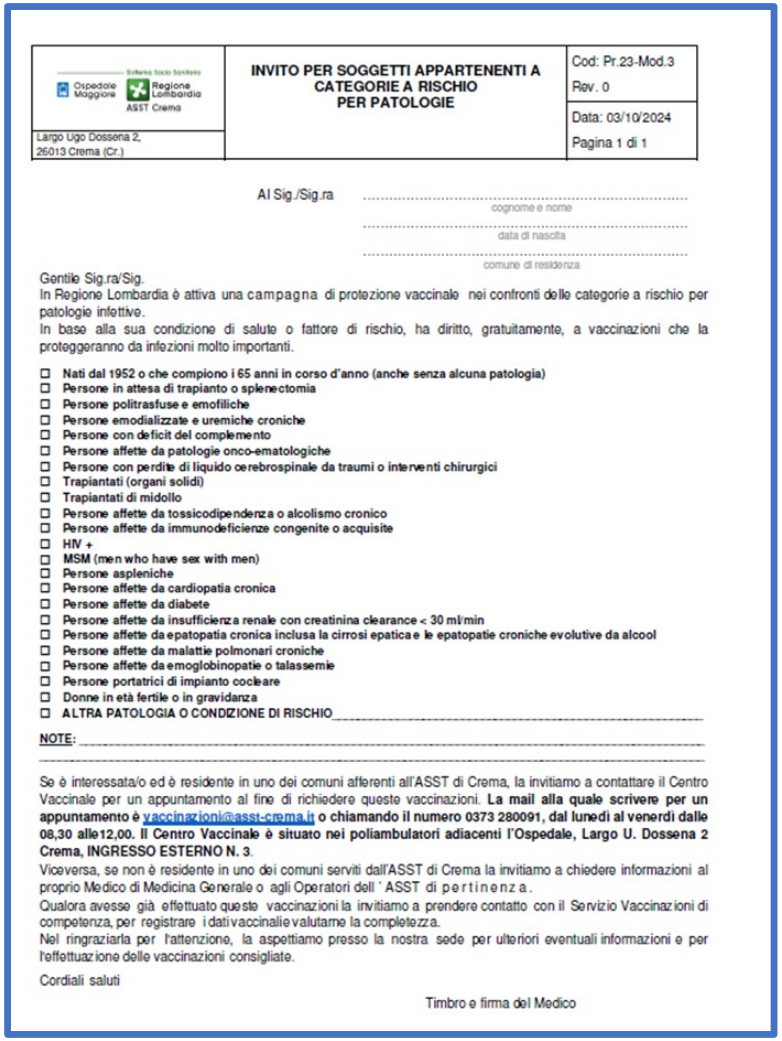
41.9% of all study patients maintained ≥4-fold increase in IgG antibodies 24 month after vaccination, accounting for 56.5% of patient who met this threshold 4 weeks after vaccination

% of patients meeting or sustaining cellular immunogenicity threshold after vaccination



54.8% of all study patients maintained ≥2-fold increase in IgG antibodies 24 month after vaccination, accounting for 65.4% of patient who met this threshold 4 weeks after vaccination

Long-term results of vaccination with adjuvanted recombinant varicella zoster glycoprotein E during initial Bruton tyrosine kinase inhibitors therapy for chronic lymphocytic leukemia or lymphoplasmacytic lymphoma. *Michael T Brady et al.* Am J Hematol 2023 Oct



Ospedale Maggiore – Regione Lombardia – ASST Crema Largo Ugo Dossena 2, 26013 Crema (Cr.)	**INVITO PER SOGGETTI APPARTENENTI A CATEGORIE A RISCHIO PER PATOLOGIE**	Cod: Pr.23-Mod.3 Rev. 0 Data: 03/10/2024 Pagina 1 di 1

Al Sig./Sig.ra .....
cognome e nome
.....
data di nascita
.....
comune di residenza

Gentile Sig.ra/Sig.
In Regione Lombardia è attiva una campagna di protezione vaccinale nei confronti delle categorie a rischio per patologie infettive.
In base alla sua condizione di salute o fattore di rischio, ha diritto, gratuitamente, a vaccinazioni che la proteggeranno da infezioni molto importanti.

- ☐ **Nati dal 1952 o che compiono i 65 anni in corso d'anno (anche senza alcuna patologia)**
- ☐ **Persone in attesa di trapianto o splenectomia**
- ☐ **Persone politrasfuse e emofiliche**
- ☐ **Persone emodializzate e uremiche croniche**
- ☐ **Persone con deficit del complemento**
- ☐ **Persone affette da patologie onco-ematologiche**
- ☐ **Persone con perdite di liquido cerebrospinale da traumi o interventi chirurgici**
- ☐ **Trapiantati (organi solidi)**
- ☐ **Trapiantati di midollo**
- ☐ **Persone affette da tossicodipendenza o alcolismo cronico**
- ☐ **Persone affette da immunodeficienze congenite o acquisite**
- ☐ **HIV +**
- ☐ **MSM (men who have sex with men)**
- ☐ **Persone aspleniche**
- ☐ **Persone affette da cardiopatia cronica**
- ☐ **Persone affette da diabete**
- ☐ **Persone affette da insufficienza renale con creatinina clearance < 30 ml/min**
- ☐ **Persone affette da epatopatia cronica inclusa la cirrosi epatica e le epatopatie croniche evolutive da alcool**
- ☐ **Persone affette da malattie polmonari croniche**
- ☐ **Persone affette da emoglobinopatie o talassemie**
- ☐ **Persone portatrici di impianto cocleare**
- ☐ **Donne in età fertile o in gravidanza**
- ☐ **ALTRA PATOLOGIA O CONDIZIONE DI RISCHIO**_____

NOTE: _____

Se è interessata/o ed è residente in uno dei comuni afferenti all'ASST di Crema, la invitiamo a contattare il Centro Vaccinale per un appuntamento al fine di richiedere queste vaccinazioni. **La mail alla quale scrivere per un appuntamento è vaccinazioni@asst-crema.it o chiamando il numero 0373 280091, dal lunedì al venerdì dalle 08,30 alle12,00. Il Centro Vaccinale è situato nei poliambulatori adiacenti l'Ospedale, Largo U. Dossena 2 Crema, INGRESSO ESTERNO N. 3.**
Viceversa, se non è residente in uno dei comuni serviti dall'ASST di Crema la invitiamo a chiedere informazioni al proprio Medico di Medicina Generale o agli Operatori dell'ASST di pertinenza.
Qualora avesse già effettuato queste vaccinazioni la invitiamo a prendere contatto con il Servizio Vaccinazioni di competenza, per registrare i dati vaccinali e valutarne la completezza.
Nel ringraziarla per l'attenzione, la aspettiamo presso la nostra sede per ulteriori eventuali informazioni e per l'effettuazione delle vaccinazioni consigliate.

Cordiali saluti

Timbro e firma del Medico

Decisione di cura

Caratteristiche cliniche

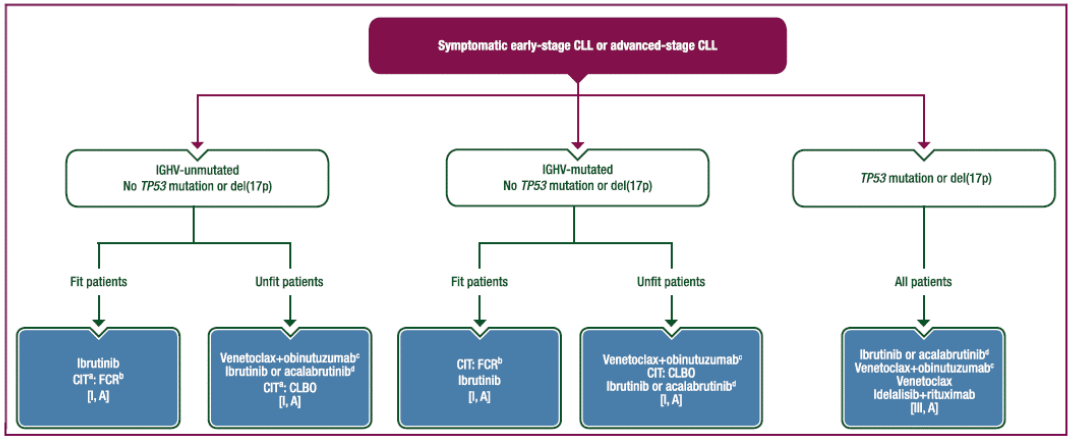
- 71 anni
- pensionato, vita attiva
- autonomo
- Abita a Mediglia (34 Km dall'Ospedale)
- iperteso in terapia con ACE inibitore

Caratteristiche biologiche

- Ripete FISH 17p e TP53 negative
- VHIg MUTATED (noto)
- Valutazione midollare : cellularità 50 % , 25% linfociti B di piccole dimensioni a distribuzione nodulare e interstiziale fenotipo B . Reperto compatibile con localizzazione di LNH a cellule B, piccoli linfociti
- VIROLOGIA HBV, HCV, HIV negativi

Quale terapia?
Aprile 23

ESMO guidelines 2020

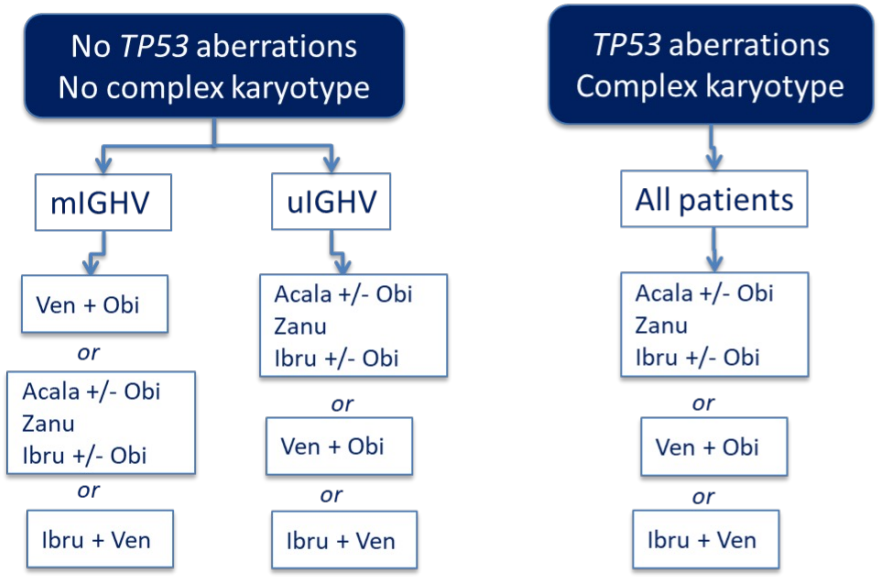


Chronic lymphocytic leukaemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up.*B. *Eichhorst,T. Robak, E. Montserrat, P. Ghia, C. U. Niemann, A. P. Kater, M. Gregor, F. Cymbalista, C. Buske,P. Hillmen, M. Hallek,U. Mey, on behalf of the ESMO Guidelines Committee.* Annals of Oncology. Volume 32 - Issue 1 - 2021

