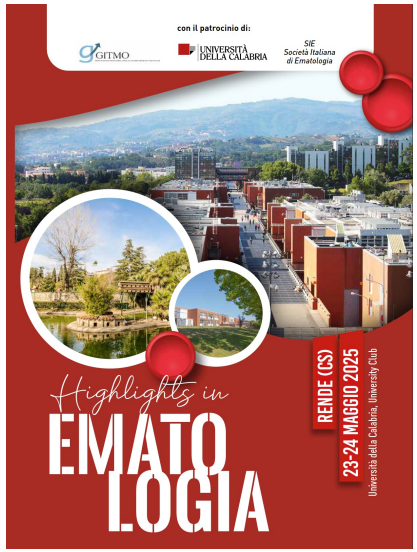

La sindrome di Richter

Gianluca Gaidano, M.D., Ph.D.

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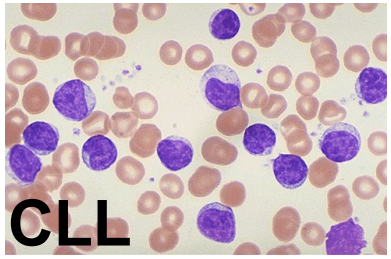
Disclosures

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Abbvie					√	√	
AstraZeneca					√	√	
BeiGene					√	√	
Hikma					√		
Incyte					√	√	
Johnson & Johnson					√	√	
Lilly					√	√	

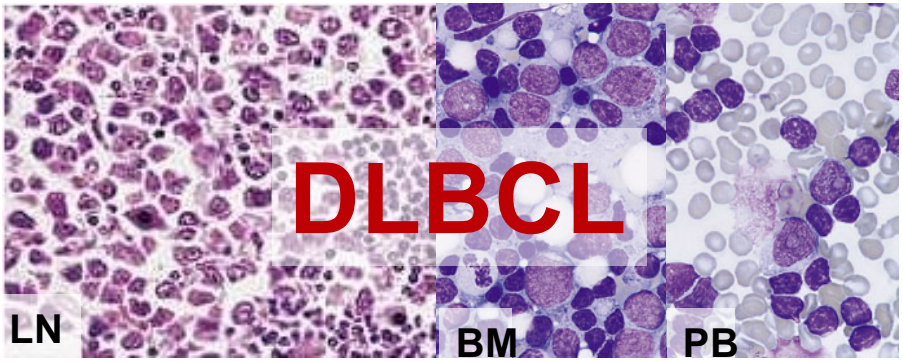
Agenda

- **Prevalence and diagnosis of Richter transformation**
- Clinical implications of Richter biology
- Therapy for Richter transformation

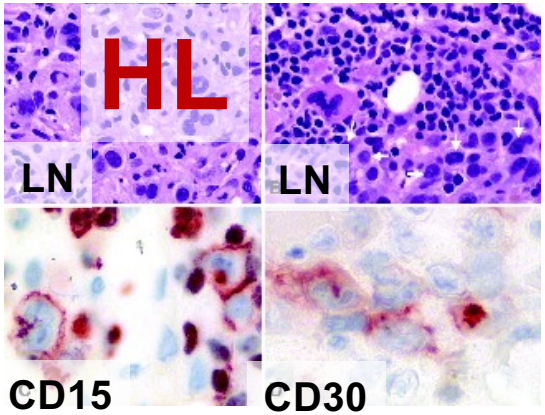
Histologies of Richter



95%



1-5%

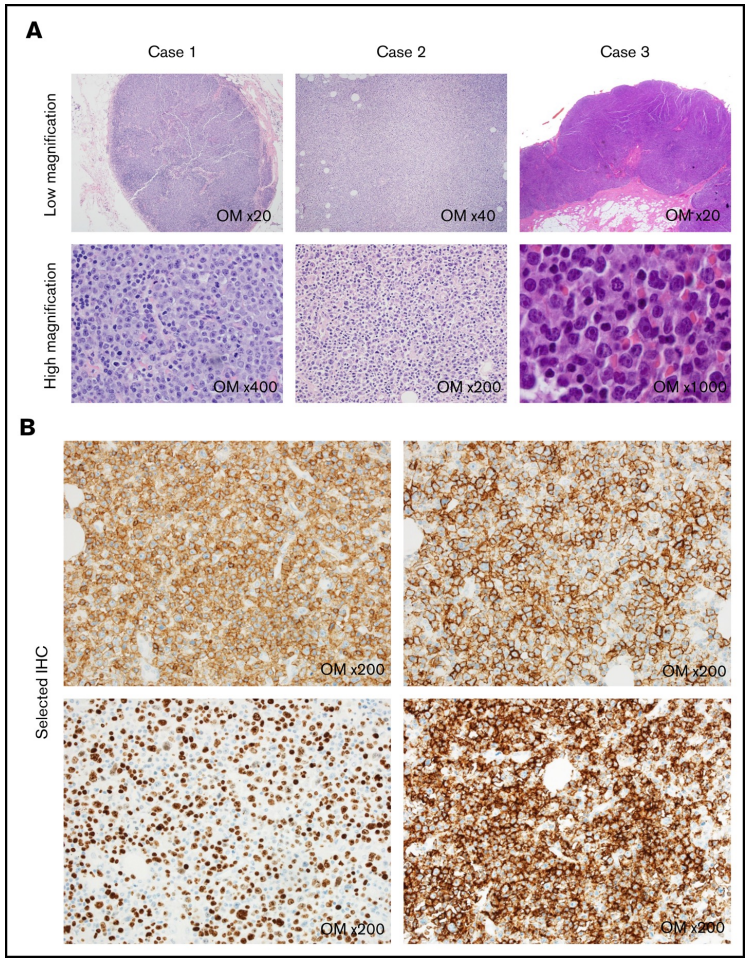


Differential diagnosis with aggressive/accelerated CLL

- large B cells with nuclear size equal or larger than macrophage nuclei or more than twice a normal lymphocyte
- a diffuse growth pattern of large cells (not just presence of small foci) with confluent proliferation centers enriched of proliferating cells

Müller-Hermelink *et al* WHO Classification 2008; Rossi *et al., Blood*. 2018.

