

Esiste un potenziale rischio di incremento della S. di Richter con l'utilizzo della "Targeted therapy"

Pellegrino Musto

Dipartimento dell'Emergenza e dei Trapianti di Organi, Scuola di Medicina, Università degli Studi "Aldo Moro", Bari.

SC di Ematologia con Trapianto, AOU Consorziale Policlinico, Bari.

L'OTTIMIZZAZIONE DELLA
**TERAPIA LEUCEMIA
LINFATICA CRONICA:**

UNA CONDIZIONE DINAMICA
ED INNOVATIVA



12-13 APRILE 2022 BOLOGNA ROYAL HOTEL CARLTON

Definition, Epidemiology, and Clinical Presentation of Richter's Syndrome (Richter Transformation)

- Richter transformation (RT) is defined as the occurrence of an **aggressive lymphoma** in patients, due to a **histopathology and biology switch** with a **previous or concomitant diagnosis of chronic lymphocytic leukemia (CLL)**.
- This **life-threatening complication** occurs in approximately **2–10% of CLL patients**, more **often during the disease course than at diagnosis**.
- Overall, **transformation rate** is approximately **0.5-1% per year**.
- **Clinical suspicion** of RT should be raised when a patient with CLL presents with the sudden clinical deterioration with prominent **constitutional symptoms**, including fever, night sweats, and loss of weight.
- On physical examination, there is an **asymmetric and rapid growth of bulky lymph nodes or extra nodal involvement** that is characteristic in 40% of all RT cases, mostly those of the gastrointestinal tract, bone marrow, central nervous system, and skin.
- **Laboratory tests** frequently present with **cytopenias**, an elevation of lactate dehydrogenase (**LDH**), **PCR**, and (less frequently) with **hypercalcemia** or **appearance of a M-component**.

Tadmor T, et al. Cancers, 2021
Petrackova A, et al. Blood Reviews, 2021
Condoluci and Rossi, Frontiers in Oncology 2022



RICHTER TRANSFORMATION

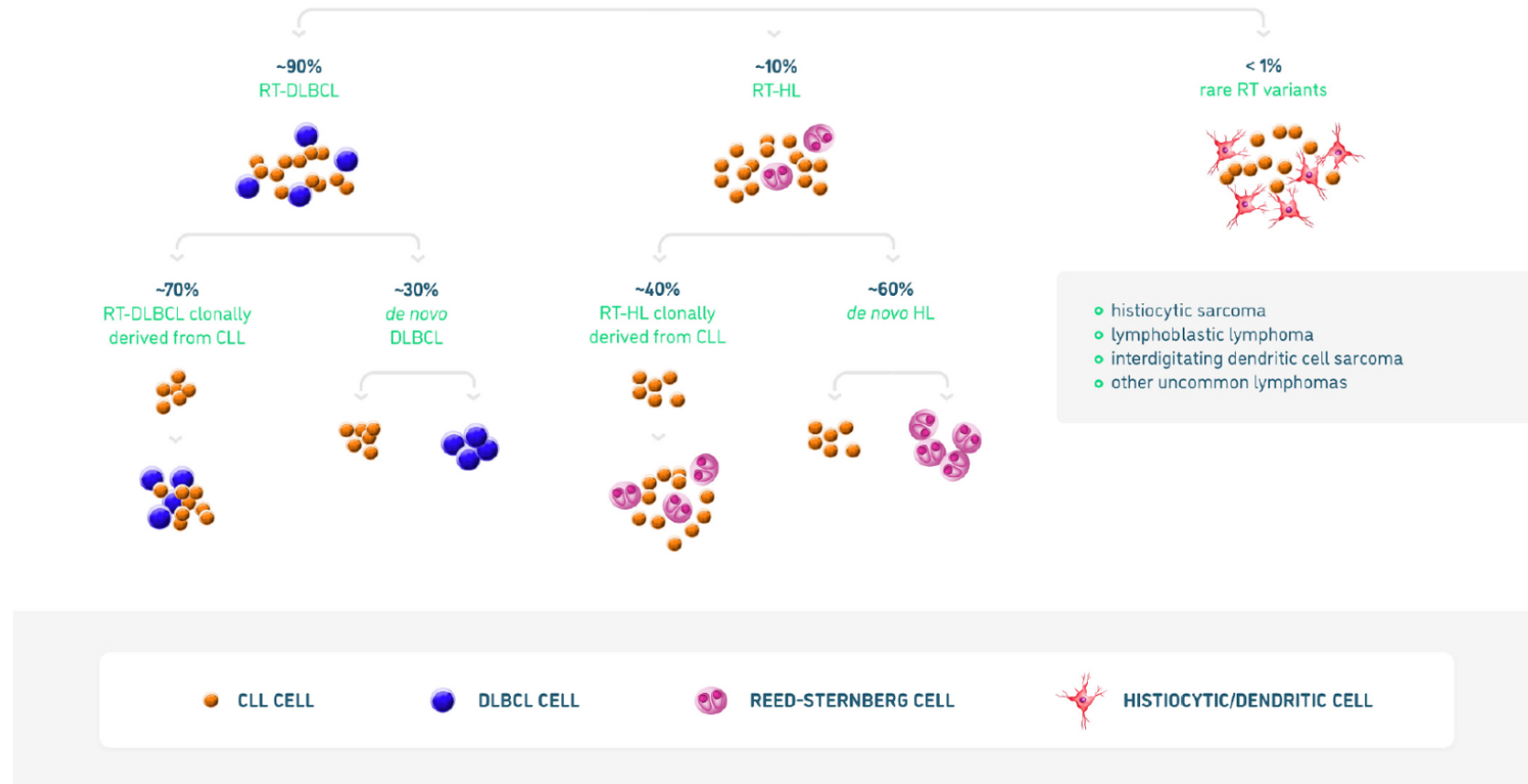
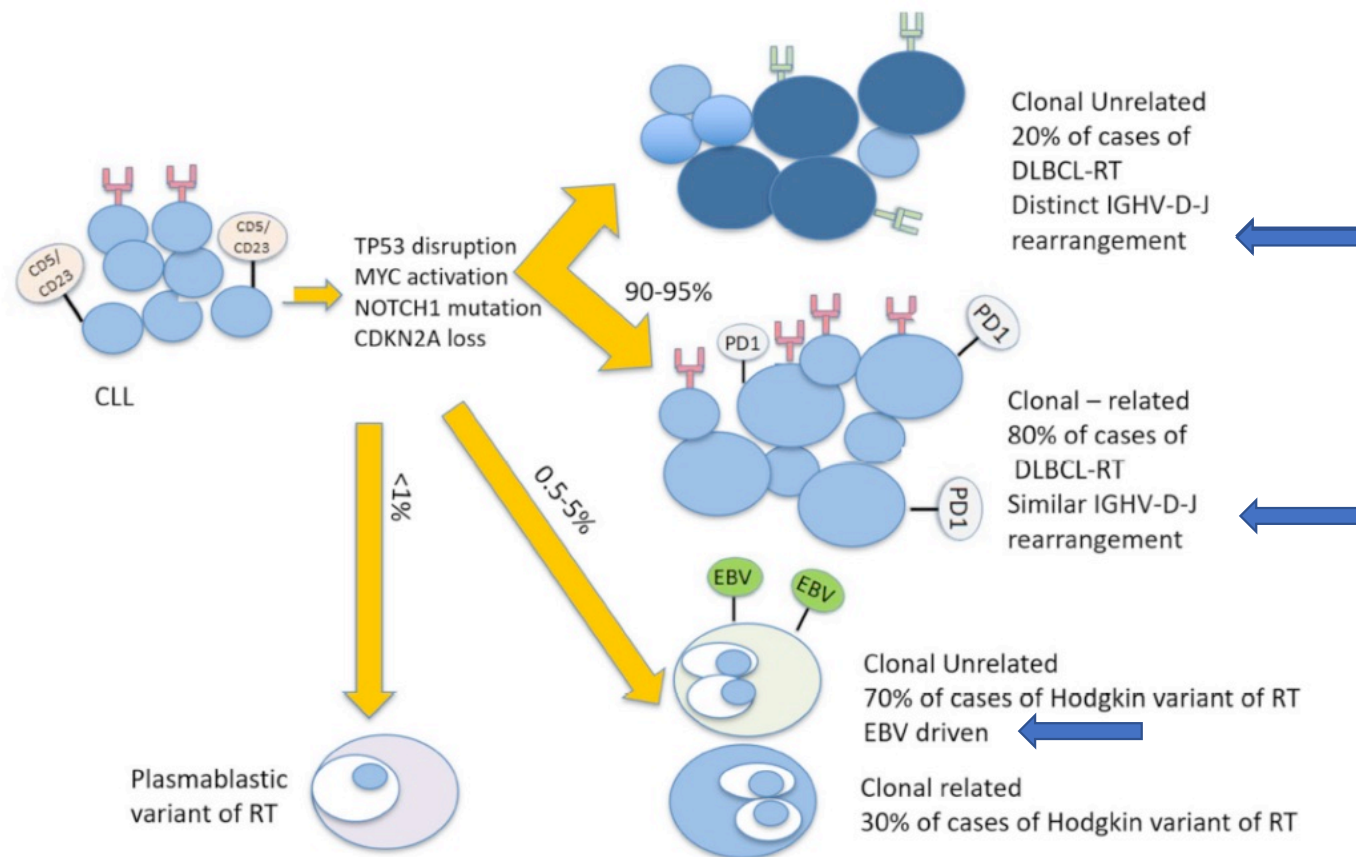


Fig. 1. Forms of RT arising on the background of CLL.

CLL: chronic lymphocytic leukaemia; DLBCL: diffuse large B-cell lymphoma; HL: Hodgkin lymphoma; RT: Richter transformation.