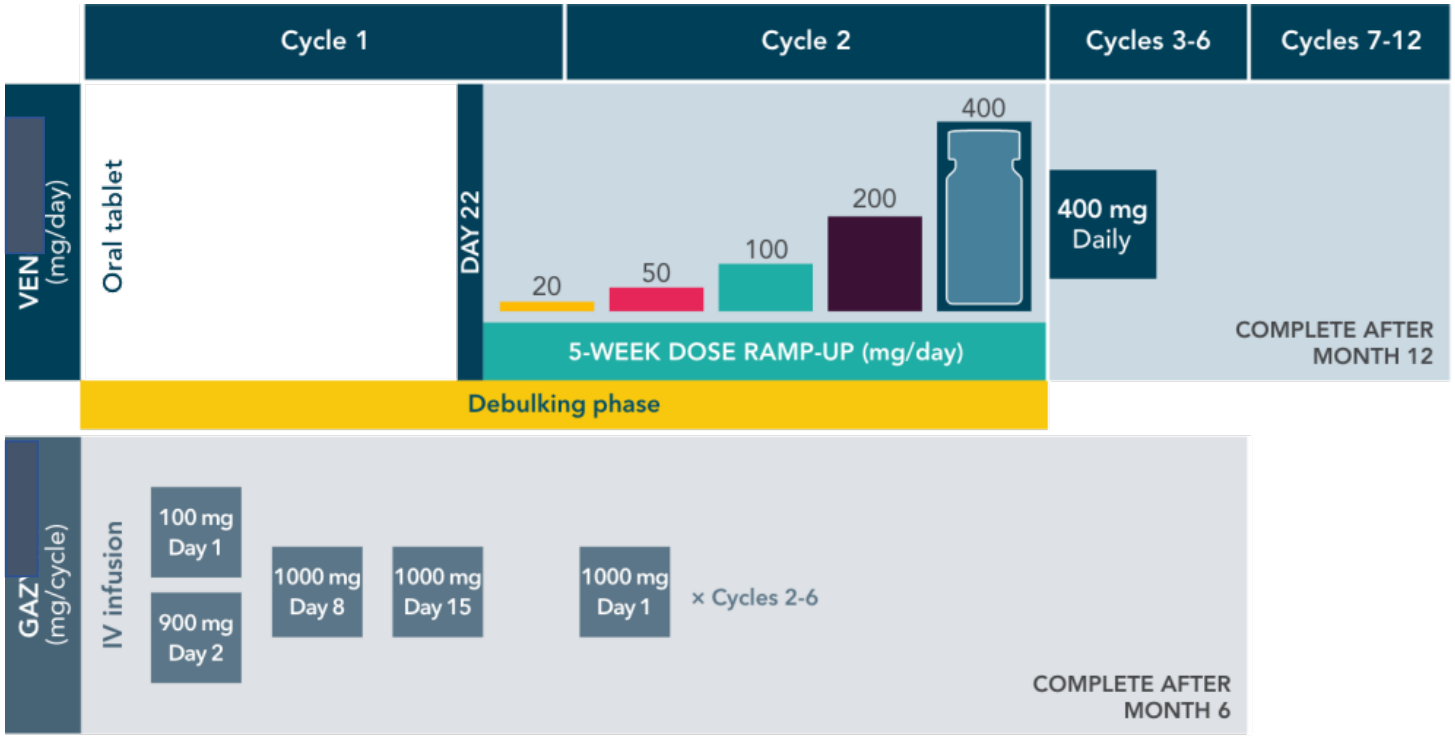
Quale terapia?

ONKOPEDIA guidelines 4/23

Symptomatic early stage or advanced-stage CLL



Avvio VEN-O

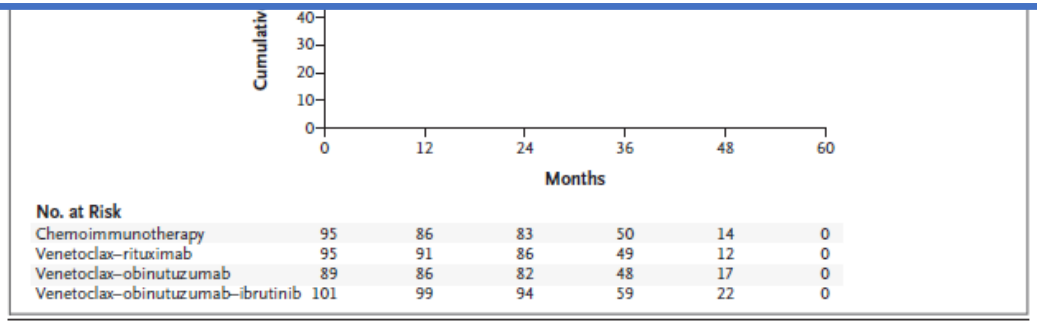


Graphic not to scale. Each cycle is 28 days.

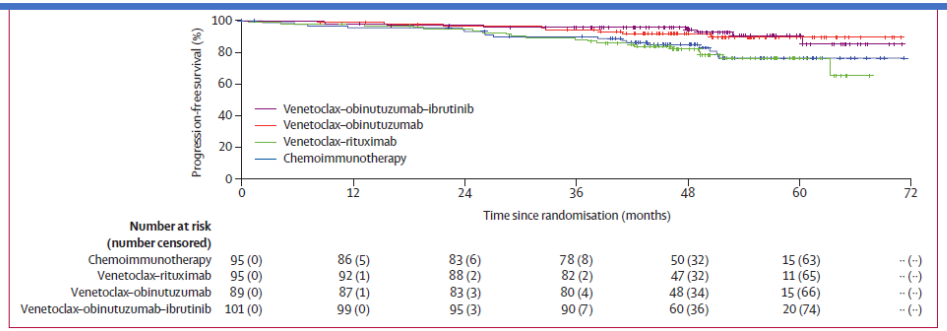
VEN-Obi (mutated TP53 WT)

4-year PFS rates were highest in the Ven-Obi-Ibr group (85.5%), followed by Ven-Obi (81.8%)

5-year PFS rates
for pts with unmutated IGHV were 33.6% (CIT), 48.3% (RV), 59.0% (GV),
for pts with **mutated** IGHV were75.9% (GIV), and 75.3% (CIT), 71.0% (RV), **82.9% (**GV), and 89.1% (GIV)
(Fürstenau,**EHA25 oral presentation)** for pts with mutated IGHV



First-Line Venetoclax Combinations in Chronic Lymphocytic Leukemia. B. Eichhorst et al. *NEJM 388;19 nejm.org May 11, 2023*.

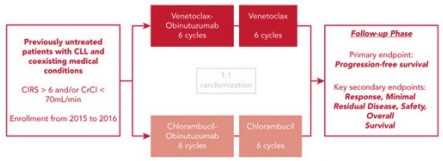


First-line venetoclax combinations versus chemoimmunotherapy in fit patients with chronic lymphocytic leukaemia (GAIA/CLL13): 4-year follow-up from a multicentre, open-label, randomised, phase 3 trial. Moritz Fürstenau et al. *Lancet Oncol* 2024; 25: 744–59

Long-Term Outcomes After Fixed-Duration Venetoclax-Obinutuzumab Treatment of Chronic Lymphocytic Leukemia (CLL)

Context or Research

- CLL14 is a randomized phase 3 trial that compares the targeted fixed-duration treatment with the BCL-2 inhibitor venetoclax in combination with the type-II CD20 antibody obinutuzumab to chemoimmunotherapy with chlorambucil and obinutuzumab, in elderly unfit patients with previously untreated CLL
- Clinical trial registration information: NCT02242942, EudraCT 2014-001810-24

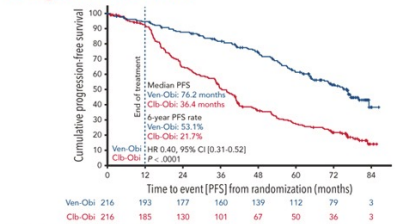


Median observation time: 76.4 months

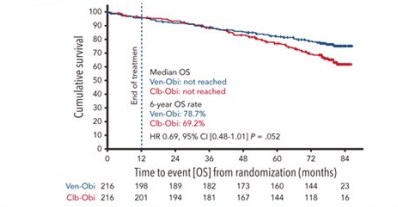
- Here we provide a long-term analysis with all patients being of study treatment for more than 5 years

Main Findings

- **Progression-free survival**



- **Overall survival**



Conclusions: One-year fixed-duration venetoclax-obinutuzumab induces durable treatment-free remissions in patients with previously untreated CLL. Minimal residual disease status at the end of treatment is associated with progression-free and overall survival.

*Al-Sawaf et al. DOI: 10.1182/**blood**.2024024631*

blood Visual Abstract

American Society of Hematology
Helping hematologists conquer blood diseases worldwide

- At a median observation time of 76.4 months
- **PFS remained superior for Ven-Obi** compared with ClbObi (median, **76.2** vs 36.4 **months**; hazard ratio [HR], 0.40; 95% confidence interval [CI], 0.31-0.52; P < .0001).
- TTNT was longer after Ven-Obi (6-year TTNT, 65.2% vs 37.1%; HR, 0.44; 95% CI, 0.33-0.58; P < .0001).
- In the Ven-Obi arm, presence of del(17p), unmutated immunoglobulin heavy-chain variable region, and **lymph node size of ≥5 cm were independent prognostic factors for shorter PFS.**
- **The 6-year OS rate was 78.7% in the Ven-Obi** and 69.2% in the Clb-Obi arm (HR, 0.69; 95% CI, 0.48-1.01; P = .052)

avvio VEN-O Area MAC G1 C1

- Ore 8 inizia premedicazione (**metilprednisone 80 mg,** paracetamolo, clorfenamina) e rasburicase
- dopo 90’ dall’inizio dell’infusione ..rash puntiforme dita delle mani
- sospende
- idrocortisone 100 mg
- riprende a velocità dimezzata
- dopo 60 minuti iperpiressia, sospende
- dimesso al domicilio dopo 2 ore di osservazione

TLS rischio

Definition of tumor lysis syndrome (TLS)

The below listed criteria defined by Cairo and Bishop[1] should be used to diagnose a laboratory or clinical tumor-lysis syndrome (TLS).

Laboratory tumor-lysis syndrome (LTLS):

Defined as the presence of two or more electrolyte changes as described below within 3 d before or 7 d after the initiation of treatment. For the purposes of this study, this window applies to the initiation of any study therapy and each dose escalation of venetoclax.

Uric acid	≥ 476 µmol/l or 25% increase from baseline
Potassium	≥ 6.0 mmol/l or 25% increase from baseline
Phosphorus	≥1.5 mmol/l (in adults) or 25% increase from baseline
Corrected calcium	<1.75 mmol/l or 25% decrease from baseline

Clinical tumor-lysis syndrome (CTLS):

CTLS is defined as the presence of LTLS (see above) and any one or more of the following criteria

Creatinine*: increase in serum creatinine level of 0.3 mg/dL or ≥ 1.5 x institutional upper limit of normal (ULN) or the presence of oliguria
Cardiac dysrhythmia or sudden death probably or definitely caused by hyperkalemia *
Seizure *

*) Not directly or probably attributable to another therapeutic agent (e.g. rise in creatinine after amphotericin administration).