Pseudo Richter transformation during temporary interruption of BTKi



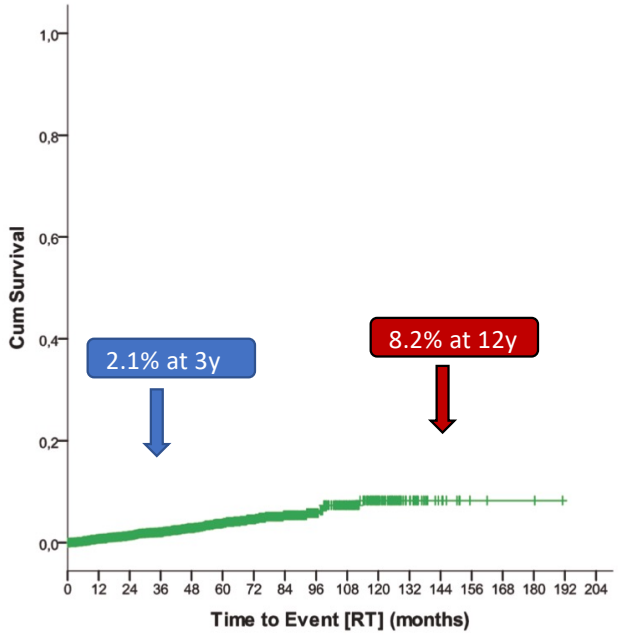
An incidental histologic diagnosis of DLBCL was identified during temporary interruption of ibrutinib treatment in patients with CLL.

In contrast to an aggressive clinical course typical of Richter transformation, these patients responded to reinitiation of ibrutinib alone.

Barnea Slonim *et al., BJH*. 2020; Hampel *et al., Blood Adv*. 2020

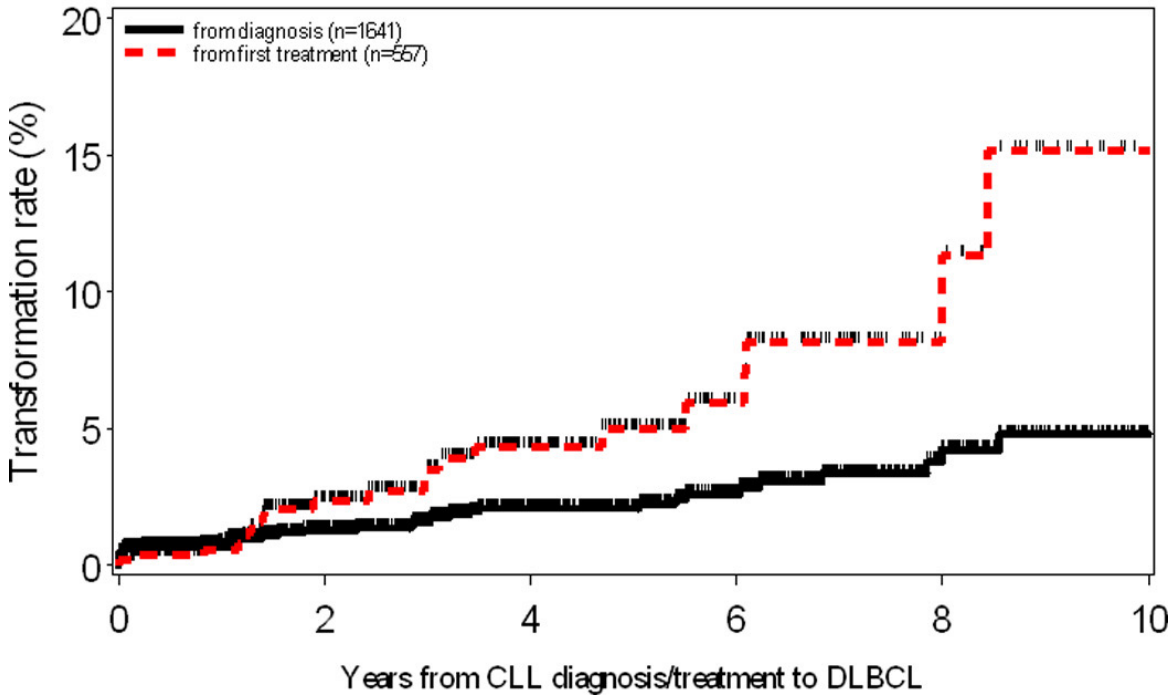
Prevalence of Richter transformation

Time to Richter transformation from first-line CLL treatment



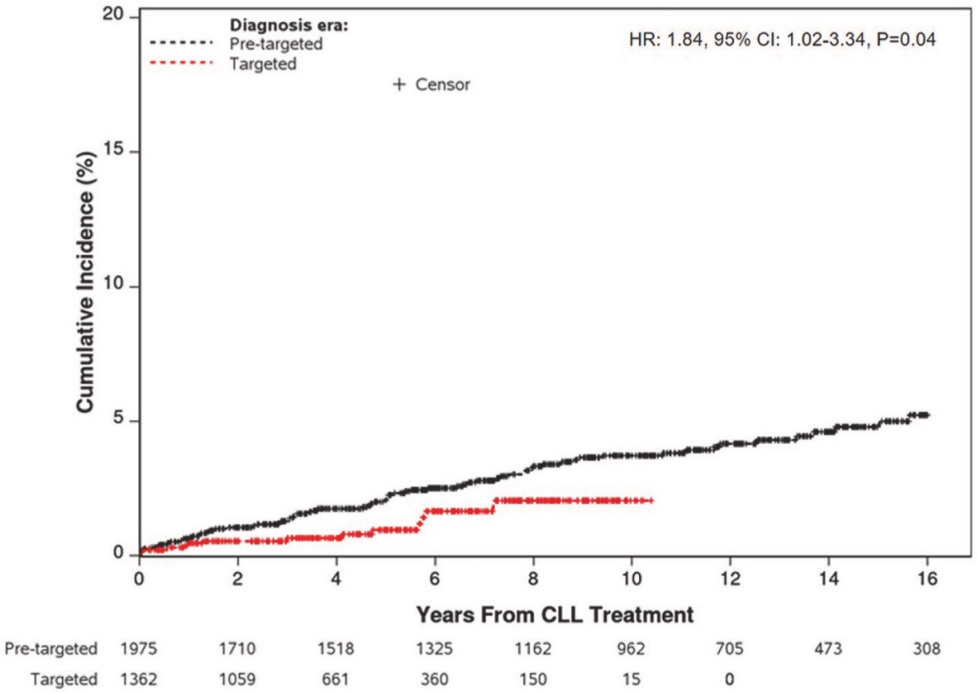
RT-free	Pts, N	Events, N	Median months	3-year Survival, %	6-year Survival, %	9-year Survival, %	12-year Survival, %
All patients	**2971**	99 (3.3)	NR	97.9	95.4	92.6	91.7