Petrackova A, et al. Blood Reviews 2021





«Similar»
outcomes to de
novo DLBCL

A possible role for
high PD-1 and at
least partial
CD5/CD23 expression
as clonality-related
markers has been
suggested

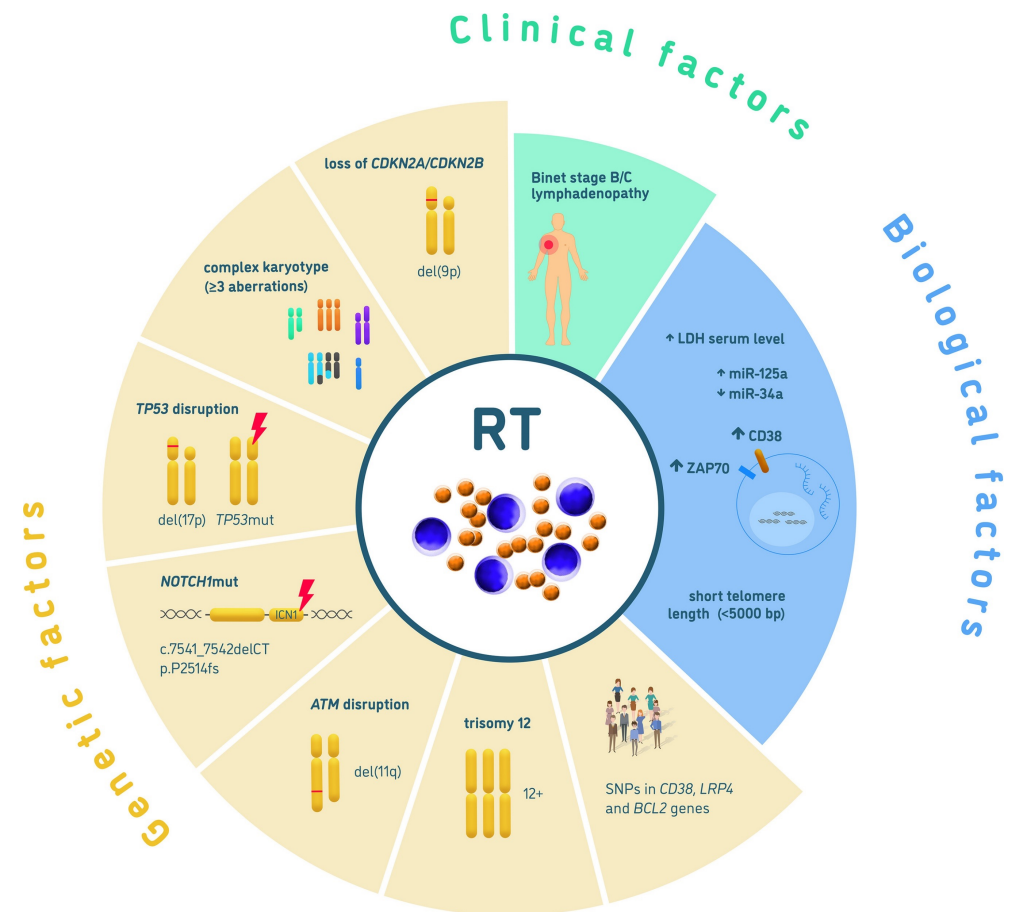
Figure 1. Biological pathways associated with Richter transformation. Legend: CDKN2A: cyclin-dependent kinase inhibitor 2A; CLL: chronic lymphocytic leukemia; DLBCL-RT: diffuse large B cell lymphoma Richter transformation; IGHV-D-J: immunoglobulin heavy chain variable D-J; TP53: tumor protein 53.

Tadmor T, et al. Cancers 2021



Risk factors associated with the development of RT-DLBCL

- Because the incidence of the **HL variant of RS is very low**, risk factors predisposing to this condition are **currently unknown** and their identification is limited by the small sample size of the available cohorts.
- Numerous **clinical and laboratory parameters** (bulky lymphadenopathy or hepato-splenomegaly, advanced stage, low platelet count, elevated beta-2-microglobulin, therapy combining purine analogues and alkylating agents, and a higher number of lines of therapy) have been nominated as candidate risk factors for RT, which **may differ from risk factors for CLL progression**.
- These clinical observations are probably only **surrogate aspects** secondary to some intrinsic biologic features of an individual tumor.



Rossi D, et al, *Seminars in Oncology* 2016
 Petrackova A, et al. *Blood Reviews* 2021



GENETIC ABNORMALITIES

Complex karyotype

Disruption of TP53 (del(17p) and/or mutation)

Mutations in NOTCH1

Loss of CDKN2A

MYC activation

11q deletion

Absence of deletion 13q

Unmutated IGHV, Stereotyped BCR subset 8

Telomere length < 5000 bp

Deregulation of microRNA expression:

miR-125a

miR-34a

miR-21

miR-146b

miR-181b

miR-150

At least one of these abnormalities/mutations is present in 90% of patients with RT.

CLINICAL FACTORS

Binet Stage B/C

Lymphadenopathy

BIOCHEMICAL FACTORS

Lactate dehydrogenase elevation

High ZAP70

CD38 Expression

In addition, **a number of previous CLL treatment lines** were associated with higher RT risk.

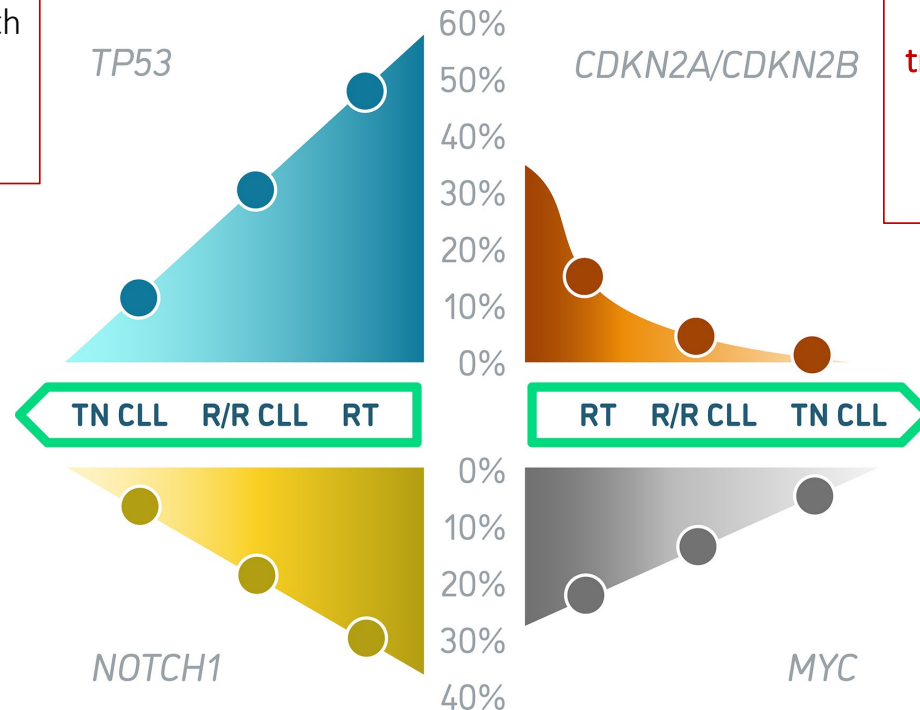
Petrackova A, et al. Blood Reviews 2021



TP53, MYC, CDKN2A aberrations and NOTCH1 expression

More than **50%** of patients with RT have a **TP53 aberration** in the **CLL clone** before transformation.

Activating mutations in the **NOTCH1 gene** are found in approximately **30%** of patients with RT **clonally derived from CLL**, and these patients **do not simultaneously carry TP53 and CDKN2A aberrations**



CDKN2A aberrations are frequently **acquired at the time of transformation** and encode for **p16^{INK4A}** protein, another negative cell cycle regulator, and **its loss** is also relatively common in RT.

Aberrant **activation of MYC** is usually due to **structural changes, e.g. translocation**, where MYC comes under an active promoter (such as **t(8;14)**), or an **amplification (8q24)**.

Petrackova A, et al. Blood Reviews 2021



ARTICLE Open Access

Distinct immune signatures in chronic lymphocytic leukemia and Richter syndrome

Yucal Wang¹, Sutapa Sinha¹, Linda E. Welik¹, Charla R. Secreto¹, Karen L. Rech², Timothy G. Call³, Sameer A. Parikh¹, Saad S. Kendeian⁴, El. Muchtar¹, Suzanne R. Hayman¹, Amber B. Koehler¹, Daniel L. Van Dyke⁵, Jose F. Les⁶, Susan L. Stage⁷, Haidong Dong⁸, Neil E. Kay⁹, Rong He² and Wei Ding¹⁰

Abstract
 Richter syndrome (RS) refers to transformation of chronic lymphocytic leukemia (CLL) to an aggressive lymphoma, most commonly diffuse large B-cell lymphoma. RS is known to be associated with a number of genetic alterations such as TP53 and NOTCH1 mutations. However, it is unclear what immune microenvironment changes are associated with RS. In this study, we analyzed expression of immune checkpoint molecules and infiltration of immune cells in nodal samples, and peripheral blood T-cell diversity in 33 CLL and 37 RS patients. Compared to CLL, RS nodal tissue had higher PD-L1 expression in histiocytes and dendritic cells (median 16.6% vs. 2.8%, $P < 0.01$) and PD expression in neoplastic B cells (median 26.0% vs. 6.2%, $P < 0.01$), and higher infiltration of FOXP3-positive T cells (median 1.7% vs. 0.4%, $P < 0.01$) and CD163-positive macrophages (median 23.4% vs. 9.1%, $P < 0.01$). In addition, peripheral blood T-cell receptor clonality was significantly lower in RS vs. CLL patients (median [25th–75th], 0.107 [0.070–0.209] vs. 0.233 [0.111–0.406], $P = 0.046$), suggesting that T cells in RS patients were more diverse than in CLL patients. Collectively these data suggest that CLL and RS have distinct immune signatures. Better understanding of the immune microenvironment is essential to improve immunotherapy efficacy in CLL and RS.

Keywords: Chromosomal microarray analysis; Richter syndrome; CLL/SLL.

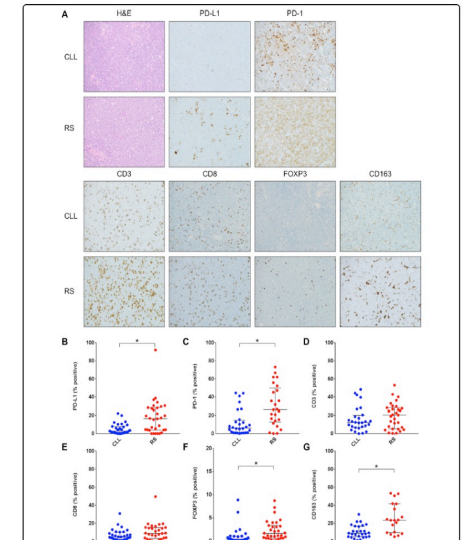


Fig. 1 Immunohistochemistry staining of immune checkpoint and immune cell markers in CLL and RS. **A**, Representative IHC and IHC images of PD-L1, PD-1, CD3, CD8, FOXP3, and CD163 staining in CLL and RS. **B–G**, Quantitative comparison of PD-L1, PD-1, CD3, CD8, FOXP3, and CD163 staining in CLL vs. RS. Asterisk (*) indicates $P < 0.01$.