Area MAC G2 CICLO 1

- Esami stabili, non alterazioni elettrolitiche e della funz renale
- Terapia infusa senza problemi

- +5 w inizia **RAMP** UP venetoclax

Trattamento

Tossicità

- Reazione infusionale g1C1
- Neutropenia G1 (4-9 m)
- Incremento transaminasi <2X e CPK<2 x (dal 10 m)

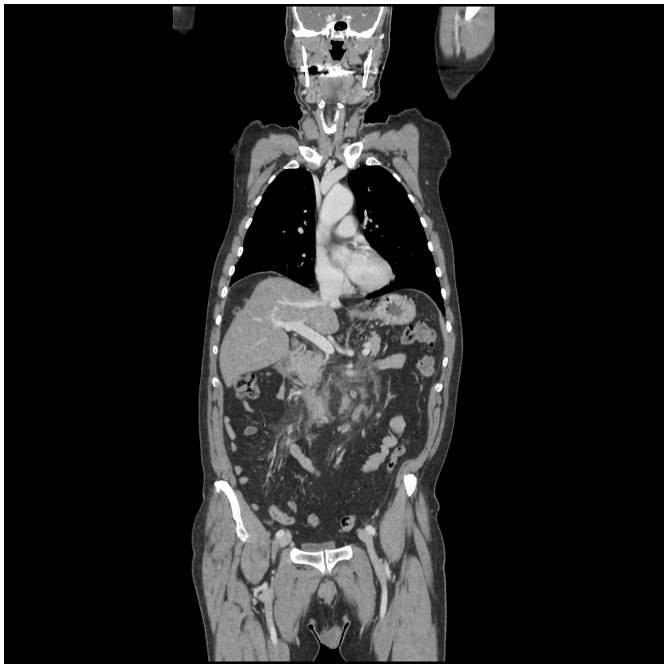
Risultati

- Riduzione adenopatie dal g15 Ciclo 1
- Normalizzazione obiettività megalie superficiali dal ciclo 4
- Ecoaddome a 6 mesi : non megalie

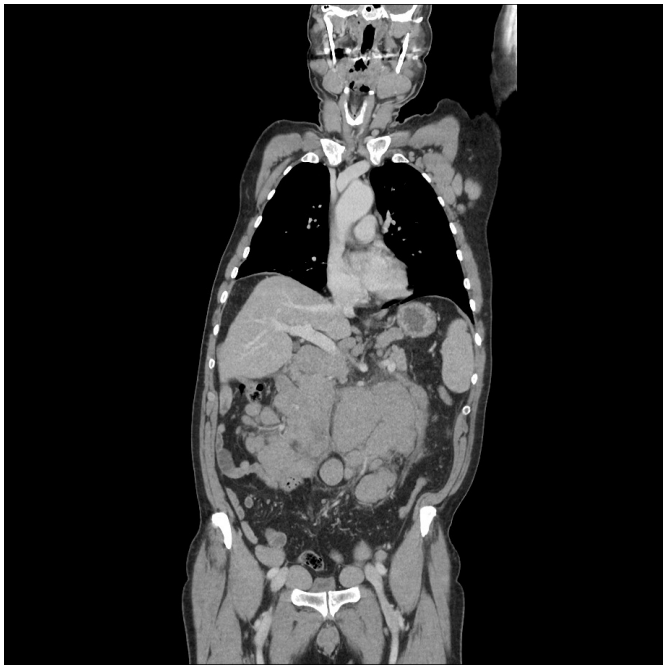
... Concluso terapia

Rivalutazione di malattia: TC

11/06/24



14/04/23



Rivalutazione di malattia

2/10/24+3 mesi

EO: asintomatico. Non LN. non epatosplenomegalia

- esami ematici : Hb 15.8 GB 4820 N 2230 L 1770
- IgG 683 IgA 139 IgM 13 beta2=4.4 EFS: non CM GOT 3.2 bil 0.6 GOT 60 GPT 73 LDH 283
- Tipizzazione linfocitaria su SP: assenza B maturi
- rivalutazione midollare : cellularità 40% staging negativo per CLL

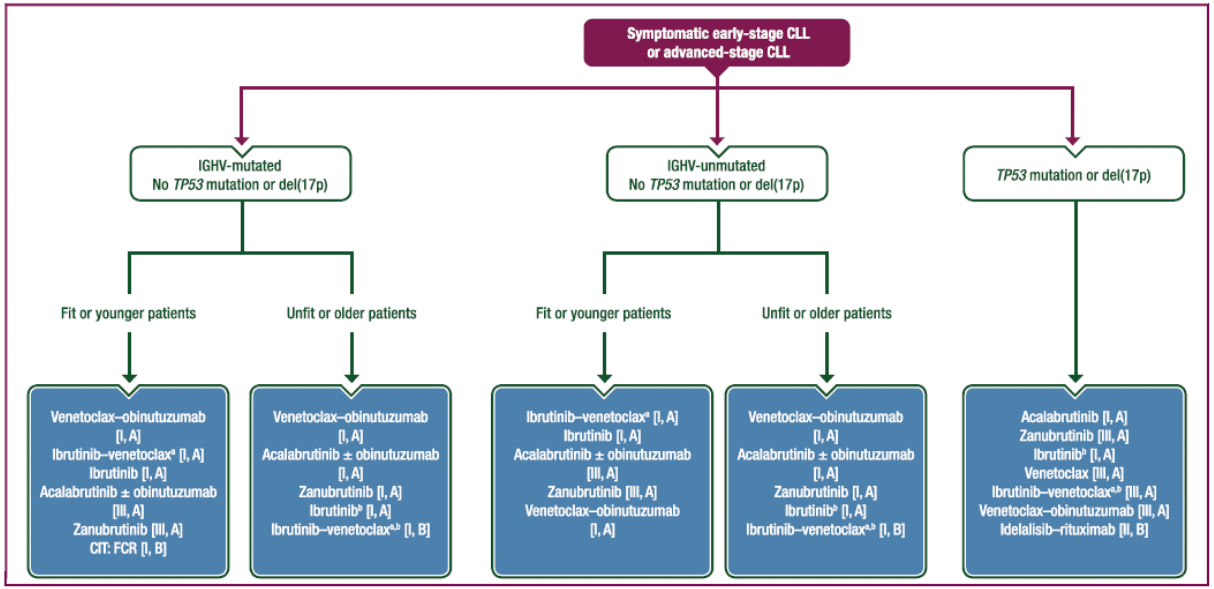
27/5/25 +12 mesi

EO: condizioni cliniche generali buone. Non eventi infettivi significativi. Non LN. non epatosplenomegalia

- Hb 15,9 g/dl, PLT 129000/mmc, GB 6950/mmc (N 3370/mmc, L 2740/mmc).
- Ecografia addome e linfonodi: fegato steatosico, non adenopatie.

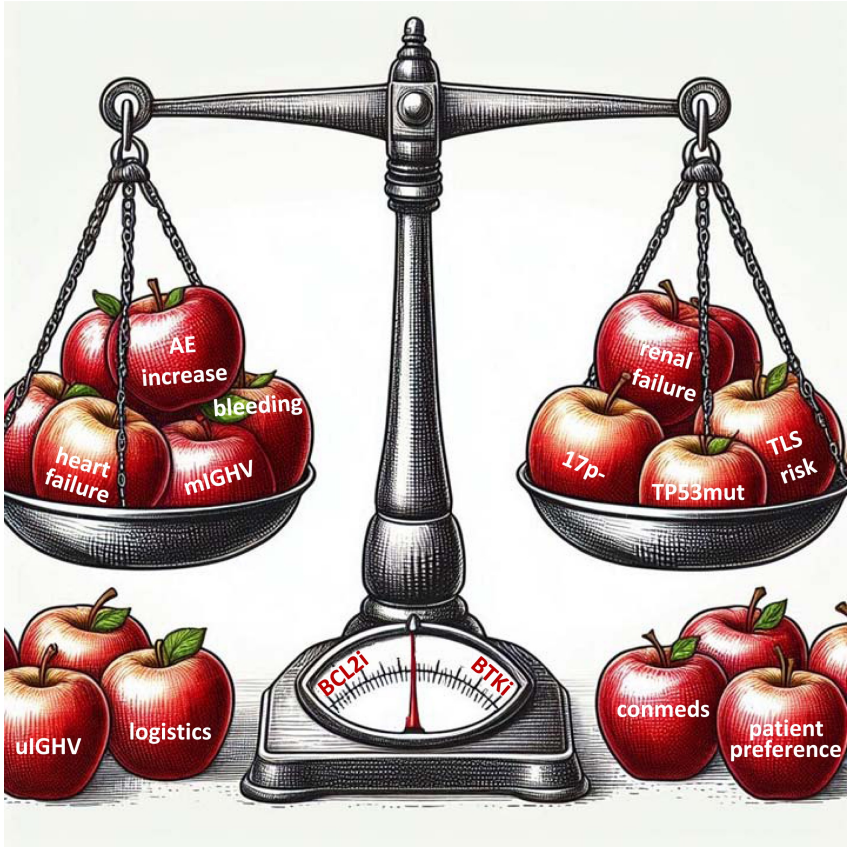
Se avessimo scelto oggi?

ESMO 2024



ESMO Clinical Practice Guideline interim update on new targeted therapiesin the first line and at relapse of chronic lymphocytic leukaemia. B. Eichhorst et al. *Annals of Oncology 2024*

Se avessimo dovuto scegliere oggi?



Patient and medical goals and priorities, including preferences where present for treatment-free remissions

potential complications in view of comorbidities and concurrent medications

the perception of treatment destination, whether sequential non-curative strategies are favored, and/or if potential curative

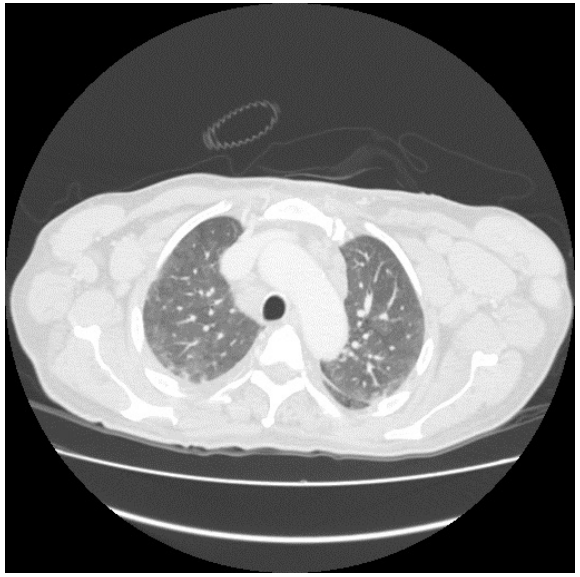
the availability of clinical trials, perception of their merits and effect on the treatment journey.