The rate of Richter transformation doubled in patients after treatment for CLL



Al-Sawaf *et al., Leukemia.* 2021; Parikh *et al., Br J Haematol.* 2013

Incidence of DLBCL Richter transformation in the targeted therapy era



Patients treated with CIT with or without targeted agents (HR: 4.8, 95% CI: 3.0–7.6, p< 0.001) had a higher risk of Richter transformation compared to untreated patients

Patients who received targeted agents alone for CLL did not (HR: 1.2; 95% CI: 0.6–2.5, p= 0.63) have an increased risk of Richter transformation compared to untreated patients

Hampel *et al., Leukemia*. 2024

blood

Title: International Consensus Statement on Diagnosis, Evaluation, and Research of Richter Transformation: ERIC Recommendations

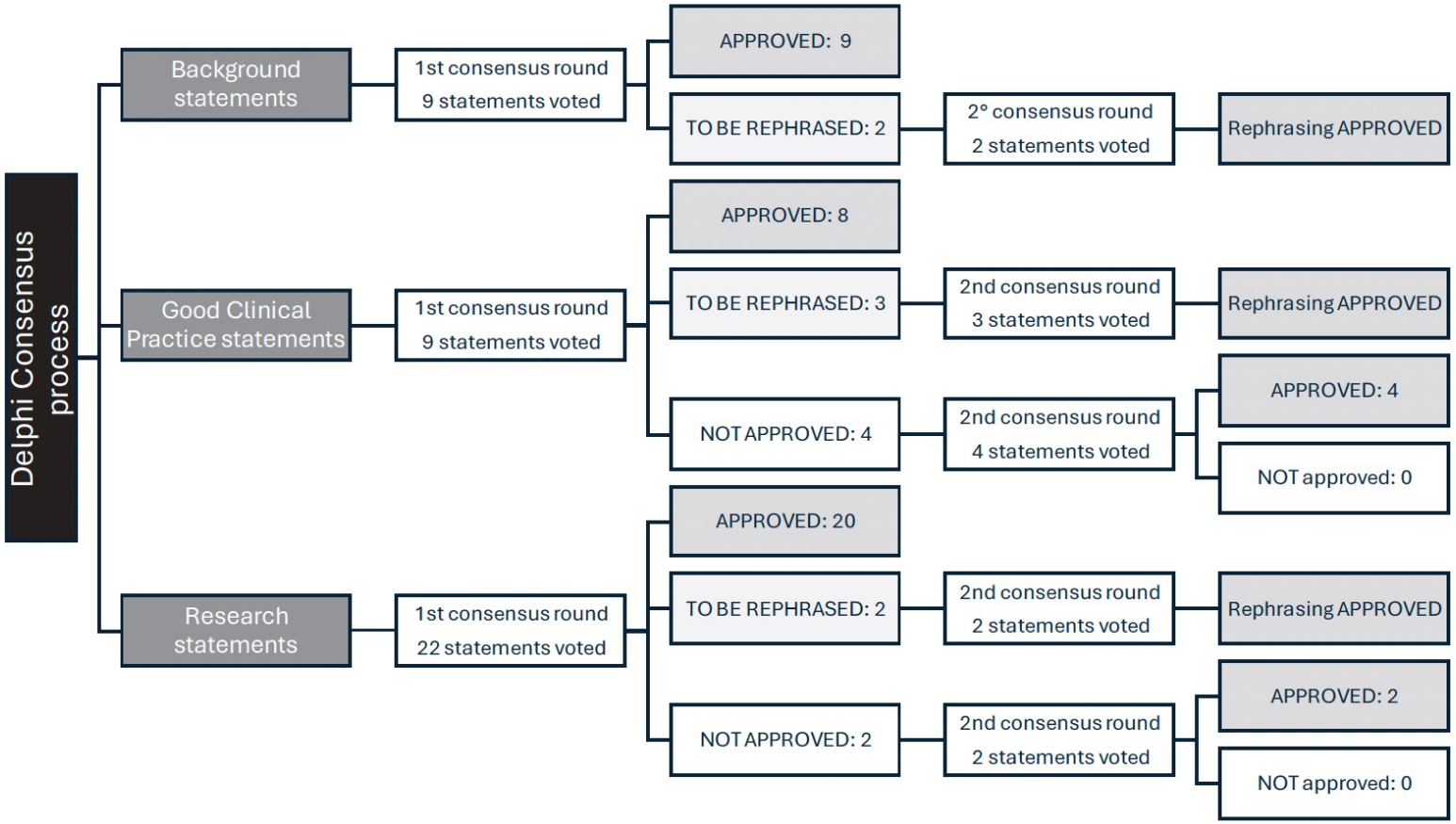
Short Title: Consensus Statements for Richter Transformation