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Clinical utility of chromosomal microarray in establishing clonality and high risk features in patients with Richter transformation

Brian Hess^{1,2}, James Kalmuk^{3,4,5}, Iya Znyozko⁶, Cynthia A. Schandl⁷, Nina Wagner-Johnston⁸, Sandra Mazzoni⁹, Lindsey Hendrickson¹⁰, Zane Chaid¹¹, Irl Brian Greenwell¹², Dayna J. Wolff¹³

¹Department of Hematology/Oncology, Wake Forest Baptist Medical Center, 7500 Balderson Blvd., Winston-Salem, NC 27157, USA
²Department of Pathology and Laboratory Medicine, Medical University of South Carolina, 17 Ashley Avenue, Charleston, SC 29425, USA
³Department of Hematology/Oncology, Sidney Kimmel Comprehensive Cancer Center, Johns Hopkins University, 1650 Orleans Street, Baltimore, MD, 21205, USA
⁴Department of Hematology/Oncology, Cleveland Clinic, 9500 Euclid Avenue, Cleveland, OH, 44195, USA
⁵Department of Hematology/Oncology, Levine Cancer Institute, Atrium Health, 1021 Meredith Medical Drive, Charlotte, NC, 28204, USA

ARTICLE INFO
ABSTRACT
 Richter transformation (RT) refers to the development of an aggressive lymphoma in patients with pre-existing chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL). It carries a poor prognosis secondary to poor response to therapy or rapid disease relapse. Currently there are no randomized trials to guide treatment. Therapeutic decisions are often influenced by the presence or absence of a clonal relationship between the underlying CLL/SLL and the new lymphoma given the poor prognosis of patients with clonally related RT. Chromosomal microarray analysis (CMA) can help to establish clonality while also detecting genomic complexity and clinically relevant genetic variations such as loss of CDKN2A and/or TP53. As a result, CMA has potential prognostic and therapeutic implications. For this study, CMA results from patients with Richter transformation were evaluated in paired CLL/SLL and transformed lymphoma samples. CMA revealed that 86% of patients had common aberrations in the two samples indicating evidence of common clonality. CMA was also useful in detecting aberrations associated with a poor prognosis in 71% of patients with RT. This study highlights the potential clinical utility of CMA to investigate the clonal relationship between CLL/SLL and RT, provide prognostic information, and possibly guide therapeutic decision making for patients with Richter transformation.

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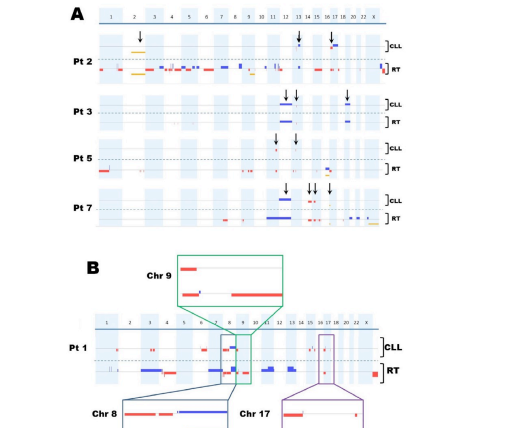


Fig. 3 A, Chromosomal microarray analysis of samples for representative cases 2, 3, 5 and 7 revealed clonal relationship between CLL and RT. Blue, red and orange bars represent genes, lines and bars of heterozygosity (H), copy number alterations with identical breakpoints. Fig. 3B, Comparative analysis of samples for case 1 did not reveal any aberrations with identical breakpoints. Thus, clonal relationship could not be established. Aberrations for representative chromosomes 8, 9 and 17 are enlarged to show.

Ferrata Storti Foundation
The complex karyotype landscape in chronic lymphocytic leukemia allows the refinement of the risk of Richter syndrome transformation

Andrea Visentini^{1,2}, Laura Bonaldi³, Gian Matteo Rigolin⁴, Francesca Romana Mauro⁵, Annalisa Martines⁶, Federica Frezzato^{3,2}, Stefano Pinnetto^{1,2}, Lella Romano Gargarella^{1,2}, Mario Antonella Bardi^{1,2}, Maurizio Cavallari^{1,4}, Eleonora Volta¹, Francesco Cazzavini¹, Mauro Nanni¹, Monica Facco^{1,2}, Francesco Piazza^{1,2}, Anna Guarini¹, Robin Foa⁵, Gianpietro Semenzato^{1,2}, Antonio Cuneo⁷ and Livio Trentin^{1,2}

¹Hematology and Clinical Immunology Unit, Department of Medicine, University of Padua, Padua; ²Verecchio Institute of Molecular Medicine, Padua; ³Immunology and Molecular Oncology Unit, Veneto Institute of Oncology IOV-IRCCS, Padua; ⁴Hematology section, Department of Medical Sciences, Azienda Ospedaliera Universitaria, Azienda S. Anna, University of Ferrara, Ferrara; ⁵Hematology division, Department of Precision and Translational Medicine, "Sapienza" University, Rome, Italy

ABSTRACT
 Complex karyotype (CK) at chronic lymphocytic leukemia (CLL) diagnosis is a negative biomarker of adverse outcome. Since the impact of CK and its subtypes, namely type-2 CK (CK with major structural abnormalities) or high-CK (CK with a5 chromosome abnormalities), on the risk of developing Richter syndrome (RS) is unknown, we carried out a multicenter real-life retrospective study to test its prognostic impact. Among 540 CLL patients, 107 harbored a CK at CLL diagnosis, 78 were classified as CK2 and 52 as high-CK. Twenty-eight patients developed RS during a median follow-up of 6.7 years. At the time of CLL diagnosis, CK2 and high-CK were more common and predicted the highest risk of RS transformation, together with advanced Binet stage, unmutated (U)-IGHV, 11q-, and TP53 abnormalities. We integrated these variables into a hierarchical model: high-CK and/or CK2 patients showed a 10-year time to RS (TTRS) of 51%; U-IGHV/11q-; TP53 abnormalities/Binet stage B-C patients had a 10-year TTRS of 12%; mutated (M)-IGHV without CK and TP53 disruption a 10-year TTRS of 5% ($P < 0.0001$). We herein demonstrate that CK landscape at CLL diagnosis allows the risk of RS transformation to be refined and we

Correspondence: LIVIO TRENTIN, livio.trentin@unipd.it
ANDREA VISENTINI, andrea.visentini@unipd.it
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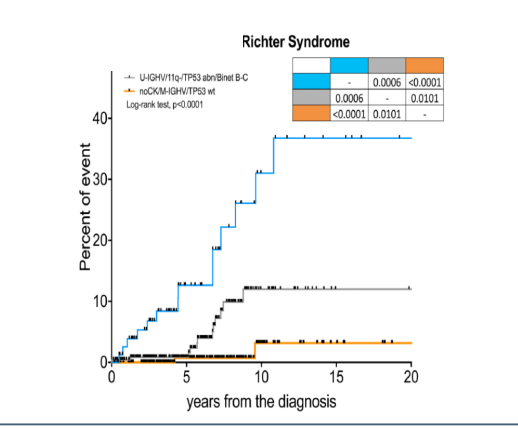


Fig. 3 The Richter syndrome scoring system. Kaplan-Meier curve of time to Richter syndrome transformation according to the Richter syndrome scoring system. Patients were classified at high risk if they were high CK and/or CK2 at CLL diagnosis (blue curve); at intermediate risk if they displayed unmutated IGHV status (U-IGHV), 11q22-23 deletion (11q), TP53 abnormalities (including deletions or mutations, TP53 abn) or Binet stage B-C (grey curve); at low risk if they were IGHV mutated (M-IGHV) patients without CK and wild type TP53 gene (TP53 not deleted nor mutated) (orange curve).

ARTICLE Check for updates

Artificial intelligence-assisted mapping of proliferation centers allows the distinction of accelerated phase from large cell transformation in chronic lymphocytic leukemia

Siba El Hussein^{1,2,4}, Pingjun Chen^{1,3,4}, L. Jeffrey Medeiros², John D. Hazle⁵, Jia Wu^{1,5,6} and Joseph D. Khoury^{1,5,6}

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Chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL) is characterized morphologically by numerous small lymphocytes and pale nodules composed of polyclonal and paraimmature blasts known as proliferation centers (PCs). Patients with CLL can undergo transformation to an aggressive lymphoma, most often diffuse large B-cell lymphoma (DLBCL), known as Richter transformation (RT). An accelerated phase of CLL (aCLL) may also be observed which correlates with subsequent transformation to DLBCL, and may represent an early stage of transformation. Distinguishing PC in CLL from aCLL or RT can be diagnostically challenging, particularly in small needle biopsy specimens. Available guidelines pertaining to distinguishing CLL from RT's progressive forms are limited, subject to the morphologist's experience and are often not completely helpful in the assessment of scant biopsy specimens. To objectively assess the extent of PCs in aCLL and RT, and enhance diagnostic accuracy, we sought to design an artificial intelligence (AI)-based tool to identify and delineate PCs based on feature analysis of the combined individual nuclear size and intensity, designated here as the heat value. Using the mean heat value from the generated heat value image of all cases, we were able to reliably separate CLL, aCLL and RT with sensitive diagnostic predictive values.

Modern Pathology; <https://doi.org/10.1038/s41379-022-01015-9>

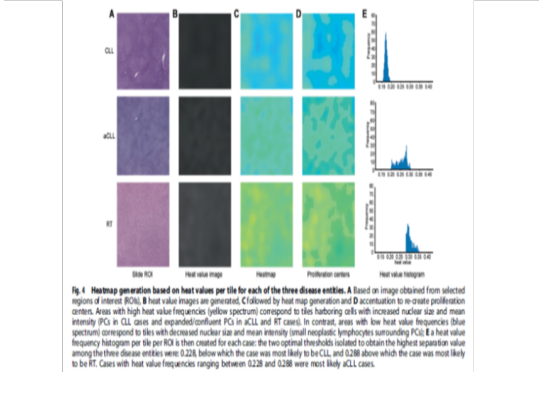


Fig. 4 Heatmap generation based on heat value per tile for each of the three disease entities. A Based on image obtained from selected regions of interest (ROI), B heat value images are generated, C followed by heat map generation and D accentuation to re-create proliferation centers. Areas with high heat value frequencies (yellow spectrum) correspond to tiles harboring cells with increased nuclear size and mean intensity PCs in CLL cases and expanded/confident PGs in aCLL and RT cases. In contrast, areas with low heat value frequencies (blue spectrum) correspond to tiles with decreased nuclear size and mean intensity (small neoplastic lymphocytes surrounding PCs). E a heat value frequency histogram per tile per ROI is then created for each case; the two optimal thresholds isolated to obtain the highest separation value among the three disease entities were 0.228, below which the case was most likely to be CLL, and 0.288 above which the case was most likely to be RT. Cases with heat value frequencies ranging between 0.228 and 0.288 were most likely aCLL cases.