CASO CLINICO 4

Uomo di 63 anni

PS ASST CREMA 25/10/2017

ACCEDE per: dispnea e lateropulsione sx con ripetuti episodi di caduta a terra



Accettata il : 25-10-2017
Stampato il : 25-10-2017
Ora : 18:32
Pag. 1 di 2

Urgente

Nato/a il : 14-11-1953 Sesso : M
Reparto : **Pronto Soccorso Medico**

Esame	*Valore*		*U.M.*	*Valori rif.*
Esame Emocromocitometrico - Morfologico				
B-Leucociti(WBC)	132,88	*	10^3/mm3	[4,00 - 11,00]
B-Eritrociti(RBC)	1,83	*	10^6/mm3	[4,00 - 6,40]
B-Emoglobina(HGB)	4,9	*	g/dl	[13,0 - 18,0]
B-Ematocrito(HCT)	18,3	**	%	[37,0 - 54,0]
Volume Globulare(MCV)	100,0		fl	[79,0 - 101,0]
Contenuto medio Hb(MCH)	26,8		pg	[26,0 - 35,0]
Concentrazione media Hb(MCHC)	26,8	*	g/dl	[31,0 - 37,0]
RDW-CV%	24,4	**	%	[11,0 - 16,0]
B-Piastrine(PLT)	128	*	10^3/mm3	[130 - 400]
Gran. Neutrofili%	5,0	**	%	[37,0 - 75,0]
Gran. Eosinofili%	1,0		%	[0,0 - 7,0]
Gran. Basofili%	0,0		%	[0,0 - 1,5]
Linfociti%	92,0	**	%	[20,0 - 50,0]
Monociti%	2,0		%	[1,0 - 13,0]

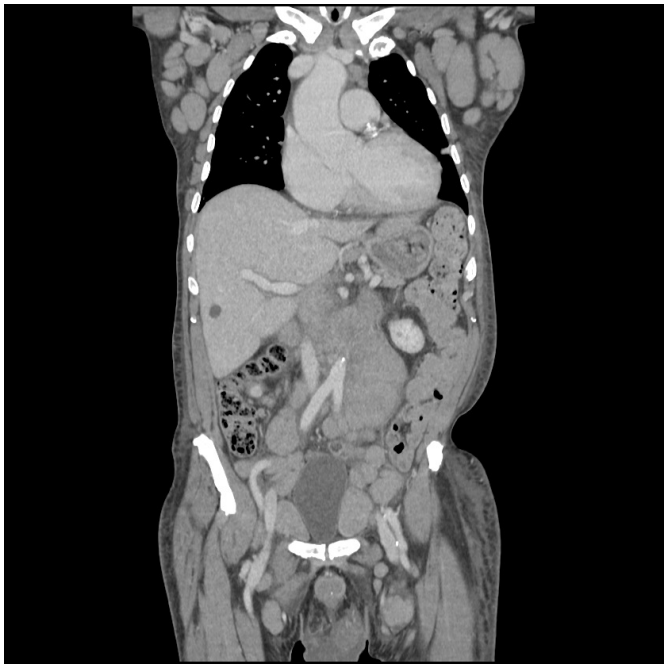
Linfocitosi, presenza di rari elementi immaturi e numerose ombre di Gumprecht. Formula letta al M.O.

PS ASST CREMA

- Pensionato
- vive solo, supportato da sorella
- (ex) alcolista

- APR:
  - Iperteso, scarsa compliance alle terapie
- APP
  - Da tempo malessere, astenia e megalie superficiali , rifiutava valutazioni mediche

PS ASST-CREMA



- Ricoverato in RIA per insuff respiratoria e instabilità emodinamica

RICOVERO in ONCOLOGIA (S.S Ematologia)

- All'ingresso in reparto paziente in condizioni generali compromesse, dispnoico e in stato di agitazione psico-motoria con episodi confusionali e di disorientamento spazio-temporale.
- Esami ematici:
  - Hb = 7.1g/dl GB = 111.430 L PLT = 114.
  - Inoltre glucosio = 148 mg/dl, urea = 106 mg/dl creatinina = 0.99 mg/dl, Calcio = 7.9 mg/dl, fosfato =7.7 mg/dl,
  - Bil tot = 4.25 mg/dl (dir = 0.56), LDH 346 mU/ml, aptoglobina non consumata, Reticolociti non incrementati DAT negativo
  - beta-2-microglobulina 5.5 mg/L (v.n. fino a 1.8). Ig policlonali nei limiti
  - BNP = 1162 pg/ml (v.n. fino a 100), TNI nei limiti,
  - ELF CM IgG lambda in zona gamma non quantizzabile (nota dall'agosto 2007)
  - PCR = 1.78 mg/dl, Urato = 13.8 mg/dl
  - HBsAg = neg, HBcAb neg, HBsAb neg HCV e HIV = neg.
- IF su SP: CLL classica
- Trattamento : steroidea endovenosa, diuretico e.v , ossigenoterapia, supporto trasfusionale, EBPM , folati

I linea di trattamento dicembre 2017

- 64 anni
- FISH negativa per 17p-, 11q-, +12 e 13q-
- BOM: 90% infiltrato piccoli linfociti
- Cariotipo : non metafasi

Trattamento

Avviato a trattamento **R-Bendamustina X 6 cicli**

- RP di malattia.
- Profilassi cotrimoxazolo e aciclovir

Non EC grado 3, buona compliance

II linea di trattamento marzo 2019

Criteri di trattamento LN e anemia

- 65 anni
- +15 mesi TTNT
- CIRS 8

- Rivalutazione FISH negativa per 17p
- TP53 WT
- VHIg UNMUTATED
- BOM : 60% infiltrato piccoli linfociti
- Cariotipo: 46 XY (15 metafasi)

Trattamento

- BTKi (ibrutinib)

Valutazioni pre terapia BTKi

Valutazione cardiologica pre trattamento

comorbidità

- iperteso non a target
- sovrappeso BMI: 27
- non diabetico
- non fumatore
- Non dislipidemia

Valutazione cardiologica

- Precedente tp : Olmesartan Medoxomil + Amlodipina
- Nuova terapia: Ramipril/Amlodipina

→ non controindicazioni cardiologiche

Valutazione cardio-oncologica (team e ambulatorio dedicato dal 6/2023)

Pazienti che iniziano un trattamento a rischio di CTR-CVT

- ✓ ECG
- ✓ esito di biomarcatori (TNI, BNP), HbA1c, profilo lipidico sec farmaco/score
- ✓ Anamnesi farmacologica

in CARDIOLOGIA

- ✓ indicazioni/modifiche circa la terapia cardiologica
- ✓ indicazioni di prevenzione
- ✓ ecocardiogramma con GLS (global longitudinal strain)
- ✓ prescrizione di eventuali ulteriori accertamenti cardiologici necessari
- ✓ idoneo SCORE per identificare la classe di rischio del paziente
- ✓ giudizio circa eventuale controindicazione assoluta alla terapia oncologica/ematologica proposta

La **circostanza ottimale** per valutare l'opportunità di implementare una strategia di prevenzione CTR- CVT nei pazienti oncologici è al momento della **diagnosi e prima di iniziare il trattamento** antineoplastico, consente al team oncologico non solo di definire la terapia antitumorale tenendo in considerazione il rischio CV, ma anche di educare il paziente sul proprio rischio CV, di personalizzare la sorveglianza CV e le strategie di follow-up

BTKi

- **Recommendation Table 12 — Recommendations for baseline risk assessment and monitoring during Bruton tyrosine kinase inhibitor therapy**

Recommendations	Class[a]	Level[b]
BP monitoring and management		
BP measurement is recommended for patients treated with BTK inhibitors at every clinical visit.[26,4]	I	B
Weekly home monitoring of BP during the first 3 months and every month thereafter should be considered for patients treated with BTK inhibitors.	IIa	C
Echocardiography		
Baseline echocardiography is recommended in high-risk patients[c] scheduled to receive BTK inhibitors.[26,7,26,8]	I	C
TTE is recommended in all patients who develop AF during BTK inhibitor therapy.	I	C
AF		
Opportunistic screening for AF by pulse-taking or ECG rhythm strip is recommended at every clinical visit during BTK inhibitor therapy.[27,3]	I	C

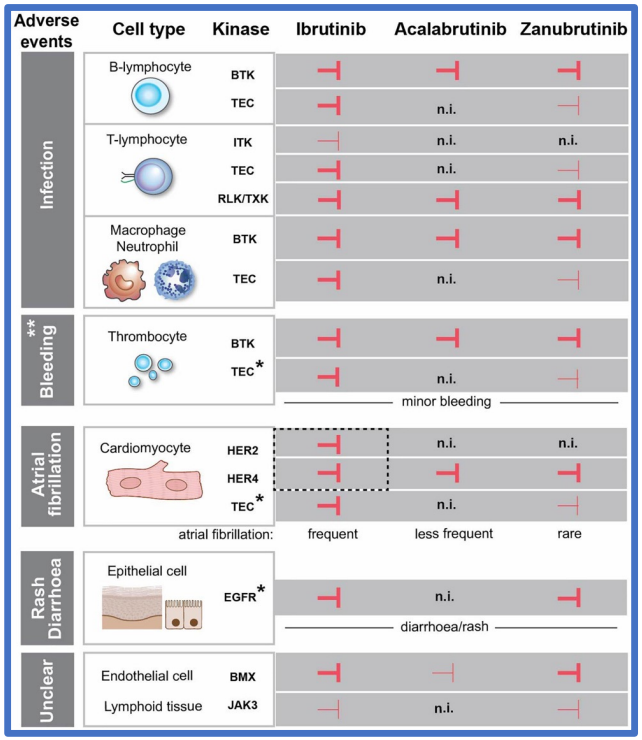
ESC European Society of Cardiology
European Heart Journal (2022) 00, 1–133
https://doi.org/10.1093/eurheartj/ehac244

ESC GUIDELINES

2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (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 (ESC)

BTKi e Tox cardiologica



Comparative Analysis of BTK Inhibitors and Mechanisms Underlying Adverse Effects. **H. Yesid Estupiñán et al.** *Front Cell Dev Biol. 2021 Mar 11;9:630942*

National Comprehensive Cancer Network®

NCCN Guidelines Version 3.2025
Chronic Lymphocytic Leukemia/Small Lymphocytic Lymphoma

Table 4. Adverse Events of BTKis

Adverse Events	Treatment-Naïve CLL			Relapsed or refractory CLL				
	ELEVATE-TN[19]	RESONATE-2[18]	SEQUOIA[20]	ELEVATE-RR[121]		ALPINE[153]		BRUIN[155,157]
	Acalabrutinib	Ibrutinib	Zanubrutinib	Acalabrutinib	Ibrutinib	Zanubrutinib	Ibrutinib	Pirtobrutinib
Most common adverse events (AEs; all grades)								
Diarrhea	40%	50%	14%	35%	46%	19%	26%	16%*
Headache	38%	–	11%	35%	20%	NR	NR	17%
Cough	22%	36%	11%	29%	21%	NR	NR	24%
Fatigue	22%	36%	11%	20%	17%	11%	15%	32%
Arthralgia	20%	26%	14%	16%	23%	17%	19%	–
Anemia	–	26%	4%	22%	19%	17%	19%	21%*
Neutropenia	12%	13% (Grade ≥3)	16%	21%	25%	32%	30%	16%*
Adverse events of special interest (AESI)								
Atrial fibrillation/Flutter								
Any grade	6%	16%	3%	9%	16%	7%	17%	3%*
Grade ≥3	1%	5%	<1%	5%	3%	3%	5%	<1%
Bleeding								
Any grade	42%	NR	45%	38%	51%	20%	22%	43%
Grade ≥3	3%	NR	4%	–	–	–	–	1%
Major bleeding								
Any grade	4%	11%	5%	–	–	–	–	21%
Grade ≥3	3%	7%	4%	–	–	–	–	1%
Hypertension								
Any grade	7%	23%	14%	9%	23%	27%	25%	6%*
Grade ≥3	3%	8%	6%	4%	9%	17%*	16%*	<1%
Infections								
Any grade	74%	26%	62%	–	–	29%*	20%*	71%
Grade ≥3	16%	–	16%	–	–	2%	1%	4%