Authors: Adam S Kittai*[1], Monia Marchetti*[2], Othman Al-Sawaf[3], Ohad Benjamini[4], Alexey V Danilov[5], Matthew S Davids[6], Barbara Eichhorst[3], Toby A Eyre[7], Anna Maria Frustaci[8], Michael Hallek[3], Paul J. Hampel[9], Yair Herishanu[10], Rodney J Hicks[11], Arnon P Kater[12], Rebecca L King[13], Jose Martin-Subero[14,15], Carolyn Owen[16], Erin Parry[6], Maurilio Ponzoni[17,18], Davide Rossi[19], Tanya Siddiqi[5], Stephan Stilgenbauer[20], Constantine S Tam[21], Elisa ten Hacken[22], Philip A Thompson[23,24], William Wierda[25], Gianluca Gaidano[#26], Jennifer A Woyach[#27], and Paolo Ghia[#18,28]

*ASK, MM – Contributed equally to this study
[#]GG, JAW, and PG – Contributed equally to this study

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

The Delphi process



Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Statements pertinent to RT diagnosis

1.2.1. RT should be suspected in patients with clinical decline, B-symptoms, elevated LDH, rapidly enlarging lymphadenopathy, and/or discordant response to CLL treatment
There should be strong consideration for RT in patients with discordant enlarging lymphadenopathy (e.g. one nodal group growing rapidly compared to others)

1.2.2. In patients with a clinical suspicion of RT, a PET-CT should be attained

1.2.3. The most accessible lesion with the highest avidity should be targeted for biopsy
SUV avidity of <5 suggests a low likelihood of RT

1.2.4. Biopsy of the affected tissue for histology assessment is needed to diagnose RT

1.2.5. We strongly recommend attaining an excisional biopsy for diagnosis

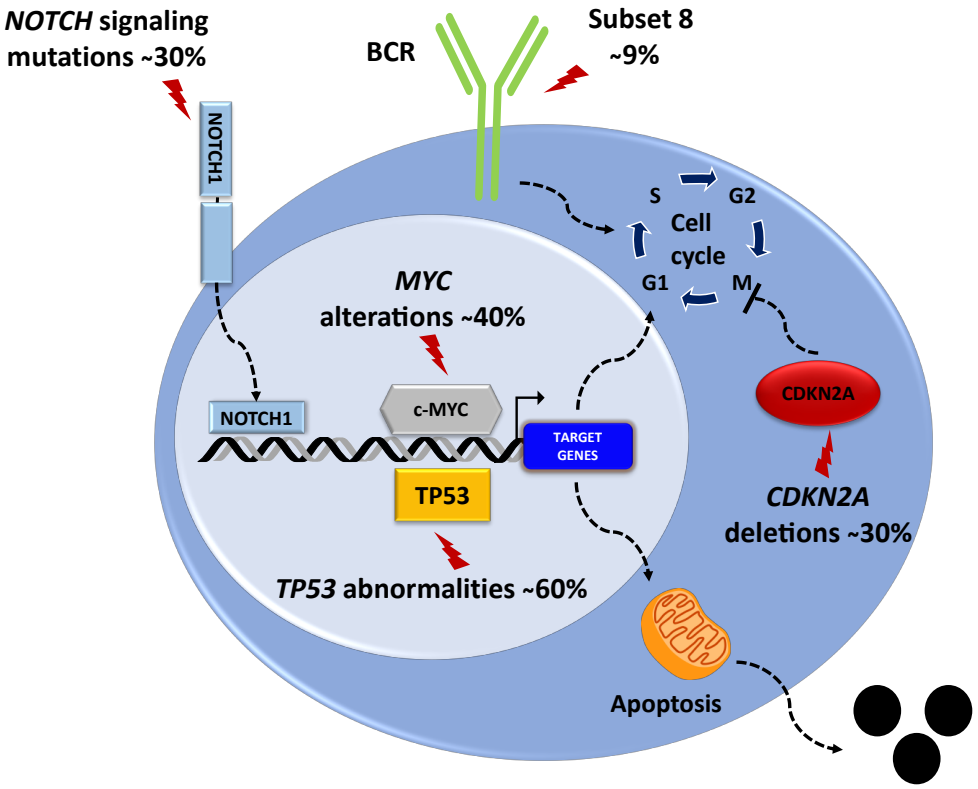
1.2.6. All efforts should be made to have pathology reviewed by an expert hemopathologist

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Agenda

- Definition and prevalence of Richter transformation
- **Clinical implications of Richter biology**
- Therapy for Richter transformation