Outcomes of Richter’s transformation of chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL): an analysis of the SEER database

Radowan Elnair¹ · Moataz Ellithi² · Avyakta Kallam¹ · Valerie Shostrom³ · Robert G. Bociek¹

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Abstract

Richter’s transformation (RT) is a rare complication arising in patients with chronic lymphocytic leukemia/small lymphocytic lymphoma (CLL/SLL) and is associated with an overall dismal outcome. The rarity of this entity poses many challenges in understanding its biology and outcomes seen and the optimal treatment approach. We utilized the SEER (Surveillance, Epidemiology and End Results) database to identify patients diagnosed with CLL/SLL between 2000 and 2016 and subsequently had a diagnosis of diffuse large B-cell lymphoma (DLBCL) or Hodgkin lymphoma (HL), thus capturing those who experienced an RT event. We compared the outcomes of those patients to those of patients in the database diagnosed with DLBCL without a preceding CLL/SLL diagnosis. We identified 530 patients who developed RT out of 74,116 patients diagnosed with CLL/SLL in the specified period. The median age at RT diagnosis was 66 years, and the median time from CLL/SLL diagnosis to RT development was roughly 4 years. Patients with RT had a dismal outcome with median overall survival of 10 months. We identified advanced Ann Arbor stage (III/IV) and prior treatment for CLL as predictors of worse outcome in patients with RT. Our study represents the largest dataset of patients with CLL/SLL and RT and adds to the existing literature indicating the poor outcomes for those patients.

Keywords Richter’s transformation · Richter’s syndrome · Diffuse large B-cell lymphoma · Chronic lymphocytic leukemia

Variable	CLL without RT (n = 73,586)	CLL with RT (n = 530)	De novo DLBCL (n = 97,415)
Median age (IQ) in years	70 (61,79)	66 (58,73)	68 (55,78)
Gender			
Male	60%	62%	55%
Female	40%	38%	45%
Chemotherapy			
Yes	16%	72%	75%
No/unknown	84%	28%	25%
Radiation			
Yes	1%	14%	20%
No/unknown	99%	86%	80%
Ann Arbor stage	N/A		
1–2		30%	43%
3–4		47%	45%
Unknown		23%	12%
Histology	N/A		N/A
DLBCL		85%	
HL		15%	
Median OS (95% CI)	101 months (99–102)	10 months (8–14)	62 months (61–64)



Table 1 Identified patients diagnosed with CLL between 2000 and 2016

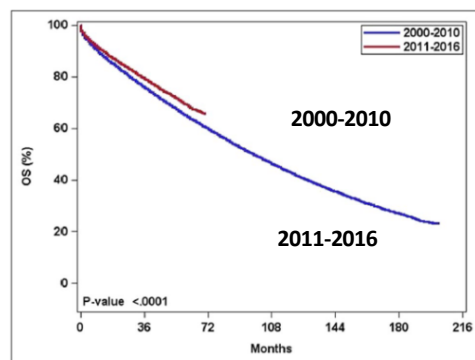


Fig. 1 KM curves for OS of CLL/SLL patients

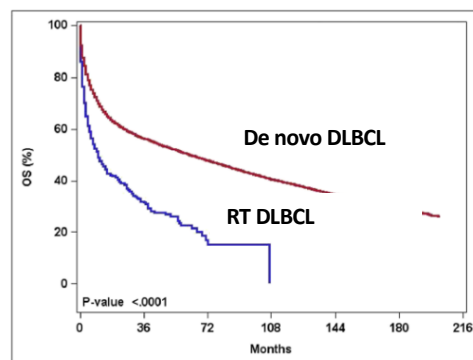


Fig. 2 KM curve for OS of de novo DLBCL versus DLBCL arising from RT

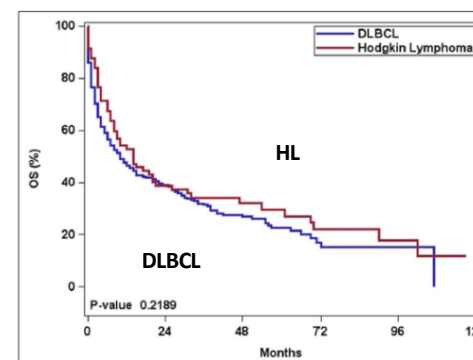


Fig. 3 KM curves for RT stratified by histology (DLBCL versus HL)

- The **largest dataset** of patients with CLL/SLL and RT (2000-2016, **0.7%**)
- The median time from CLL/SLL diagnosis to RT development was roughly **4 years**.
- Patients with RT had a **dismal outcome** with median OS of **10 months**.
- Ann Arbor **stage III/IV** and **prior treatment** for CLL predictors of worse outcome in RT patients.



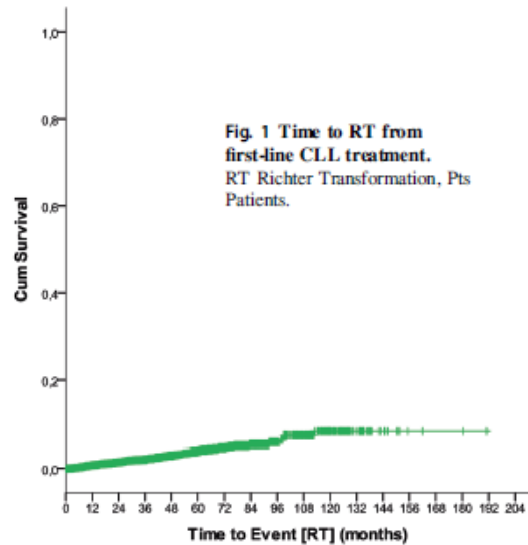
ARTICLE

Chronic lymphocytic leukemia

Richter transformation in chronic lymphocytic leukemia (CLL)—a pooled analysis of German CLL Study Group (GCLLSG) front line treatment trials

O. Al-Sawaf¹ · S. Robrecht¹ · J. Bahlo¹ · A. M. Fink¹ · P. Cramer¹ · J. v Tresckow¹ · E. Lange² · M. Kiehl³ · M. Dreyling⁴ · M. Ritgen⁵ · J. Dürig⁶ · E. Tausch⁷ · C. Schneider⁷ · S. Stilgenbauer^{7,8} · C. M. Wendtner⁹ · K. Fischer¹ · Goede V^{1,10} · M. Hallek¹ · B. Eichhorst¹

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RT-free	Pts, N	Events, N	Median months	3-year Survival, %	6-year Survival, %	9-year Survival, %	12-year Survival, %
All patients	2971	99 (3.3)	NR	97.9	95.4	92.6	91.7

- A total of 2975 pts with advanced CLL were reviewed for incidence of RT.
- 103 pts developed RT (3%): 95 DLBCL (92%) and eight pts HD (8%) after receiving first-line chemo- or chemoimmunotherapy.
- Median observation time was 53 months
- Median OS from initial CLL diagnosis for pts without RT was 167 months vs 71 months for pts with RT.
- Median OS after diagnosis of RT was 9 months.
- Three pts after CHOP underwent Allo-SCT and two Auto-SCT

Table 2 First-line treatment for CLL in RT patients.

Prior front-line treatment regimen before RT diagnosis, N (%)	103
BR	14 (13.6)
F	21 (20.4)
FC	38 (36.9)
FCR	20 (19.4)
CLB	4 (3.9)
RCLB	4 (3.9)
GCLB	2 (1.9)

BR bendamustine, rituximab, F fludarabine, FC fludarabine, cyclophosphamide, FCR fludarabine, cyclophosphamide, rituximab, CLB chlorambucil, R-CLB rituximab, chlorambucil, G-CLB obinutuzumab, chlorambucil.

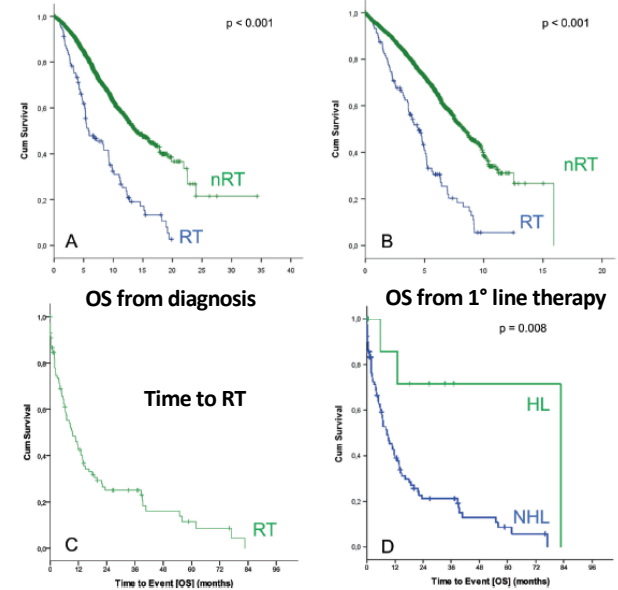


Fig. 2 Overall survival with and without RT after diagnosis of CLL (a), after first-line treatment of CLL (b), after diagnosis of RT (c), and according to type of RT after diagnosis of RT (d). RT Richter Transformation, nRT No Richter Transformation, HL Hodgkin's lymphoma, NHL Non-Hodgkin's Lymphoma, OS overall survival.

Table 3 Treatment for RT.

Treatment, N (% of 103)	62
CHOP	47 (46)
BEACOPP	2 (1.9)
ABVD	1 (1.0)
Other	12 (11.7)

R-CHOP rituximab, cyclophosphamide, doxorubicin, vincristine, prednisolone, BEACOPP bleomycin, etoposide, doxorubicin, cyclophosphamide, vincristine, procarbazine, prednisolone, ABVD doxorubicin, bleomycin, vinblastine, dacarbazine.