*Data from BRUIN CLL-321 study

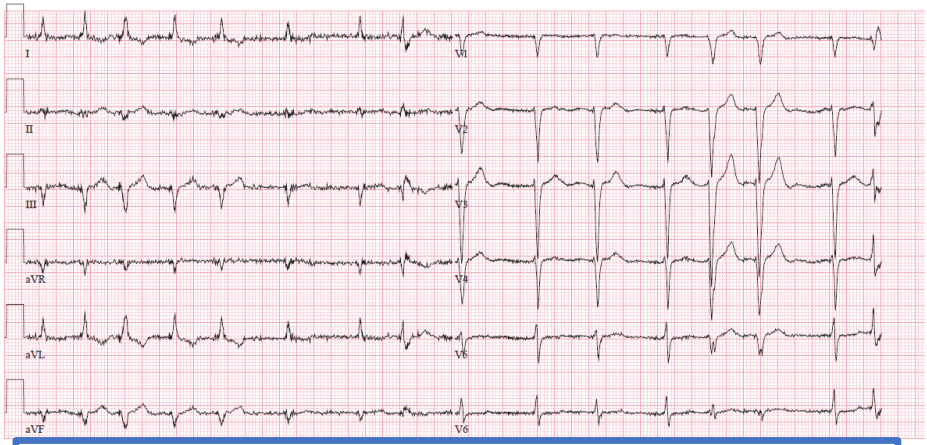
In corso di trattamento ……gennaio 21 (+22 m)

Durante il prelievo in MAC… riferisce dispnea da sforzo

ASST CREMA
U.O.ONCOLOGIA
MAC ONCOLOGIA – EMATOLOGIA

SCHEDA DI RILEVAZIONE SINTOMI

	DATA								
	P.S.(ECOG)								
SINTOMI/SEGNI	Dolore								
	Febbre								
	Dispnea								
	Nausea/vomito								
	Mucosite								
	Disfagia								
	Diarrea								
	Stipsi								
	Ittero								
	Edemi								
	Emorragia/ Sanguinamento								
	Vertigini								
	tremori								
TOSSICITA' CUTANEA	Sindrome mano/piede								
	Follicolite								
	eritema								
	ulcerazioni								
	prurito								
	NESSUNO								
	Complicanze cvc								
PARAMETRI	P.A.								
	F.C.								
	S.O.								
ALTRO									
FIRMA									



- Beta bloccante
- DOAC : edoxaban

PROSEGUE IBRUTINIB

III linea di terapia giugno 2023

- Motivo del trattamento: adenopatie e anemia
- TC (4/23) plurimi LN LC, adenopatie ascellari fino a 5 cm a sn, mediastinici e addominali fino a 6 cm
- Biopsia (Tru-cut) LN ascellare : non evoluzione in s. di Richter

Conclusioni: delezione della regione 17p13 (TP53) nel 14.6% dei nuclei analizzati.

TP53	NM_000546	c.856G>A/p.(Glu286Lys)	2.22%	Oncogenica
TP53	NM_000546	c.818G>T/p.(Arg273Leu)	1.40%	Oncogenica

Quale terapia? giugno 2023

- 69 anni
- CIRS 9
- eGFR 80 mL/min

- RR CIT e BTKi
- 17p deleto e TP53 mutato
- VHIg UNMUTATED

III linea di trattamento giugno 2023

- G1 inizia RAMP UP venetoclax + idratazione e rasburicase
- G2 edemi colonnari , diuretico
- Controlli intermedi, GB 111,000/mm3 bilirub 4,5mg/dl indiretta 4 mg/dl LDH 278, iniziale riduzione adenopatia ascellare.. idratazione orale

- G8 incrementa VEN 50 GB 92,000/mm3…idratazione orale
- G15 dispnea da minimi sforzi…SCC GB 92900/mm3 Crea 1,14 mg/dl BNP 404 pg/ml

→ ricovero

III linea ricovero 20/6 al 3/7/23

- Diuretici, O2
- Rivalutazione cardiologica
- Sospende ACE inibitore e calcio antagonista per peggioramento funz renale e riduce posologia edoxaban

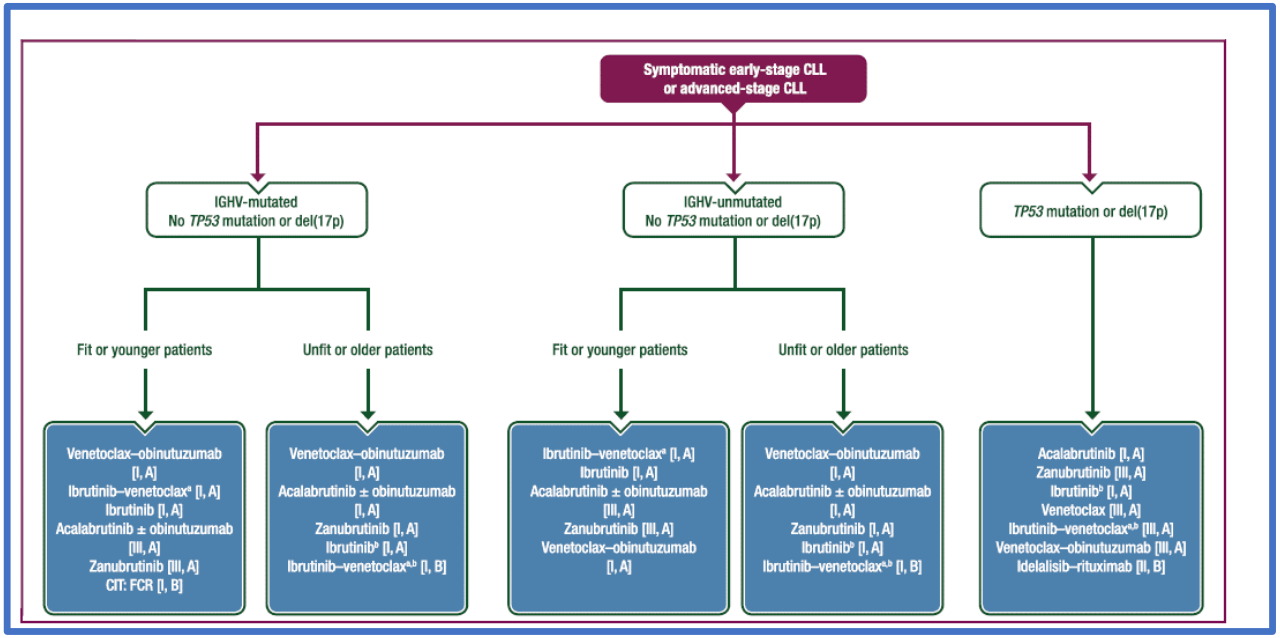
- Prosegue venetoclax 3^ step a 4 settimane

III linea area MAC nov 23-giugno 25

- Dal 21/11/23 venetoclax 400 mg al giorno
- Maggio 2024 rivalutazione cardio-oncologia per adeguamento terapia
- Luglio 2024 ridotto diuretico per peggioramento funzione renale (eGFR 40 ml/min)
- Visita nefrologica: danno renale da deplezione volume extra cellulare. Diuretico a basso dosaggio.
- Marzo 2024 Risposta completa
- 23/9/24 creatinina 1.59 mg/dl, non adenopatie superficiali.
- In attesa di intervento per ernia inguinale.
- **Maggio 2025(+ 23 m) RC di malattia**

Se avessimo scelto oggi? 1 linea

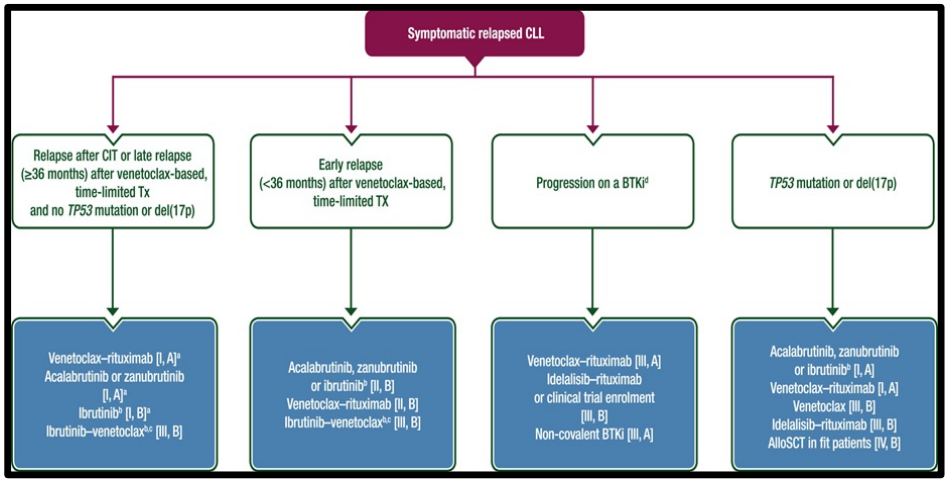
ESMO 2024



ESMO Clinical Practice Guideline interim update on new targeted therapiesin the first line and at relapse of chronic lymphocytic leukaemia. B. Eichhorst et al. *Annals of Oncology 2024*

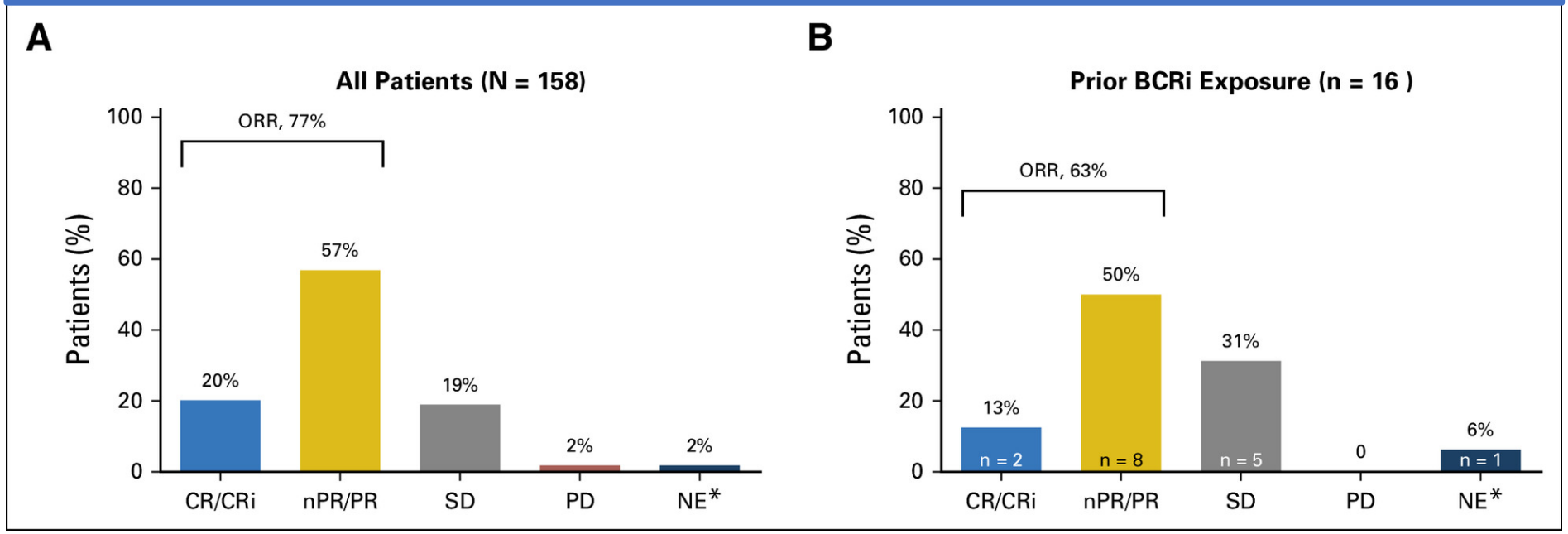
Se avessimo scelto oggi? 2 e succ linee

ESMO 2024



ESMO Clinical Practice Guideline interim update on new targeted therapiesin the first line and at relapse of chronic lymphocytic leukaemia. B. Eichhorst et al. *Annals of Oncology 2024*

Venetoclax in relapsed or refractory chronic lymphocytic leukaemia with 17p deletion: a multicentre, open-label, phase 2 study.