Potential molecular predictors of Richter transformation

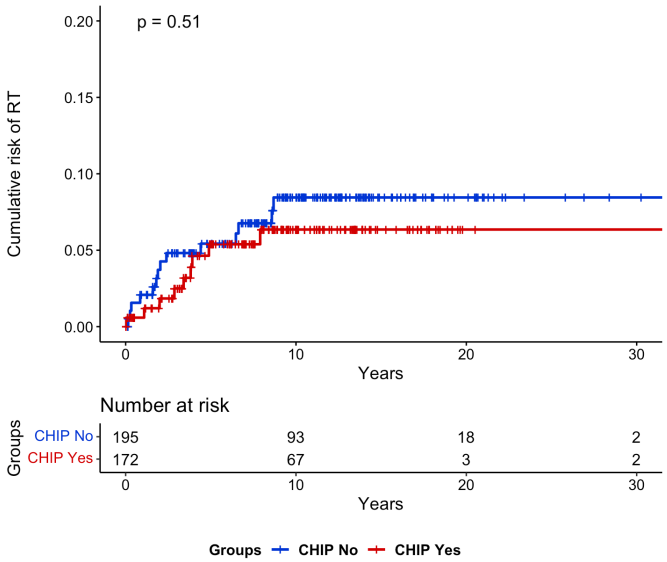


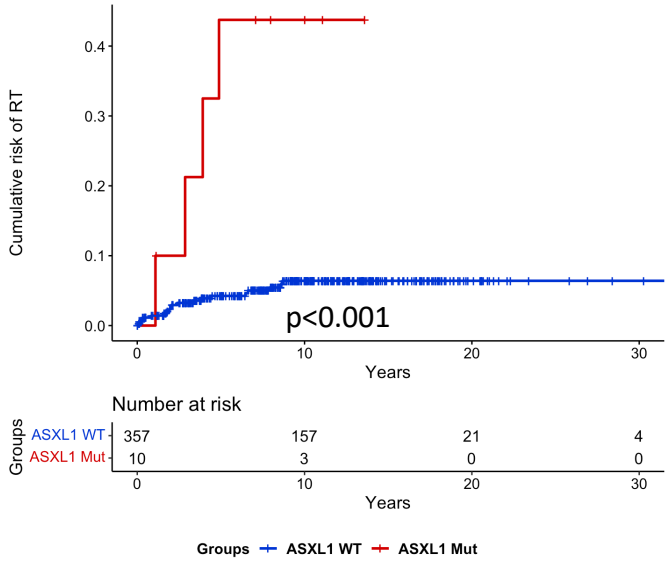
CLL- and patient- related features associated with higher risk of Richter transformation

- *NOTCH1* mutations
- *TP53* abnormalities
- Subset #8
- *XPO1* mutations
- Previous CIT
- CHIP-related *ASXL1* mutations

Rossi *et al., Semin Oncol.* 2016; Rossi *et al., Clin Cancer Res*. 2009; Moia *et al., BJH*. 2023; Kittai *et al., Blood Cancer J*. 2025; Cosentino *et al., ASH 2024*.

ASXL1 mutations associate with higher risk of Richter transformation





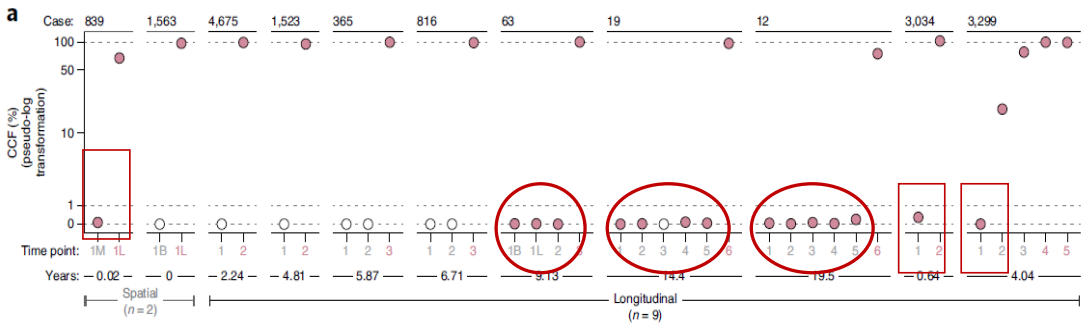
- CHIP as a whole does not predispose to Richter transformation
- *ASXL1* mutations independently associate with shorter time to Richter transformation
- Single cell analysis is required to clarify the relationship between *ASXL1* mutations (myeloid compartment?) and Richter transformation

Variable	N	Hazard ratio	p
NOTCH1 Mut	302	1.96 (0.56, 6.91)	0.29
TP53 Mut/Del	302	3.97 (1.27, 12.43)	0.02
ASXL1 Mut	302	6.80 (1.54, 30.14)	0.01

1 2 5 10 20

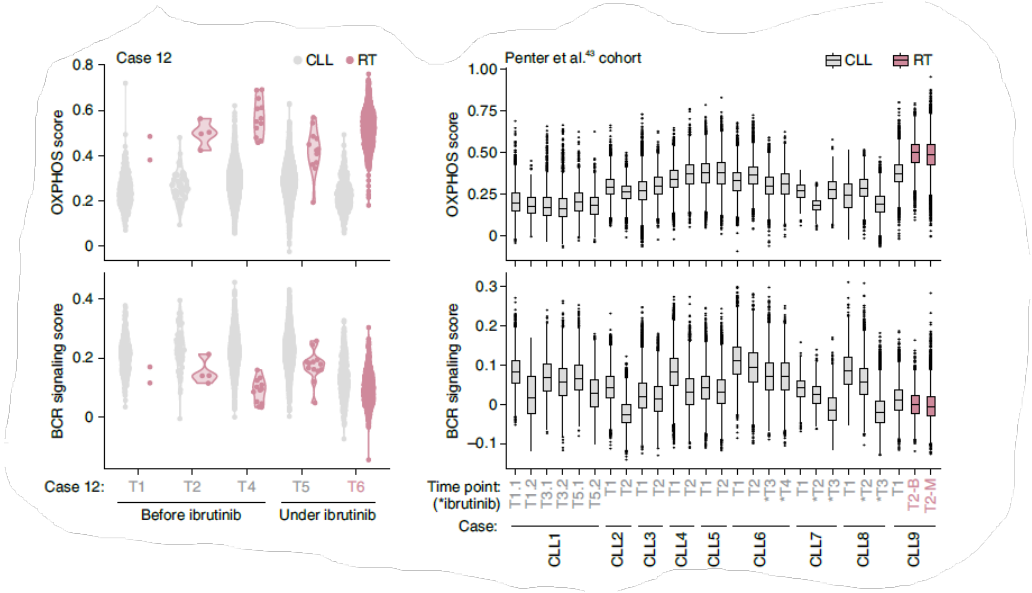
Moia et al, ASH 2024

Early seeding and OXPHOS signaling in Richter transformation



The RS subclone was present at low cancer cell fraction in CLL samples collected before clinical manifestation in 56% of patients