Richter transformation of chronic lymphocytic leukaemia: a British Society for Haematology Good Practice Paper

Toby A. Eyre,¹ John C. Riches,² Piers E. M. Patten,^{3,4} Renata Walewska,⁵ Helen Marr,⁶ George Follows,⁷ Peter Hillmen,^{8,9} Anna H. Schuh^{1,10} On behalf of the Haemato-Oncology Task Force of the British Society for Haematology

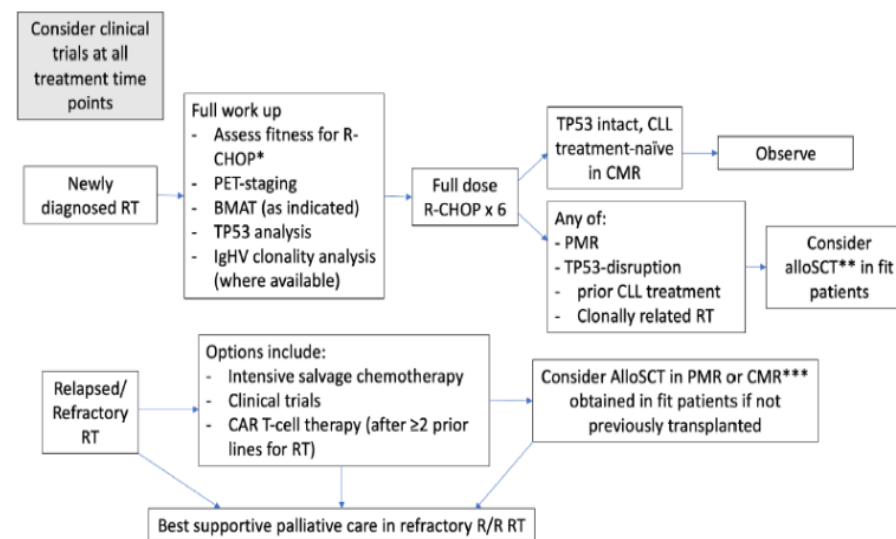
¹Department of Haematology, Cancer and Haematology Centre, Oxford University Hospitals NHS Foundation Trust, Oxford, ²Centre for Haemato-Oncology, Barts Cancer Institute, Queen Mary University of London, ³Comprehensive Cancer Centre, School of Cancer and Pharmaceutical Sciences, King's College London, ⁴Department of Haematology, King's College Hospital, ⁵Department of Haematology, University Hospitals Dorset, Bournemouth, ⁶Northern Centre for Cancer Care, Newcastle Upon Tyne Hospitals NHS Trust, Newcastle Upon Tyne, ⁷Department of Haematology, Addenbrookes, Cambridge, ⁸St. James's Institute of Oncology, ⁹Leeds Institute of Cancer and Pathology, University of Leeds, Leeds, and ¹⁰Department of Oncology, University of Oxford, John Radcliffe Hospital, Oxford, UK

Recommendations

- All patients with a clinical suspicion of transformed CLL and an SUVmax >5 should undergo PET-targeted biopsy of the most safely accessible 18F-FDG-avid site (1B).
- A surgical excisional or incisional biopsy is strongly recommended to establish the diagnosis (1B). Where this is not possible, a core needle biopsy is an alternative (2B).
- Patients should have viral serology for human immunodeficiency virus, hepatitis B and hepatitis C, EBV and CMV (1C).
- Consider a bone marrow aspiration and biopsy in RT cases to assess CLL/RT infiltration with unexplained pancytopenia (2C).
- TP53 mutation and 17p deletion analysis should be performed (1B).
- If available and analysis is possible, include IgHV rearrangement analysis (genetic sequencing) of CLL and RT tissue to establish relatedness of the clone (2B).
- Ensure specialist haemato-pathology review, clinicopathological correlation and multi-disciplinary review when considering RT diagnosis (1B).

Recommendations

- Due to the poor outcome of most RT patients with standard therapy, all patients should be offered clinical trials when available (2B).
- Offer R-CHOP in patients considered appropriate for anthracycline-based treatment (1B).
- Consider consolidation in first remission with either autologous or allogeneic stem cell transplantation in fit patients typically <70 years old (2B).
- Consider observation following R-CHOP for TP53-intact, previously treatment-naïve patients across all ages obtaining a complete metabolic remission (2B).
- Consider ABVD in anthracycline-fit patients developing HL-RT (2B).
- Autologous or allogeneic stem cell transplantation in first remission is not typically considered in HL-RT (2B).



Not unfit for full dose R-CHOP consider R-miniCHOP, R-GCP, R-CEOP in appropriate patients (but no data in RT). **Autologous SCT can be considered and discussed in chemo-sensitive disease. ***CMR post CAR-T can be reasonably observed. Abbreviations: RT: Richter transformation, CAR: chimeric antigen receptor, BMAT: bone marrow aspirate and trephine, PET: positron emission tomography, CMR: complete metabolic response, PMR: partial metabolic response, R-CHOP: rituximab, cyclophosphamide, vincristine, prednisolone

Recommendations

- Consider early introduction of palliative-care support in heavily pre-treated patients with CLL and comorbidities who develop DLBCL-RT on a targeted inhibitor (2B).
- Consider clinical trial enrolment in patients with relapsed RT (2B).
- Consider CAR-T in RT patients who have received two or more prior DLBCL standard-of-care treatments including R-CHOP (2C).

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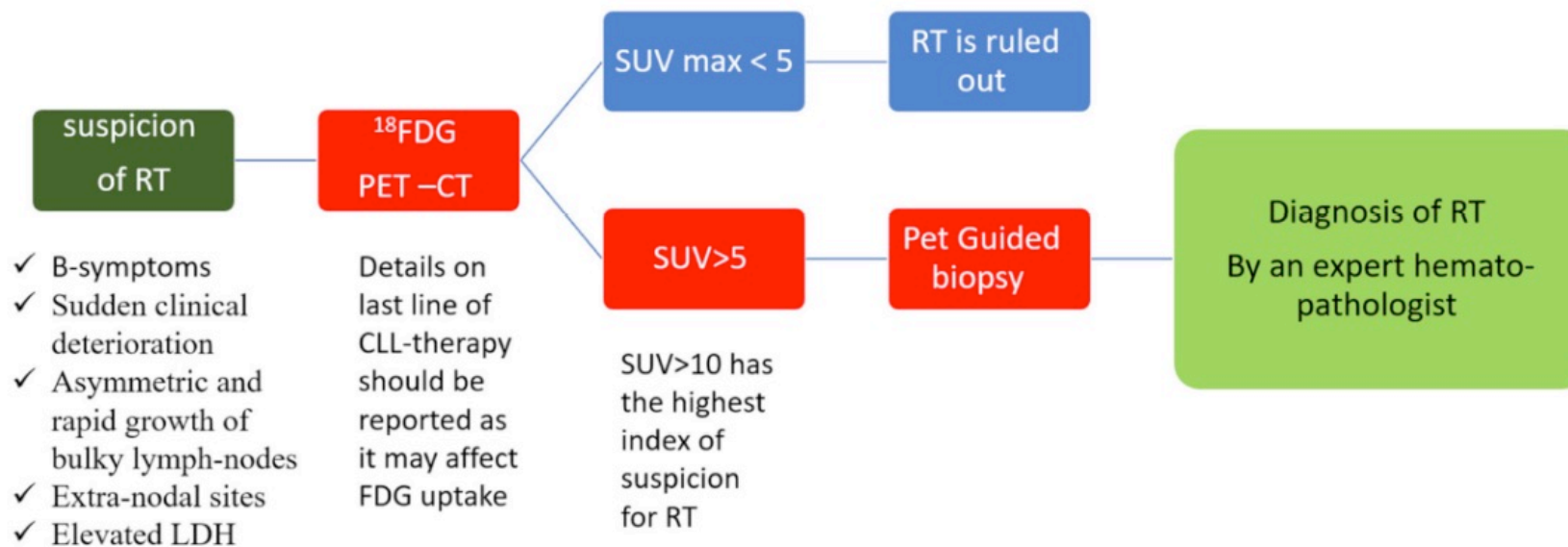


Figure 2. Diagnosis of Richter transformation. Legend: 18-FDG-PET-CT: positron emission tomography with 2-deoxy-fluorine-18-fluoro-D-glucose; CLL: chronic lymphocytic leukemia; LDH: lactate dehydrogenase; RT: Richter transformation; SUV: standardized uptake values.

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Richter Transformation of Chronic Lymphocytic Leukemia

- **Historically**, in the era prior to the use of novel oral agents, **studies** that tested the **prevalence of RT** mainly **focused** on CLL patients who had received **prior chemotherapy or chemoimmunotherapy (CIT)**.
- First reports on **genetic aberrations** associated with **RT-DLBCL** that developed **on novel agents** include the **same abnormalities** in **TP53, CDKN2A, MYC, and NOTCH1** genes as RT that developed on chemoimmunotherapy.
- **The largest body** of information on the genetic nature of RT in the era of **novel agents** is available on patients treated with **ibrutinib**.

Petrackova A, et al. Blood Reviews 2021
Ding W, et al. Hematology 2018



Epidemiology of Richter transformation reported in clinical trials

Chemo-immunotherapy

The role of chemotherapy and chemoimmunotherapy in the development of RS (2-10%) remains controversial. ²

Trial Reference	Treatment	Del(17p)	Incidence of Richter Transformation
Tsimberidou, 2006	Chemo-immunotherapy	NA	3.7%
Parikh, 2013	Chemo-immunotherapy	3.3%	2.3%
Robak, 2004	Cladribine, Alkylating	NA	0.9%
Rossi, 2009	Chemo-immunotherapy	NA	8.8%
Catvosky, 2007	F vs. FC vs. Chl	NA	1.7%
Solh, 2013	F vs. Chl vs. F and Chl	NA	6.5%
Fischer, 2016	FC vs. FCR	6.2%	4.0%

Tadmor T, et al. Cancers 2021
Parikh A, et al. Curr Hematol Malig Rep 2014



Epidemiology of Richter transformation reported in clinical trials

Novel Agents CLL R/R Setting

Trial Reference	Treatment	Del(17p)	Incidence of Richter Transformation
Munir, 2019	Ibrutinib	32%	10%
O'Brien, 2016	Ibrutinib	100%	12%
Chanan-Khan, 2016	Ibrutinib and BR	0	0
Ahn, 2017	Ibrutinib	60%	9%
Furman, 2014	Idelalisib and R	42%	NA
Jones, 2017	Idelalisib and O	40%	NA
Zelenetz, 2017	Idelalisib and BR	33%	2%
Roberts, 2017	Venetoclax	30%	16%
Stilgenbauer, 2016	Venetoclax	100%	10%
Seymour, 2017	Venetoclax and R	31%	10%

Tadmor T, et al. Cancers 2021



Epidemiology of Richter transformation reported in clinical trials

Novel Agents CLL R/R Setting

- In the era of novel agents, one **raised concern** was whether there was an **increased rate of this rare and aggressive transformation** among patients treated with **Bruton tyrosine kinase inhibitors (BTKis) or BCL2 inhibitors (BCL2is)**.
- Indeed, in the first clinical trials using novel agents, **2–15% incidence** rates of RT have been described in **relapsed/refractory (R/R)** patients with CLL **treated with Ibrutinib, Venetoclax, or Idelalisib**.
- These alarming reports were probably related to the **recruitment of patients with R/R disease or even already in the early stages of transformation**.