Stilgenbauer S et al. Lancet Oncol. 2016 Jun;17(6):768-778

Activity of venetoclax in patients with R/R CLL: analysis of the VENICE-1 multicentre, open-label, single-arm, phase 3b trial

The study included **258 pts** with R/R CLL: **191 BCRi naive** and **67 BCRi pretreated (20-22% TP53 e/o 17p-)**

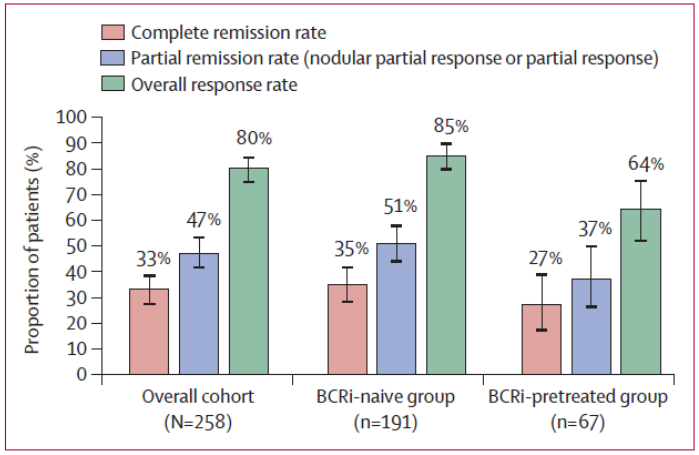
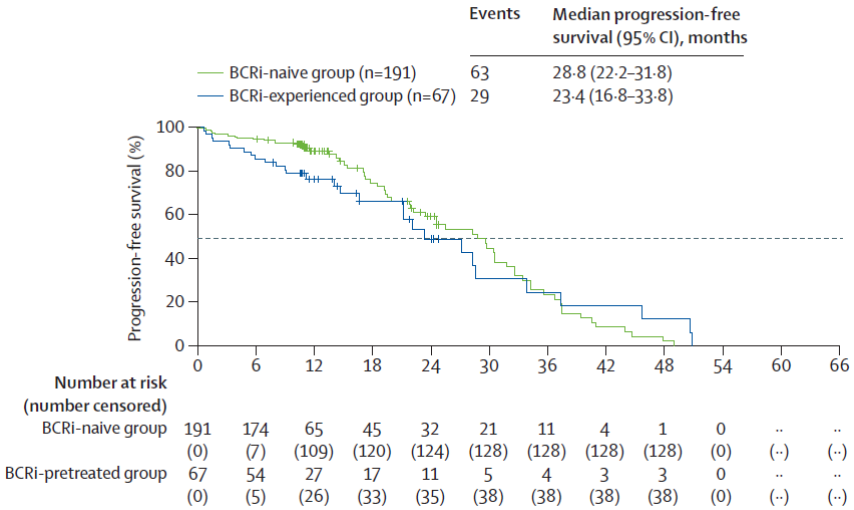


Figure 2: **Response rates for patients with relapsed or refractory chronic lymphocytic leukaemia treated with venetoclax monotherapy at week 48**
BCRi=B-cell receptor pathway inhibitor. Partial response needed to be confirmed later than 7 weeks or more for overall response.

ORR 80%

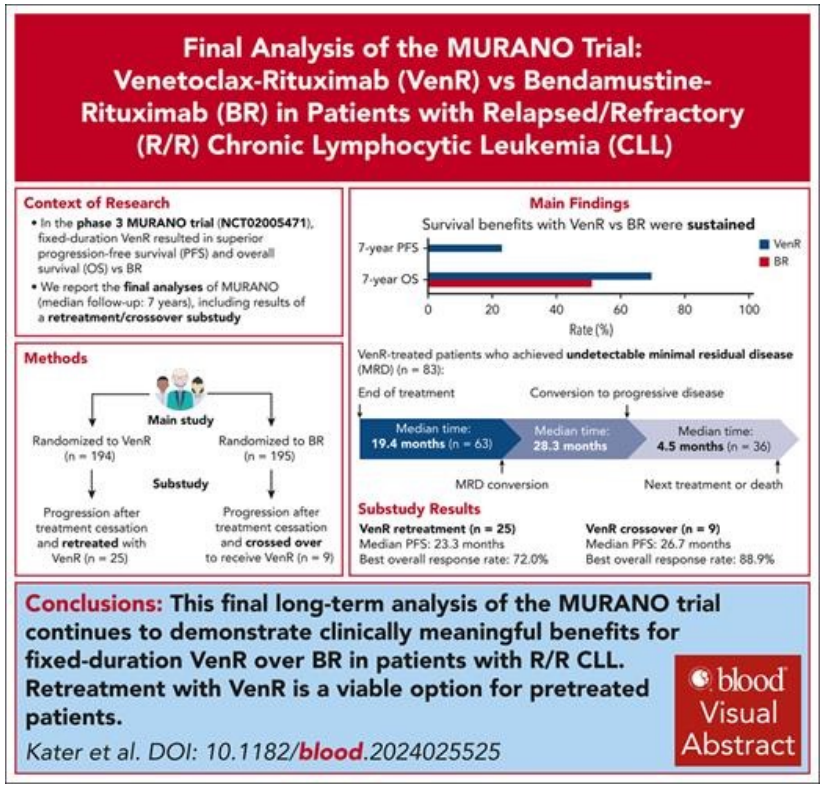
Median PFS 28.8 months in BCRi naive and 23.4 in BCRi pretreated pts

B



Five-year survival estimates were 71% (95% CI 65·0–76·5), 75% (95% CI 67·5–80·6), and 61% (95% CI 47·7–71·6) for the overall, BCRi-naive, and BCRi-experienced patients

Kater, Arnon P et al. **The Lancet Oncology 2024**, Volume 25, Issue 4, 463 – 47



- VenR arm, the 7-year :
  - PFS rate was 23%
  - OS rates was 69.6%

mutated TP53 and/or del(17p)

- PFS rate was 5.0%
- OS rate was 50.6%

Table 3. Phase III Randomized Studies of Small-Molecule Inhibitor Therapy for Relapsed or refractory CLL/SLL

Trial	Regimen	No. of Patients	Patient Characteristics	Median Follow-up	ORR	PFS	OS
ASCEND[151]	**Acalabrutinib**	155 [del(17p), n = 28; mutated *TP53*, n = 39]	Median age 67–68 years with ECOG PS ≤2 and adequate hematologic, hepatic, and renal function	47 months	83%	Median: Not reached 42-month: 62% (HR, 0.28; *P* < .0001)	Median: Not reached 42-month: 78%
	Idelalisib + rituximab (IdR) or Bendamustine + rituximab (BR)	155 (IdR, n = 119; BR, n = 36); [del(17p), n = 21; mutated *TP53*, n = 34]			84%	Median: 17 months 42-month: 23%	Median: Not reached 42-month: 65%
ELEVATE-RR[121]	**Acalabrutinib**	268	≥18 years; ECOG PS ≤2 and the presence of del(17p) and/or del(11q)	41 months	81% (3% CR)	Median: 38 months (for both treatment arms)	Median: Not reached (in either arm)
	Ibrutinib	265			77% (4% CR)		
RESONATE[152]	**Ibrutinib**	195 [del(17p), n = 63; mutated *TP53*, n = 79]	Median age 67 years	74 months	91% (11% CR)	Median: 44 months 60-month: 40%	Median: 68 months
	Ofatumumab	196 [del(17p), n = 64; mutated *TP53*, n = 68]			–	Median: 8 months 60-month: 3%	Median: 65 months
ALPINE[153]	**Zanubrutinib**	327 [del(17p) and/or mutated *TP53*, n = 41]	Median age 67 years; ECOG PS ≥1; relapsed or refractory disease after ≥1 prior systemic therapy	42.5 months	86% (12% CR)	36-month: 65% (HR, 0.67; *P* = .002)	36-month: 83%
	Ibrutinib	325 [del(17p) and/or mutated *TP53*, n = 38]			75% (8% CR)	36-month: 54%	36-month: 80%
MURANO[92,93]	**Venetoclax + rituximab (VenR)**	194 [del(17p), n = 46; mutated *TP53*, n = 48]	≥18 years; ECOG PS 0–1; relapsed or refractory disease requiring therapy and adequate bone marrow, liver, and kidney function	59 months	92% (8% CR)	Median: 54 months (HR, 0.19; *P* < .0001)	5-year: 82% (HR, 0.40; *P* < .0001)
	BR	195 [del(17p), n = 46; mutated *TP53*, n = 51]			72% (4% CR)	Median: 17 months	5-year: 62%

PS1573

Treatment Effectiveness in Patients with Chronic Lymphocytic Leukemia (CLL) Receiving Venetoclax-based Therapy (Venetoclax) After Progression on a Covalent Bruton Tyrosine Kinase Inhibitor (cBTKi)

Isabelle Fleury[1], Brian T. Hill[2], Toby A. Eyre[3], Chaitra Ujjani[4], Beenish S. Manzoor[5], Jennifer R. Brown[6], Hande H. Tuncer[6], Nicole Lamanna[7], Catherine C. Coombs[8], Nilanjan Ghosh[9], Lori A. Leslie[10], Lindsey E. Roeker[11], Nicolas Martinez-Calle[12], Paul M. Barr[13], Matthew S. Davids[6], Nnadozie Emechebe[5], Joanna M. Rhodes[14], Alan P. Skarbnik[15], Wendy Sinai[5], Laurie Pearson[16], Frederick Lansigan[17], Yun Choi[18], Jenny Cui[18], Christopher E. Jensen[19], Bita Fakhri[20], Meghan C. Thompson[21], Deborah M. Stephens[19], Stephen J. Schuster[22], Michael Coyle[23], Andres Chang[24], Irina Pivneva[25], Talissa Watson[25], Annie Guerin[25], Mazyar Shadman[4]

[1]Hôpital Maisonneuve-Rosemont, University of Montreal, Canada; [2]Cleveland Clinic, Cleveland, OH, USA; [3]Churchill Hospital, Oxford University, Oxford, UK; [4]Fred Hutchinson Cancer Research Center, Seattle, WA, USA; [5]AbbVie, Inc., North Chicago, IL, USA; [6]Dana-Farber Cancer Institute, Boston, MA, USA; [7]Columbia University, New York, NY, USA; [8]University of California Irvine, Irvine, CA, USA; [9]Levine Cancer Institute/Atrium Health, Charlotte, NC, USA [10]John Theurer Cancer Center, Hackensack Meridian Health, Hackensack, NJ, USA; [11]Mayo Clinic, Rochester, MN, USA; [12]Nottingham University Hospitals, NHS Trust, Nottingham, UK; [13]Wilmot Cancer Institute, University of Rochester Medical Center, Rochester, NY, USA; [14]Rutgers Cancer Institute of New Jersey, New Brunswick, NJ, USA; [15]Lymphoma and CLL Program, Novant Health Cancer Institute, Charlotte, NC, USA; [16]University of Massachusetts, Worcester, MA, USA; [17]Dartmouth-Hitchcock Medical Center, Lebanon, NH, USA; [18]Tufts Medical Center, Boston, MA, USA; [19]Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, NC, USA; [20]Stanford Cancer Institute, Stanford University, Stanford, CA, USA; [21]CLL Program, Leukemia Service, Division of Hematologic Malignancies, Memorial Sloan Kettering Cancer Center, New York, NY, USA; [22]University of Pennsylvania, Philadelphia, PA, USA; [23]Lowell General Hospital, Lowell, MA, USA; [24]Winship Cancer Institute of Emory University, Atlanta, GA, [25]Analysis Group, Inc., Montreal, Canada.