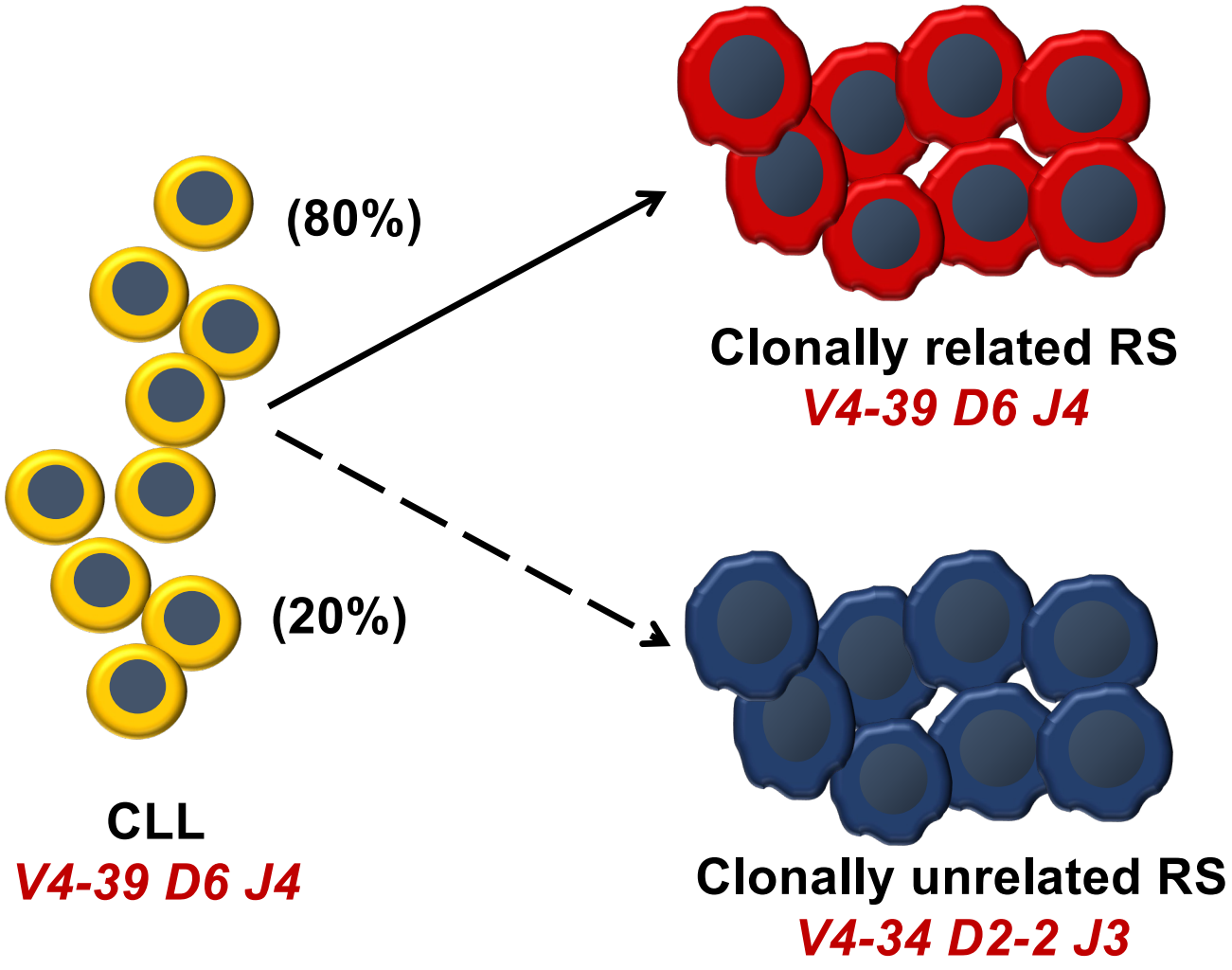
In some cases, the clone remained stable for many years, in others rapidly expanded driving to clinical manifestation

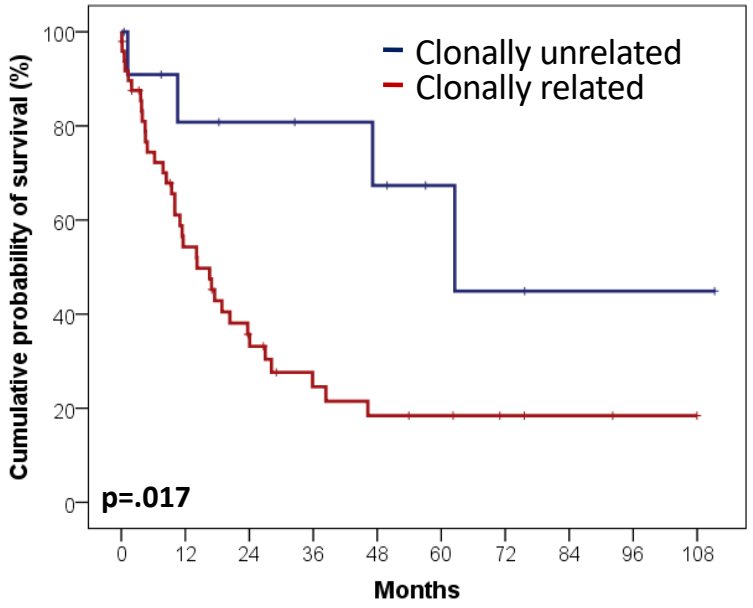


The epigenome and transcriptome of RT converge to an **OXPHOS^{high}–BCR^{low} axis,** which is detectable also before therapy with BCRi → selection and rapid expansion of small RT subclones under therapy with BCRi.