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Epidemiology of Richter transformation reported in clinical trials Novel Agents CLL Treatment Naive Setting

Trial Reference	Treatment	Del(17p)	Incidence of Richter Transformation
Burger, 2015	Ibrutinib	0	0
Ahn, 2017	Ibrutinib	60%	4%
Woyach, 2018	Ibrutinib Ibrutinib and R	5% 8%	0 1%
Moreno, 2019	Ibrutinib and O	12%	0.9%
Shanafelt, 2019	Ibrutinib and R	0.6%	NA
Sharman, 2020	Acalabrutinib Acalabrutinib and O	8.9% 9.5%	3% 1%
O'Brien, 2015	Idelalisib and R	14%	0
Lampson, 2019	Idelalisib and O	17%	NA
Fischer, 2019	Venetoclax and O	12%	1%

In clinical trials involving **treatment-naïve patients with CLL treated with novel agents**, the **incidence of RT was reported to be 0–4%** indicating that there is **no increase in the number of cases of RT** during therapy with these novel and effective biological agents.

Tadmor T, et al. *Cancers* 2021



Article

Long-Term Efficacy and Safety of Ibrutinib in the Treatment of CLL Patients: A Real Life Experience

Alessandro Broccoli ^{1,2}, Lisa Argani ², Alice Morigi ^{1,2}, Laura Nanni ^{1,2}, Beatrice Casadei ^{1,2}, Cinzia Pellegrini ¹, Vittorio Stefoni ^{1,2} and Pier Luigi Zinzani ^{1,2,*}

¹ IRCCS Azienda Ospedaliero-Universitaria di Bologna, Istituto di Ematologia "Seragnoli", 40138 Bologna, Italy; alessandro.broccoli@studio.unibo.it (A.B.); alice.morigi2@studio.unibo.it (A.M.); laura.nanni@libero.it (L.N.); bea.casadei@gmail.com (B.C.); cinzia.pellegrini5@unibo.it (C.P.); vittorio.stefoni2@unibo.it (V.S.)

² Dipartimento di Medicina Specialistica, Diagnostica e Sperimentale, Università di Bologna, 40138 Bologna, Italy; lisa.argani@unibo.it

* Correspondence: pierluigi.zinzani@unibo.it

Abstract: Ibrutinib has demonstrated a significant clinical impact in patients with de novo and relapsed/refractory chronic lymphocytic leukemia (CLL), even in cases with unfavorable cytogenetics and molecular markers. All CLL patients' data treated at our Institute with ibrutinib have been retrospectively reviewed. Forty-six patients received ibrutinib either as frontline (10) or second or more advanced treatment (36). Five patients presented with TP53 mutations; 11 had the deletion of chromosome 17p; 17 displayed an unmutated immunoglobulin variable heavy chain status. The median number of cycles administered was 26. Among patients treated frontline, the best overall response rate (ORR) was 90.0%. In patients receiving ibrutinib as a second or later line ORR was 97.2%. Median progression-free survival was 28.8 and 21.1 months for patients treated frontline and as second/later line, respectively. Median overall survival was not reached for those treated frontline and resulted in 4.9 years for patients treated as second/later line. Grade 3–4 hematological toxicities were neutropenia, thrombocytopenia, and anemia. Grade 3–4 extrahematological toxicities included diarrhea, cutaneous rash, utero-vesical prolapse, vasculitis, and sepsis. Ibrutinib is effective and well tolerated in CLL. Responses obtained in a real-life setting are durable and the safety profile of the drug is favorable.



Citation: Broccoli, A.; Argani, L.; Morigi, A.; Nanni, L.; Casadei, B.; Pellegrini, C.; Stefoni, V.; Zinzani, P.L. Long-Term Efficacy and Safety of Ibrutinib in the Treatment of CLL Patients: A Real Life Experience. *J. Clin. Med.* **2021**, *10*, 3845. <https://doi.org/10.3390/jcm10245845>

RT 5/56 pts, (11%) at a median time of 16 months from first ibrutinib dose

Acalabrutinib Versus Ibrutinib in Previously Treated Chronic Lymphocytic Leukemia: Results of the First Randomized Phase III Trial

original reports

John C. Byrd, MD¹; Peter Hillmen, MD, MBChB, PhD²; Paolo Ghia, MD, PhD^{3,4}; Arnon P. Kater, MD, PhD⁵; Asher Chanan-Khan, MD⁶; Richard R. Furman, MD⁷; Susan O'Brien, MD⁸; Mustafa Nuri Yenerel, MD⁹; Arpad Illés, MD¹⁰; Neil Kay, MD¹¹; Jose A. Garcia-Marco, MD, PhD¹²; Anthony Mato, MD¹³; Javier Pinilla-Ibarz, MD, PhD¹⁴; John F. Seymour, PhD¹⁵; Stéphane Lepretre, MD^{16,17}; Stephan Stilgenbauer, MD¹⁸; Tadeusz Robak, PhD¹⁹; Wayne Rothbaum, MS²⁰; Raquel Izumi, PhD²⁰; Ahmed Hamdy, MD²⁰; Priti Patel, MD²¹; Kara Higgins, MS²¹; Sophia Sohoni, MD²¹; and Wojciech Jurczak, MD, PhD²²

PURPOSE Among Bruton's tyrosine kinase inhibitors, acalabrutinib has greater selectivity than ibrutinib, which we hypothesized would improve continuous therapy tolerability. We conducted an open-label, randomized, non-inferiority, phase III trial comparing acalabrutinib and ibrutinib in patients with chronic lymphocytic leukemia (CLL).

METHODS Patients with previously treated CLL with centrally confirmed del(17)(p13.1) or del(11)(q22.3) were randomly assigned to oral acalabrutinib 100 mg twice daily or ibrutinib 420 mg once daily until progression or unacceptable toxicity. The primary end point was independent review committee-assessed noninferiority of progression-free survival (PFS).

RESULTS Overall, 533 patients (acalabrutinib, n = 268; ibrutinib, n = 265) were randomly assigned. At the data cutoff, 124 (46.3%) acalabrutinib patients and 109 (41.1%) ibrutinib patients remained on treatment. After a median follow-up of 40.9 months, acalabrutinib was determined to be noninferior to ibrutinib with a median PFS of 38.4 months in both arms (95% CI acalabrutinib, 33.0 to 38.6 and ibrutinib, 33.0 to 41.6; hazard ratio: 1.00; 95% CI, 0.79 to 1.27). All-grade atrial fibrillation/atrial flutter incidence was significantly lower with acalabrutinib versus ibrutinib (9.4% v 16.0%; P = .02); among other selected secondary end points, grade 3 or higher infections (30.8% v 30.0%) and Richter transformations (3.8% v 4.9%) were comparable between groups and median overall survival was not reached in either arm (hazard ratio, 0.82; 95% CI, 0.59 to 1.15), with 63 (23.5%) deaths with acalabrutinib and 73 (27.5%) with ibrutinib. Treatment discontinuations because of adverse events occurred in 14.7% of acalabrutinib-treated patients and 21.3% of ibrutinib-treated patients.

CONCLUSION In this first direct comparison of less versus more selective Bruton's tyrosine kinase inhibitors in CLL, acalabrutinib demonstrated noninferior PFS with fewer cardiovascular adverse events.

J Clin Oncol 39:3441-3452. © 2021 by American Society of Clinical Oncology

abstract

Median FU 41 months: RT Acalabrutinib 3.8% vs Ibrutinib 4.9%

JAMA Oncol, 2021 Aug 1;7(8):1213-1219. doi: 10.1001/jamaoncol.2021.1649.

Ibrutinib Plus Venetoclax for First-line Treatment of Chronic Lymphocytic Leukemia: A Nonrandomized Phase 2 Trial registration: ClinicalTrials.gov Identifier: NCT02756897.

Nitin Jain et al.

A single-center, phase 2 nonrandomized trial enrolled patients from August 17, 2016, to June 5, 2018. Participants **included previously untreated patients with CLL**

Therapy consisted of **ibrutinib**, 420 mg/d, monotherapy for 3 cycles, thereafter combined with **venetoclax** (standard weekly dose ramp-up to 400 mg/d) for a total of **24 cycles** of combination treatment.