OBJECTIVES

To assess clinical outcomes in patients who initiated venetoclax as time-limited (i.e., FTD Ven+anti-CD20 [VO/VR]) or continuous therapy (i.e., continuous Vmono) after progressing on a prior cBTKi

CONCLUSIONS

After progressing on a cBTKi, patients who received venetoclax regimens in the R/R setting achieved durable remission and meaningful PFS and TTNT-D, with high OS across regimen types and lines of therapy

These real-world findings build on previous clinical trial results (e.g., MURANO, and VENICE-1), further suggesting that even after progressing on a cBTKi, venetoclax demonstrates clinical benefits, particularly for time-limited therapies[3-5]

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DV-015678

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CORE

EHA2025 Congress — Presented at the EHA Congress 2025, June 12-15, 2025 / Milan, Italy

INTRODUCTION

- Venetoclax is approved for patients with relapsed/refractory (R/R) CLL, as a time-limited (i.e., with rituximab [VR]) or continuous therapy (i.e., venetoclax monotherapy [continuous Vmono]) [illegible] updated NCCN guidelines recommending time-limited th[illegible]th obinutuzumab (i.e., VO) or VR in 2L or subsequent lines [illegible] period of remission[1-2]
- Clinical trials have demonstrated venetoclax effectiveness in the R/R setting, both for VR (e.g., MURANO trial) and Continuous Vmono (e.g., VENICE-1)[3-5]
- However, there is limited real-world data on venetoclax outcomes in the R/R setting, particularly following progression on a covalent BTKi (cBTKi)[6-7]

METHODS

- This study relied on data from 25 sites of the CLL Collaborative Study of Real-World Evidence (CORE), a retrospective, observational, global study on patients with CLL
- Patients were included if they met the following eligibility criteria:
  - ≥ 18 years at time of CLL/SLL diagnosis
  - Received venetoclax (i.e., FTD Ven+anti-CD20 (i.e., VO/VR); continuous Vmono) after progressing on a cBTKi, with cBTKi progression defined as (i) progression event documented on a cBTKi, or (ii) a reason for discontinuing cBTKi was 'due to progression' or 'R/R disease'
  - Had ≥ 1 month of follow-up after venetoclax start
- Patient demographics and clinical characteristics were described at venetoclax start
- Clinical outcomes assessed included:
  - Overall response rate (ORR): proportion of patients with physician-assessed complete/partial response, as recorded in medical charts
  - Progression-free survival (PFS): time from venetoclax start to disease progression/death (i.e., event) or last follow-up (i.e., censor)
  - Time to next treatment or death (TTNT-D): time from venetoclax start to subsequent treatment/death (i.e., event) or last follow-up (i.e., censor)
  - Overall survival (OS): time from venetoclax start to death (i.e., event) or last follow-up (i.e., censor)
- Median PFS, TTNT-D, and OS along with their 95% confidence intervals were estimated using Kaplan-Meier (KM) methodology. 18-month KM estimates for these time-to-event outcomes were also calculated
- Clinical outcomes were stratified by regimen (FTD Ven+anti-CD20; continuous Vmono) and for those who initiated venetoclax during second line (2L) or third line (3L)

RESULTS

Patient and clinical characteristics

- In CORE, 1,615/2,696 (59.9%) patients received a cBTKi in ≥ 1 line; 422 progressed on a cBTKi
- A total of 175/422 (41.5%) patients received venetoclax (FTD Ven+anti-CD20: 79 [45.1%]; VR: 56 [70.9%]; VO: 23 [29.1%]; continuous Vmono: 96 [54.9%]) after progressing on a cBTKi and were included in this analysis **(Table 1 and 2)**

Table 1. Patient and clinical characteristics

Patient characteristics	FTD Ven+anti-CD20			Continuous Vmono		
	Overall N = 79	2L N = 29	3L N = 36	Overall N = 96	2L N = 25	3L N = 33
Age at venetoclax initiation, mean ± SD [median]	67.7 ± 1[illegible] [60.6[illegible]	67.2 ± 12.3 [70.2]	67.6 ± 10.7 [69.4]	70.7 ± 9.5 [71.7]	71.5 ± 9.9 [71.8]	70.3 ± 10.9 [71.6]
Time from diagnosis to venetoclax initiation, mean ± SD [median] (months)	89.0 ± 57.2 [85.0]	47.6 ± 35.7 [34.1]	101.2 ± 52.7 [96.0]	94.4 ± 55.7 [78.7]	56.2 ± 34.5 [50.2]	84.0 ± 37.8 [75.4]
Male sex, N (%)	53 (67.1%)	20 (69.0%)	25 (69.4%)	66 (68.8%)	15 (60.0%)	22 (66.7%)
ECOG assessed, N (%)	63 (79.7%)	27 (93.1%)	24 (66.7%)	74 (77.0%)	21 (84.0%)	28 (84.8%)
Grade 0	22 (34.9%)	10 (37.0%)	8 (32.0%)	26 (27.1%)	10 (40.0%)	7 (21.2%)
Grade 1 - 2	41 (65.1%)	17 (63.0%)	16 (64.0%)	45 (46.9%)	10 (40.0%)	19 (57.6%)
Grade 3 - 4	0 (.0%)	0 (.0%)	0 (.0%)	3 (3.1%)	1 (4.0%)	2 (6.1%)
Rai stage assessed, N (%)	47 (59.5%)	16 (55.2%)	26 (72.2%)	74 (77.0%)	22 (88.0%)	26 (78.8%)
Stage 0 - II	23 (48.9%)	8 (50.0%)	11 (42.3%)	33 (34.4%)	12 (48.0%)	15 (45.5%)
Stage III - IV	24 (51.0%)	8 (50.0%)	10 (38.5%)	41 (42.7%)	10 (40.0%)	11 (33.3%)
Chromosomal abnormality tested[1], N (%)	54 (68.4%)	19 (65.5%)	25 (69.4%)	68 (70.8%)	16 (64.0%)	24 (72.7%)
del(17p)/TP53 mutation, N (%)	11 (20.4%)	5 (26.3%)	5 (20.0%)	22 (32.4%)	8 (50.0%)	6 (25.0%)
IGHV mutation status tested[1], N (%)	54 (68.4%)	19 (65.5%)	25 (69.4%)	44 (45.8%)	9 (36.0%)	15 (45.5%)
Unmutated IGHV, N (%)	25 (69.4%)	8 (61.5%)	11 (68.8%)	35 (79.5%)	9 (100.0%)	11 (73.3%)
Comorbidity burden[2], mean ± SD [median]	2.4 ± 1.9 [2.0]	2.4 ± 1.7 [2.0]	2.4 ± 2.1 [2.0]	1.7 ± 1.6 [1.5]	2.2 ± 1.7 [2.0]	1.6 ± 1.6 [1.0]
Cardiovascular conditions, N (%)	46 (58.2%)	17 (58.6%)	20 (55.6%)	50 (52.1%)	13 (52.0%)	16 (48.5%)

[1] Categories are not mutually exclusive.
[2] Comorbidity burden was defined as the total number of comorbidities a patient has.

Table 2. Treatment characteristics and response

Treatment characteristics	FTD Ven+anti-CD20			Continuous Vmono		
	Overall N = 79	2L N = 29	3L N = 36	Overall N = 96	2L N = 25	3L N = 33
Follow-up duration (months)[1,2], mean ± SD [median]	22.0 ± 17.3 [18.4]	21.3 ± 15.5 [17.8]	25.0 ± 20.3 [21.1]	24.6 ± 20.9 [20.7]	24.8 ± 20.2 [23.6]	24.0 ± 20.2 [21.9]
Venetoclax treatment duration (months), mean ± SD [median]	20.7 ± 16.2 [18.1]	21.[illegible] ± 15.6 [illegible]	22.9 ± 18.4 [19.3]	20.8 ± 17.6 [18.2]	18.8 ± 14.8 [17.9]	19.5 ± 14.6 [21.2]
Time between first and last dose of venetoclax (months), mean ± SD [median]	15.2 ± 10.4 [13.6]	15.[illegible] ± 11.6 [12.2]	16.9 ± 10.2 [18.3]	16.0 ± 14.5 [13.3]	14.1 ± 11.5 [10.8]	18.2 ± 14.4 [16.6]
Prior cBTKi treatment duration (months), mean ± SD [median]	31.8 ± 25.3 [24.9]	25.9 ± 19.9 [16.6]	36.2 ± 27.7 [29.1]	30.5 ± 20.4 [27.9]	30.0 ± 20.2 [30.0]	24.9 ± 17.6 [24.0]
Time between first and last dose of prior cBTKi (months), mean ± SD [median]	25.5 ± 25.5 [15.0]	17.3 ± 18.3 [10.9]	30.9 ± 29.0 [17.7]	26.7 ± 21.1 [23.1]	24.4 ± 19.6 [17.8]	21.9 ± 18.3 [23.5]
Patients still on venetoclax therapy	36 (45.6%)	13 (44.8%)	20 (55.6%)	47 (49.0%)	12 (48.0%)	14 (42.4%)
Patients who ended their venetoclax therapy	43 (54.4%)	16 (55.2%)	16 (44.4%)	49 (51.0%)	13 (52.0%)	19 (57.6%)
Reasons for ending venetoclax, N (%)[3,4]						
Disease progression	4 (9.3%)	1 (6.3%)	1 (6.3%)	11 (22.4%)	1 (7.7%)	8 (42.1%)
Treatment intolerance	8 (18.6%)	1 (6.3%)	3 (18.8%)	13 (26.5%)	2 (15.4%)	5 (26.3%)
Refractory to treatment	2 (4.7%)	1 (6.3%)	0 (0.0%)	4 (8.2%)	1 (7.7%)	1 (5.3%)
Proportion of patients who had prior CT/CIT exposure[5,6], N (%)	43 (54.4%)	0 (0.0%)	30 (83.3%)	60 (62.5%)	0 (0.0%)	25 (75.8%)
Overall Response Rate						
ORR	77.6%	87.5%	78.3%	81.3%	94.7%	76.9%

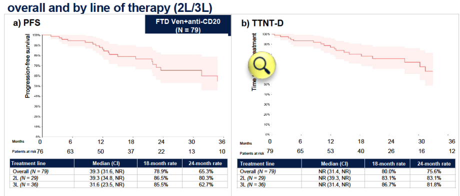
[1] Median follow-up duration was estimated from initiation of venetoclax. The duration for 4L+ was 15.7 ± 10.0 [13.9] months for FTD Ven+anti-CD20 and 25.1 ± 22.4 [18.6] months for continuous Vmono.
[2] Among the 56 VR patients, 22 had a treatment duration of ≥ 24 months.
[3] Categories are not mutually exclusive.
[4] The most prevalent reasons were reported. Other reasons for ending venetoclax include *patient's request* — FTD Ven+anti-CD20 [Overall: 0 (0.0%), 2L: 0 (0.0%), 3L: 0 (0.0%)]; continuous Vmono [Overall: 4 (8.2%), 2L: 1 (7.7%), 3L: 2 (10.5%)] *watchful waiting due to low or no disease activity* — FTD Ven+anti-CD20 [Overall: 7 (16.3%), 2L: 2 (12.5%), 3L: 3 (18.8%)]; continuous Vmono [Overall: 2 (4.1%), 2L: 1 (7.7%), 3L: 0 (0.0%)].
[5] Prior CT/CIT exposure included patients with CT/CIT use in any line before their cBTKi → venetoclax treatment sequence (e.g., if a patient had the following treatment sequence they would be counted: 1L: R-CHOP; 2: acalabrutinib; 3L: ibrutinib; 4L: venetoclax monotherapy).
[6] In 4L+, 13 FTD Ven+anti-CD20 patients and 35 continuous Vmono patients had CT/CIT exposure.