Nadeu *et al., Nat Med.* 2022

Clonal relationship in Richter transformation

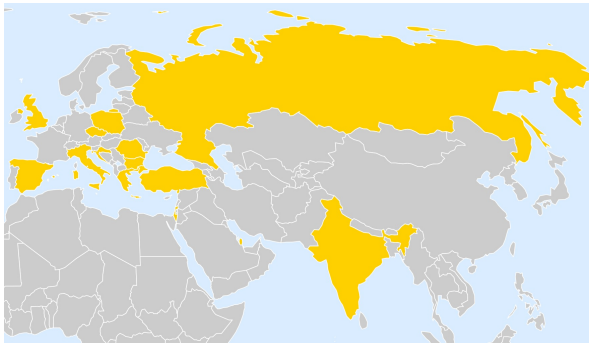




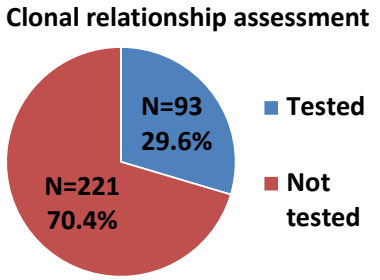
Rossi *et al., Blood.* 2011

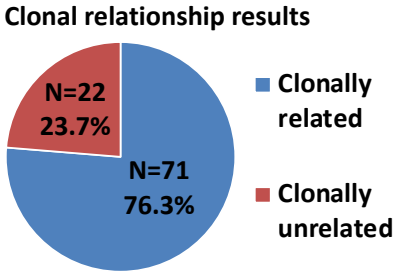
Clonal relationship in Richter transformation – an ERIC study

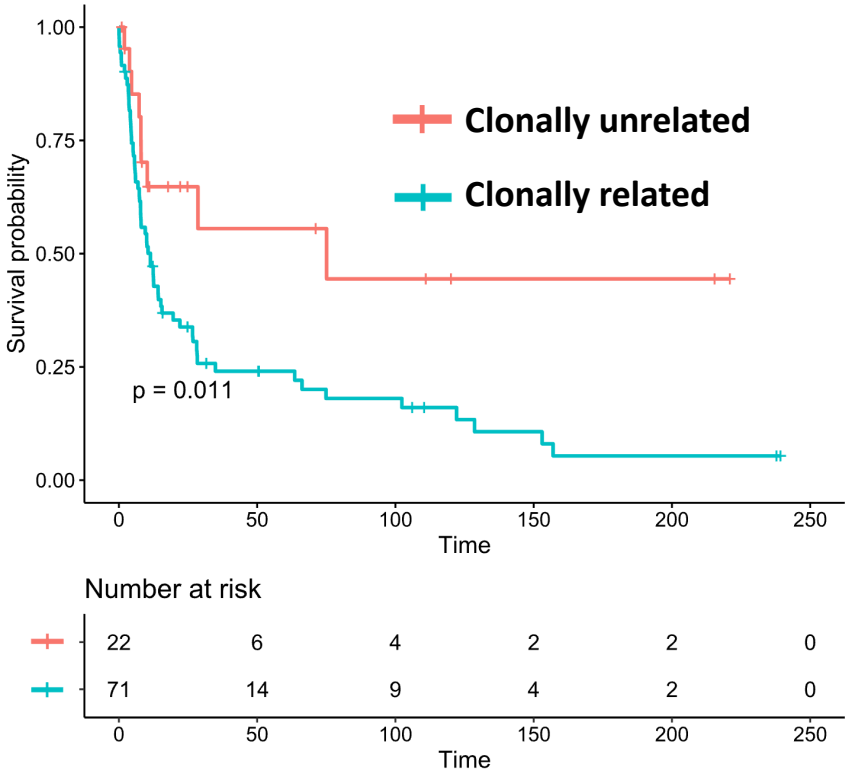
A total of 316 Richter transformation cases were collected from 24 hematological centers in 14 countries



ERIC countries involved till now in the project







Clonally related Richter significantly associated with shorter survival

Moia *et al., EHA* 2024

Statements pertinent to RT diagnosis

1.2.7. Clonal relationship of the RT tissue and antecedent CLL cells should be tested, as it is one of the strongest prognostic factors for RT survival: patients with clonally unrelated RT have a markedly better prognosis

2.2.1. Clonality should be determined by comparing IG gene rearrangement from the RT tissue to the IG gene rearrangement in the CLL cells

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Agenda

- Definition and prevalence of Richter transformation
- Clinical implications of Richter biology
- **Therapy for Richter transformation**

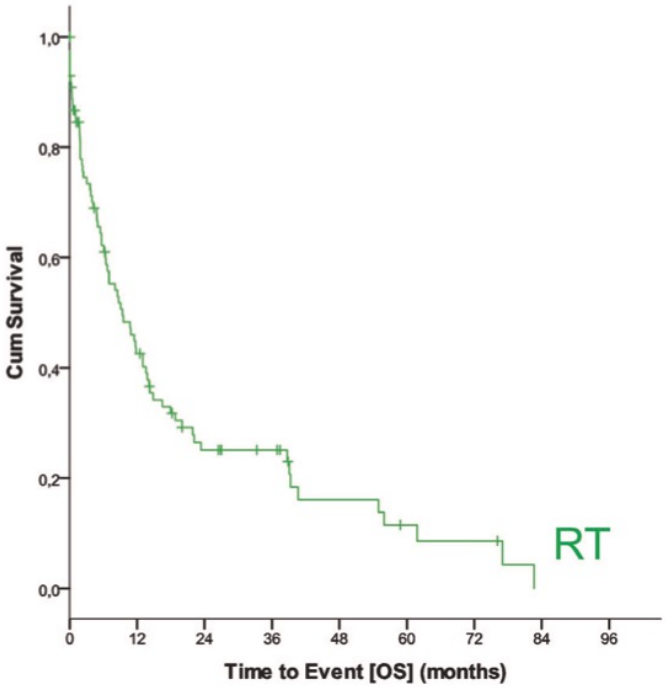
Statements pertinent to testing, prognostication and staging of RT

2.3.1. We recommend using a pre-treatment PET-CT to establish the extent of the disease

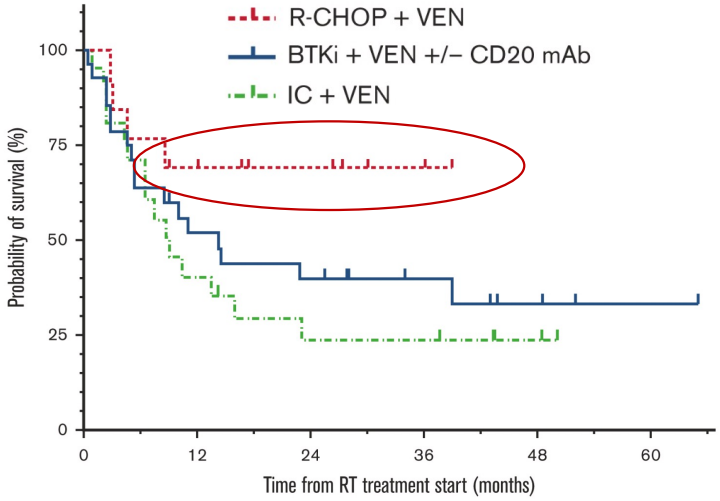
2.3.2. Unlike standard DLBCL, we recommend bone marrow biopsy at time of treatment to determine presence of bone marrow disease, and to assess status of CLL