Eighty patients (57 [71%] men) were treated; median age was 65 years (range, 26-83 years). **The median follow-up for all 80 patients was 38.5 months**

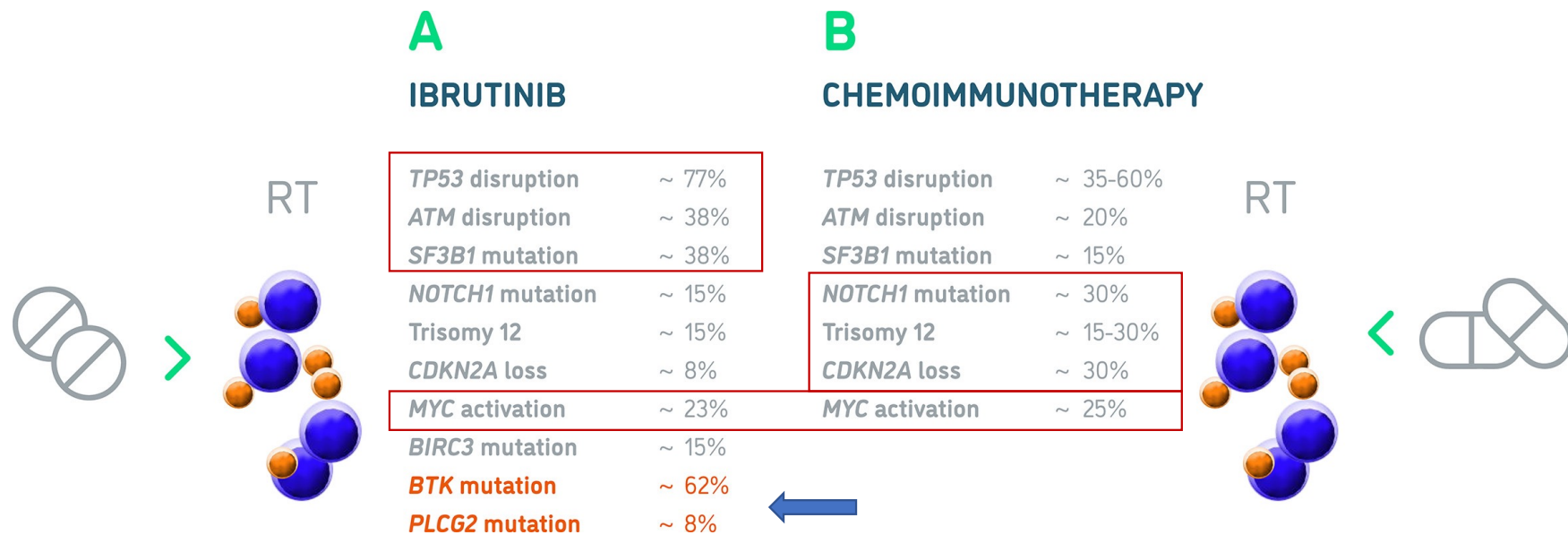
On an intent-to-treat analysis of combined treatment, **60 (75%) patients achieved bone marrow U-MRD remission as their best response**. Responses were seen **across all high-risk subgroups**, independent of the immunoglobulin heavy-chain variable gene mutation status, fluorescence in situ hybridization category, or TP53 mutation. The **3-year progression-free survival was 93%**, and **3-year overall survival was 96%**. No patient had CLL progression; **2 patients developed Richter transformation**.

The findings of this study suggest that combination therapy with ibrutinib and venetoclax might be beneficial for previously untreated patients with CLL. Remissions appeared to be durable during a follow-up of more than 3 years, with activity seen across high-risk disease subgroups, **including those with del(17p)/TP53-mutated CLL**.

80 pts, median FU 38.5 months, 2 pts RT (2.5%)



Genetic pathogenesis of RT-DLBCL developed on novel agents



- Studies have shown that **>70% of patients developing RT on ibrutinib had *TP53* abnormalities.**
- Frequent abnormalities of ***MYC*, *CDKN2A*, *TP53*, and *NOTCH1* genes in RT**, and most of these changes (60–95%) **were present in both the CLL clone and RT tissue.**
- **Early manifestation of RT on ibrutinib may be associated with the cooperation of pre-existing genetic events predisposing to transformation, antigen stimulated BCR and blocking of BCR signalling by the inhibitor.**

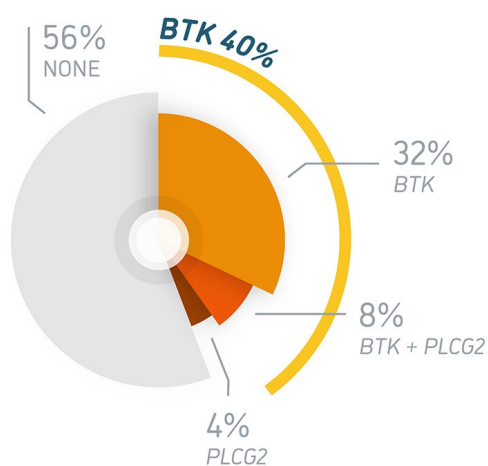
Petrackova A, et al. Blood Reviews 49 2021
Kadri S, et al. Blood Advances 2017



Clonal evolution underlying leukemia progression and Richter transformation in patients with Ibrutinib-relapsed CLL

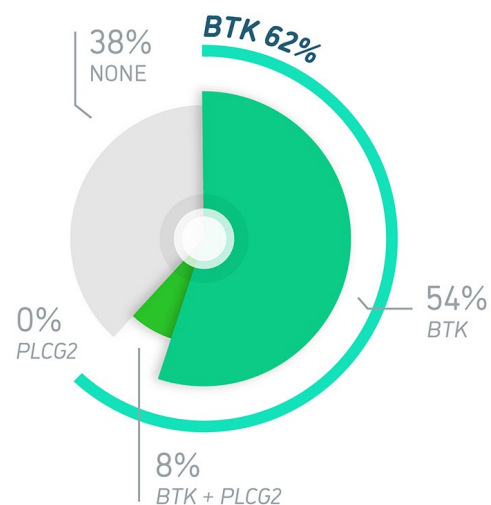
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RT – ALL STUDIES



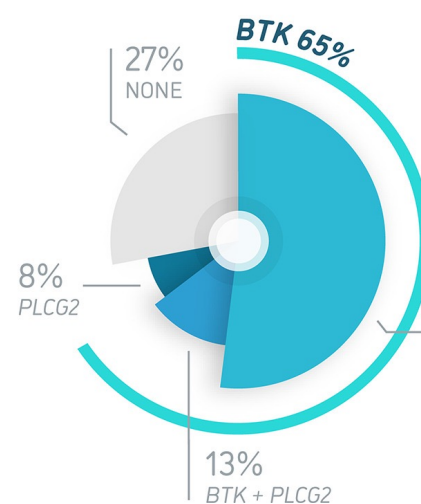
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RT – ONLY STUDIES ANALYSING TRANSFORMED-PROVEN TISSUE



C

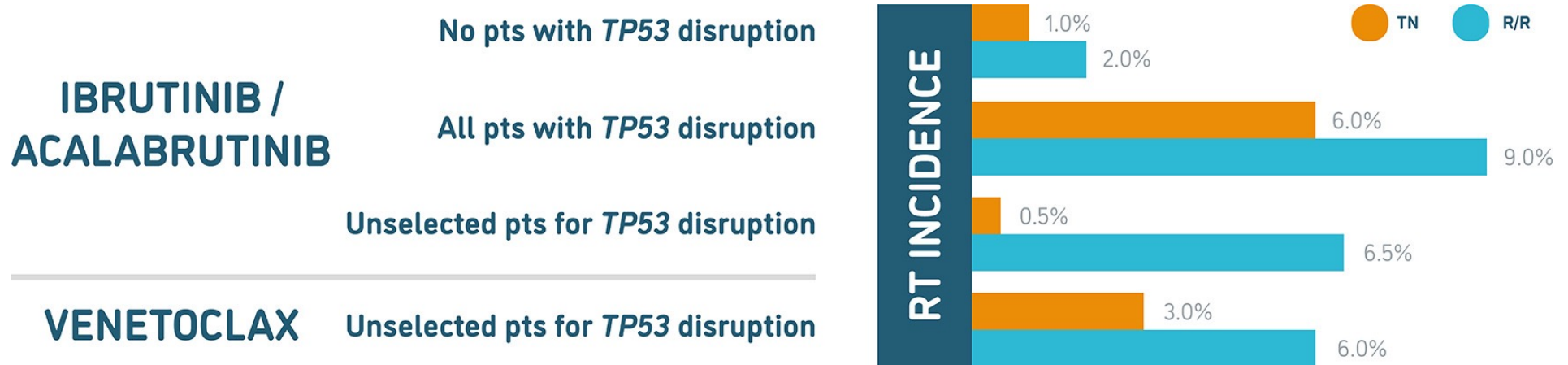
CLL PROGRESSION



- The occurrence of **resistance-associated mutations in BTK and PLCG2 genes** on ibrutinib is reported as being **lower in RT than in CLL progression**, where these mutations have been detected in up to 73% of cases.
- The possible explanations for the lower incidence of BTK/PLCG2 mutations in RT may lie in i) the **different underlying biology** of RT compared to CLL progression, and/or ii) **difficulties in collection of transformed material** for genetic analysis.
- However, when only the studies that **analysed the RT-transformed tissue** in all patients were evaluated, the **incidence of BTK/PLCG2 mutations in RT was similar to CLL progression**



The incidence of RT in CLL patients treated with BTKi and Venetoclax in TN and R/R CLL patients subdivided according to the TP53 disruption