Abbreviations: 2L (second-line), 3L (third-line), cBTKi (covalent Bruton Tyrosine Kinase inhibitors), CI (confidence interval), CR (complete response), CT/CIT (chemotherapy/chemoimmunotherapy), ECOG (Eastern Cooperative Oncology Group), IGVH (immunoglobulin heavy-chain variable region gene), NR (not reached), ORR (overall response rate), OS (overall survival), PD (progressive disease), PFS (progression-free survival), SD (stable disease; standard deviation), TTNT-D (time to next treatment or death), FTD Ven+anti-CD20 (venetoclax combination therapy), continuous Vmono (venetoclax monotherapy), VR (venetoclax + rituximab)

LIMITATIONS

- As with other real-world studies, data entry differences or errors across centers may impact the interpretability of the results
- Not all progressive events may be accounted for, as some patients did not complete their venetoclax therapy and were lost to follow
- As ongoing data collection continues, outcome estimates with longer follow-up will be reported in future analyses

Figure 1. Clinical outcomes for post-cBTKi progression FTD Ven+anti-CD20, overall and by line of therapy (2L/3L)

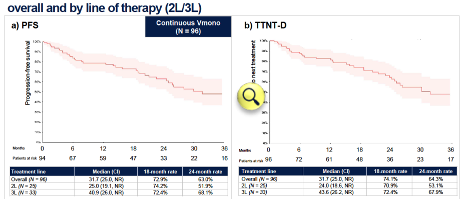


Footnotes:

[1] 21 of 79 patients had a PFS event (deaths: 12; progression: 9). 20 of 79 patients had a TTNT-D event (deaths: 12; next treatment: 8).

[2] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Figure 2. Clinical outcomes for post-cBTKi progression continuous Vmono, overall and by line of therapy (2L/3L)



Footnotes:

[1] 38 of 96 patients had a PFS event (deaths: 21; progression: 17). 40 of 96 patients had a TTNT-D event (deaths: 21; next treatment: 19).

[2] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

METHODS

- This study relied on data from 25 sites of the CLL Collaborative Study of Real-World Evidence (CORE), a retrospective, observational, global study on patients with CLL
- Patients were included if they met the following eligibility criteria:
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  - Had ≥ 1 month of follow-up after venetoclax start
- Patient demographics and clinical characteristics were described at venetoclax start

RESULTS

Patient and clinical characteristics

- In CORE, 1,615/2,696 (59.9%) patients received a cBTKi in ≥ 1 line; 422 progressed on a cBTKi
- A total of 175/422 (41.5%) patients received venetoclax (FTD Ven+anti-CD20: 79 [45.1%]; VR: 56 [70.9%]; VO: 23 [29.1%]; continuous Vmono: 96 [54.9%]) after progressing on a cBTKi and were included in this analysis **(Table 1 and 2)**

Table 1. Patient and clinical characteristics

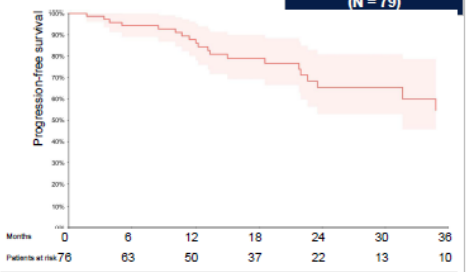
Patient characteristics	FTD Ven+anti-CD20			Continuous Vmono		
	Overall N = 79	2L N = 29	3L N = 36	Overall N = 96	2L N = 25	3L N = 33
Age at venetoclax initiation, mean ± SD [median]	67.7 ± 11.1 [60.6]	67.2 ± 12.3 [70.2]	67.6 ± 10.7 [69.4]	70.7 ± 9.5 [71.7]	71.5 ± 9.9 [71.8]	70.3 ± 10.9 [71.6]
Time from diagnosis to venetoclax initiation, mean ± SD [median] (months)	89.0 ± 57.2 [85.0]	47.6 ± 35.7 [34.1]	101.2 ± 52.7 [96.0]	94.4 ± 55.7 [78.7]	56.2 ± 34.5 [50.2]	84.0 ± 37.8 [75.4]
Male sex, N (%)	53 (67.1%)	20 (69.0%)	25 (69.4%)	66 (68.8%)	15 (60.0%)	22 (66.7%)
ECOG assessed, N (%)	63 (79.7%)	27 (93.1%)	24 (66.7%)	74 (77.0%)	21 (84.0%)	28 (84.8%)
Grade 0	22 (34.9%)	10 (37.0%)	8 (32.0%)	26 (27.1%)	10 (40.0%)	7 (21.2%)
Grade 1 - 2	41 (65.1%)	17 (63.0%)	16 (64.0%)	45 (46.9%)	10 (40.0%)	19 (57.6%)
Grade 3 - 4	0 (.0%)	0 (.0%)	0 (.0%)	3 (3.1%)	1 (4.0%)	2 (6.1%)
Rai stage assessed, N (%)	47 (59.5%)	16 (55.2%)	26 (72.2%)	74 (77.0%)	22 (88.0%)	26 (78.8%)
Stage 0 - II	23 (48.9%)	8 (50.0%)	11 (42.3%)	33 (34.4%)	12 (48.0%)	15 (45.5%)
Stage III - IV	24 (51.0%)	8 (50.0%)	10 (38.5%)	41 (42.7%)	10 (40.0%)	11 (33.3%)
Chromosomal abnormality tested[1], N (%)	54 (68.4%)	19 (65.5%)	25 (69.4%)	68 (70.8%)	16 (64.0%)	24 (72.7%)
del(17p)/TP53 mutation, N (%)	11 (20.4%)	5 (26.3%)	5 (20.0%)	22 (32.4%)	8 (50.0%)	6 (25.0%)
IGHV mutation status tested[1], N (%)	54 (68.4%)	19 (65.5%)	25 (69.4%)	44 (45.8%)	9 (36.0%)	15 (45.5%)
Unmutated IGHV, N (%)	25 (69.4%)	8 (61.5%)	11 (68.8%)	35 (79.5%)	9 (100.0%)	11 (73.3%)
Comorbidity burden[2], mean ± SD [median]	2.4 ± 1.9 [2.0]	2.4 ± 1.7 [2.0]	2.4 ± 2.1 [2.0]	1.7 ± 1.6 [1.5]	2.2 ± 1.7 [2.0]	1.6 ± 1.6 [1.0]
Cardiovascular conditions, N (%)	46 (58.2%)	17 (58.6%)	20 (55.6%)	50 (52.1%)	13 (52.0%)	16 (48.5%)

[1] Categories are not mutually exclusive.
[2] Comorbidity burden was defined as the total number of comorbidities a patient has.

Figure 1. Clinical outcomes for post-cBTKi progression FTD Ven+anti-CD20, overall and by line of therapy (2L/3L)

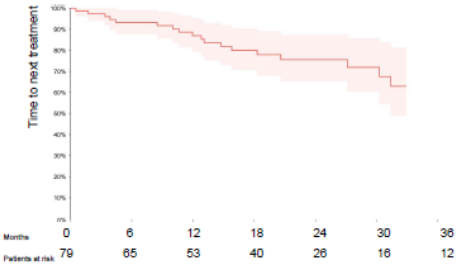
a) PFS

FTD Ven+anti-CD20 (N = 79)



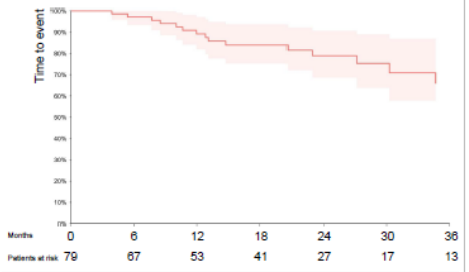
Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 79)*	39.3 (31.6, NR)	78.9%	65.3%
2L *(N = 29)*	39.3 (34.8, NR)	86.5%	80.3%
3L *(N = 36)*	31.6 (23.5, NR)	85.5%	62.7%

b) TTNT-D



Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 79)*	NR (31.4, NR)	80.0%	75.6%
2L *(N = 29)*	NR (39.3, NR)	83.1%	83.1%
3L *(N = 36)*	NR (31.4, NR)	86.7%	81.8%

c) OS



Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 79)*	NR (39.3, NR)	83.9%	78.9%
2L *(N = 29)*	NR (39.3, NR)	83.0%	83.0%
3L *(N = 36)*	NR (NR, NR)	93.3%	83.2%

Footnotes:

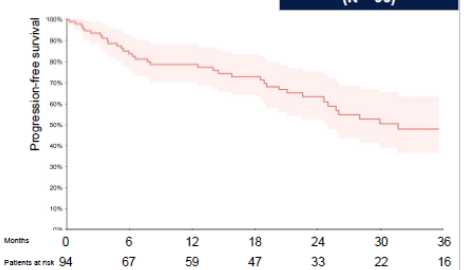
[1] 21 of 79 patients had a PFS event (deaths: 12; progression: 9). 20 of 79 patients had a TTNT-D event (deaths: 12; next treatment: 8).

[2] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

Figure 2. Clinical outcomes for post-cBTKi progression continuous Vmono, overall and by line of therapy (2L/3L)

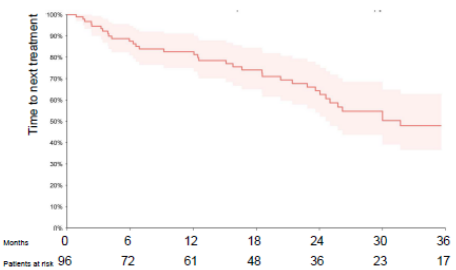
a) PFS

Continuous Vmono (N = 96)



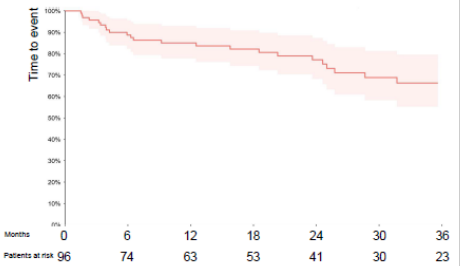
Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 96)*	31.7 (25.0, NR)	72.9%	63.0%
2L *(N = 25)*	25.0 (19.1, NR)	74.2%	51.9%
3L *(N = 33)*	40.9 (26.0, NR)	72.4%	68.1%

b) TTNT-D



Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 96)*	31.7 (25.0, NR)	74.1%	64.3%
2L *(N = 25)*	24.0 (18.6, NR)	70.9%	53.1%
3L *(N = 33)*	43.6 (26.2, NR)	72.4%	67.9%

c) OS



Treatment line	Median (CI)	18-month rate	24-month rate
Overall *(N = 96)*	NR (54.7, NR)	82.2%	77.2%
2L *(N = 25)*	NR (31.7, NR)	81.2%	75.0%
3L *(N = 33)*	NR (NR, NR)	79.2%	79.2%

Footnotes:

[1] 38 of 96 patients had a PFS event (deaths: 21; progression: 17). 40 of 96 patients had a TTNT-D event (deaths: 21; next treatment: 19).

[2] As ongoing data collection continues, outcome estimates with longer follow-up will be reported.

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