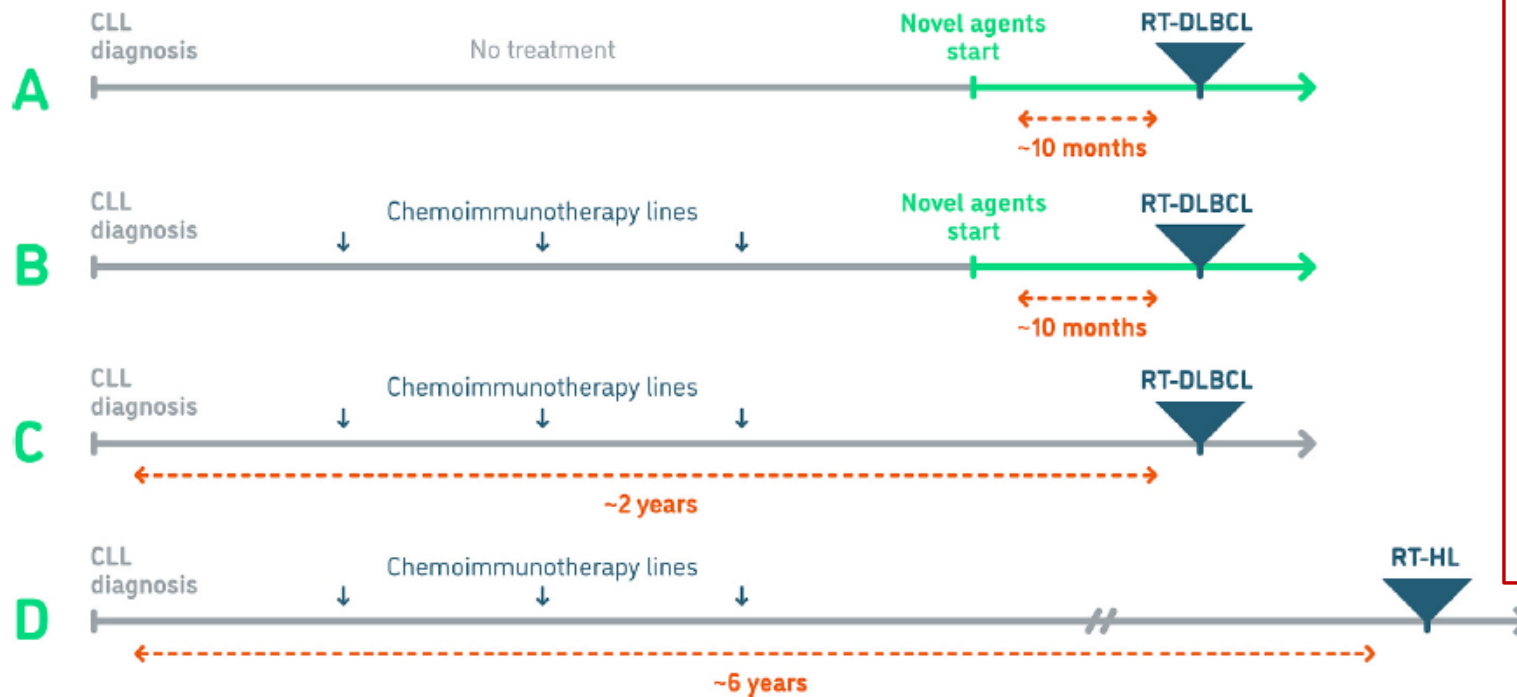


- The RT incidence is lower in patients who received novel agents in the front-line setting (TN) and were unselected for risk genetic factors, reaching the median incidence of 1% when treated with Ibrutinib/Acalabrutinib and 3% for Venetoclax, respectively.
- The median RT incidence in R/R CLL patients, as well as in treatment-naive CLL patients with TP53 disruption, was similar in on Ibrutinib/Acalabrutinib, as well as on Venetoclax (6%).
- When considering only heavily pre-treated R/R patients that experienced progressive disease on Venetoclax, from three clinical trials, 21% developed RT-DLBCL and 4% RT-HL.
- Regarding Idelalisib/Duvelisib, only a few studies were published, reporting a low incidence of RT of 1%.

Petrackova A, et al. Blood Reviews 2021



The timeline of RT development on Novel Agents



- It is difficult to compare the time to RT development on novel agents to that on chemo-immunotherapy (CIT), as studies on RT on CIT report, only on the time from CLL diagnosis to RT.
- This has led to the misperception that RT in patients on CIT is a late event.
- RT in patients treated with novel agents usually occurs as an early event during the first 18 months of treatment, with a median OS of approximately 6 months.
- Regarding CLL progression without transformation on novel agents, it occurs as a late event when compared to transformation, usually between 2-4 years of treatment.

Petrackova A, et al. Blood Reviews 49 2021



Table 2. Chemo-immunotherapy outcomes in the treatment of RT.

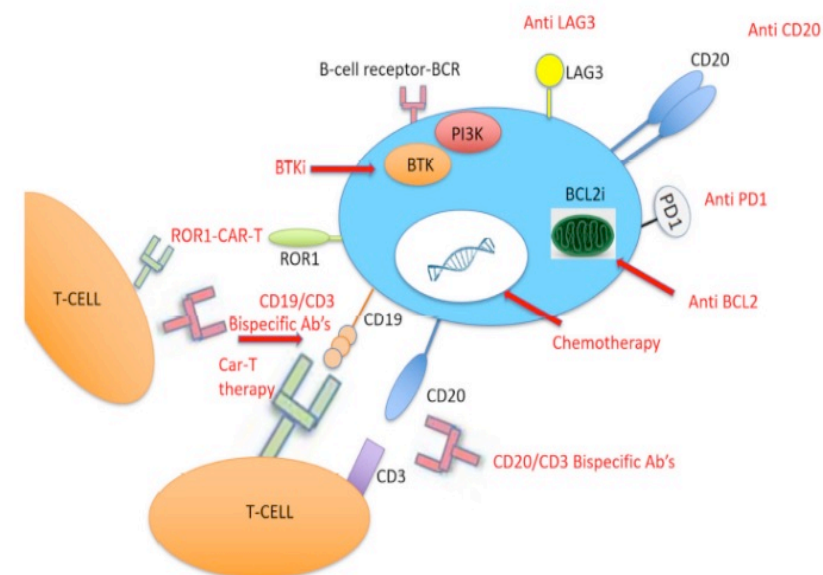
Regimen	Author, Year	Institution	No. of Patients	Median Age (Years)	CR (%)	ORR (%)	Median PFS (mo)	Median OS (mo)
OFAR-2	Tsimberidou, 2013 [69]	MDACC	35	63	6	39	3	7
OFAR-1	Tsimberidou, 2008 [68]	MDACC	20	66	20	50	4	8
R-CHOP	Langerbeins, 2014 [70]	GCLLSG	15	69	7	67	10	21
O-CHOP	Eyre, 2016 [71]	UK	37	66	25	44	6	11
R-Hyper-CVAD	Tsimberidou, 2013 [69]	MDACC	35	NA	NA	46	6	9
R-EPOCH	Rogers, 2018 [72]	OSU	46	67	20	38	4	6
DHAP, ESHAP	Durot, 2015 [73]	France	28	63	25	43	7	8
R-Hyper-CVXD	Tsimberidou, 2003 [75]	MDACC	30	59	27	43	6	8
Hyper-CVXD	Dabaja, 2001 [74]	MDACC	29	61	38	41	NA	10

Legend: CR: complete remission; mo: months; No: number; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

Table 3. Novel agent evaluated for the treatment of RT.

Regimen	Author, Year	Institution	No. of Pts	Median Age (yrs)	CR (%)	ORR (%)	Median PFS (mo)	Median OS (mo)
Ibrutinib	Tsang, 2015 [82]	Mayo	4	67	50	75	NA	NA
Ibrutinib	Visentin, 2019 [83]	Italy	4	69	0	25	NA	NA
Ibrutinib and O	Jaglowski, 2015 [84]	Ohio	3	64	0	33	NA	NA
Acalabrutinib	Hillmen, 2016 [85]	San Diego	25	NA	9.5	38	2.1	NA
Veneto	Davids, 2017 [87]	Dana-Farber	7	73	0	43	1	6
Veneto	Bouclet, 2021 [88]	France	7	67	0	29	NA	1.1
Veneto and R-EPOCH	Davids, 2020 [89]	Dana-Farber	27	63	48	59	16.3	16.3
PDCD1	Rogers, 2019 [91]	Ohio	10	69	10	10	NA	2
Pembro	Ding, 2017 [92]	Mayo	9	69	11	44	5.4	10.7
Pembro	Armand, 2020 [93]	Dana-Farber	23	NA	4.3	13	1.6	3.8
Nivo and Ibru	Jain, 2016 [94]	MDACC	23	65	35	43	NA	13.8
Bispecific	Alderuccio, 2019 [95]	Italy	1	NA	0	100	NA	NA
CAR-T	Turtle, 2017 [96]	Hutchinson	5	65	NA	71	NA	NA
CAR-T and Ibru	Gauthier, 2020 [97]	Hutchinson	4	65	NA	83	NA	NA
CAR-T	Benjamini, 2020 [98]	Israel	8	64	71	71	NA	NA
CAR-T	Kittai, 2020 [99]	Ohio	8	64	62	100	NA	NA
DTRM-55	Mato, 2020 [100]	Memorial Sloan	13	71	NA	45	NA	NA

Legend: CR: complete remission; Ibru: ibrutinib; mo: months; Nivo: nivolumab; No: number; O: ofatumumab; ORR: overall response rate; OS: overall survival; Pembro: pembrolizumab; PFS: progression-free survival.



Tadmor T, et al. Cancers 2021



Acalabrutinib monotherapy for treatment of chronic lymphocytic leukaemia (ACE-CL-001): analysis of the Richter transformation cohort of an open-label, single-arm, phase 1-2 study

Toby A Eyre, Anna Schuh, William G Wierda, Jennifer R Brown, Paolo Ghia, John M Pagel, Richard R Furman, Jean Cheung, Ahmed Hamdy, Raquel Izumi, Priti Patel, Min Hui Wang, Yan Xu, John C Byrd, Peter Hillmen

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See Comment page e868
Cancer and Haematology

Overall cohort (n=25)	
Overall response rate (complete response plus partial response)	10 (40%; 95% CI 21.1-61.3)
Best response	
Complete response	2 (8%)
Partial response	8 (32%)
Stable disease	3 (12%)
Progressive disease	10 (40%)
Unknown	2 (8%)
Median time to initial response, months (IQR)	1.9 (1.6-2.1)
Median duration of response, months (95% CI)	6.2 (0.3-14.8)

Table 3: Response to acalabrutinib in patients with Richter transformation

Venetoclax plus dose-adjusted R-EPOCH for Richter Syndrome

Single-arm, investigator-sponsored, phase 2 trial of Venetoclax plus dose-adjusted rituximab, etoposide, prednisone, vincristine, cyclophosphamide, and doxorubicin (VR-EPOCH).

Treatment Scheme

R-EPOCH for 1 cycle, then after count recovery, accelerated daily Venetoclax ramp-up to 400 mg, then VR-EPOCH for up to 5 more 21-day cycles. Responders received venetoclax maintenance or cellular therapy off-study.

Daivids MS, et al. Blood 2022

Results

Patients treated → 26
CR → 13/26 (50%) (11 undetectable MRD).
PR → Three additional patients achieved partial response (overall response rate, 62%).

Median PFS (months) → 10.1

Median OS (months) → 19.6

Safety

Grade ≥3 neutropenia (65%) and thrombocytopenia (50%), Febrile neutropenia in 38%.
No patients experienced TLS with daily venetoclax ramp-up.

Conclusions

VR-EPOCH is active in RS, with deeper, more durable responses than historical regimens. Studies comparing venetoclax with chemoimmunotherapy to chemoimmunotherapy alone are warranted.



Something to take-home

- Despite significant improvements in CLL therapy with the introduction of novel agents, patients continue to transform to RT with a **similar incidence** as previously and to have a **extremely poor prognosis**.
- RT patients who received **prior therapies have a worse prognosis and shorter survival** when compared to previously untreated patients.
- **After appropriate evaluations, the RT incidence on novel agents has been found similar to chemoimmunotherapy** and is **lower** in patients treated with **novel agents in the front line** and **without TP53 disruption** compared to relapsed/refractory cases.
- However, RT on **novel agents develops as an early event**, usually occurring **during the first year of treatment**, with an **aggressive** disease course.
- **Early recognition** of RT helps to avoid multiple lines of therapies that, being targeted on CLL progression/acceleration, are of little efficacy for the transformed clone (monitoring of risk factors and adequate diagnosis), while RT-adapted treatments are required.
- Several **novel approaches** are under investigation and enrollment in a **clinical trial** is strongly recommended.