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

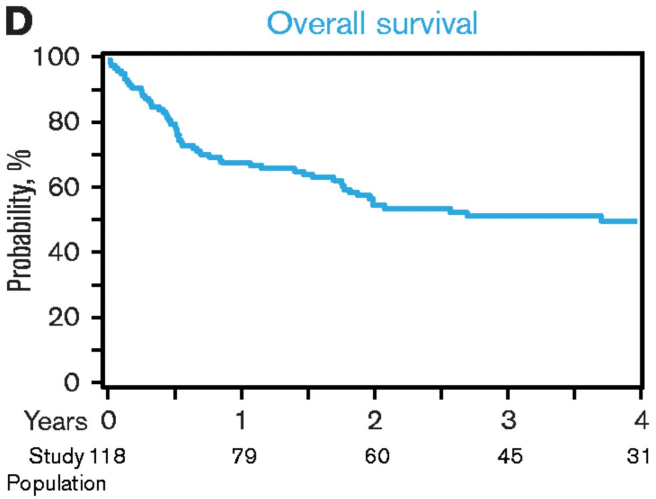
Outcomes of Richter transformation in the chemo-immunotherapy era



Median survival < 1 year



Allotraspant



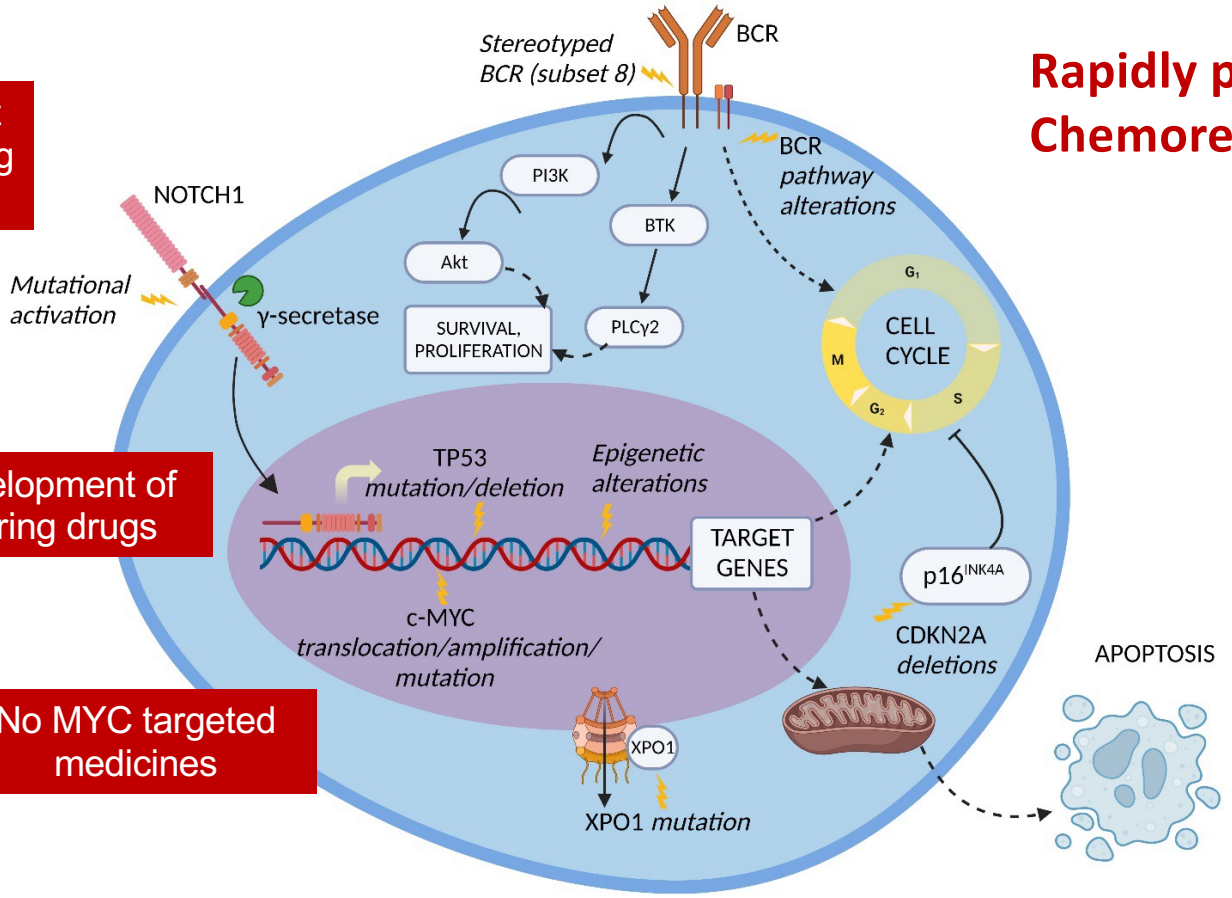
Al-Sawaf *et al., Leukemia.* 2020; Hampel *et al., Blood Adv*. 2024; Herrera *et al., Blood Adv.* 2021

Reasons for treatment failure in Richter syndrome

Slow development of NOTCH targeting medicines

Difficult development of TP53 restoring drugs

No MYC targeted medicines



Rapidly progressive kinetics
Chemorefractoriness

Mouhssine and Gaidano, Cancers, 2022

Richter transformation biology and treatment insights

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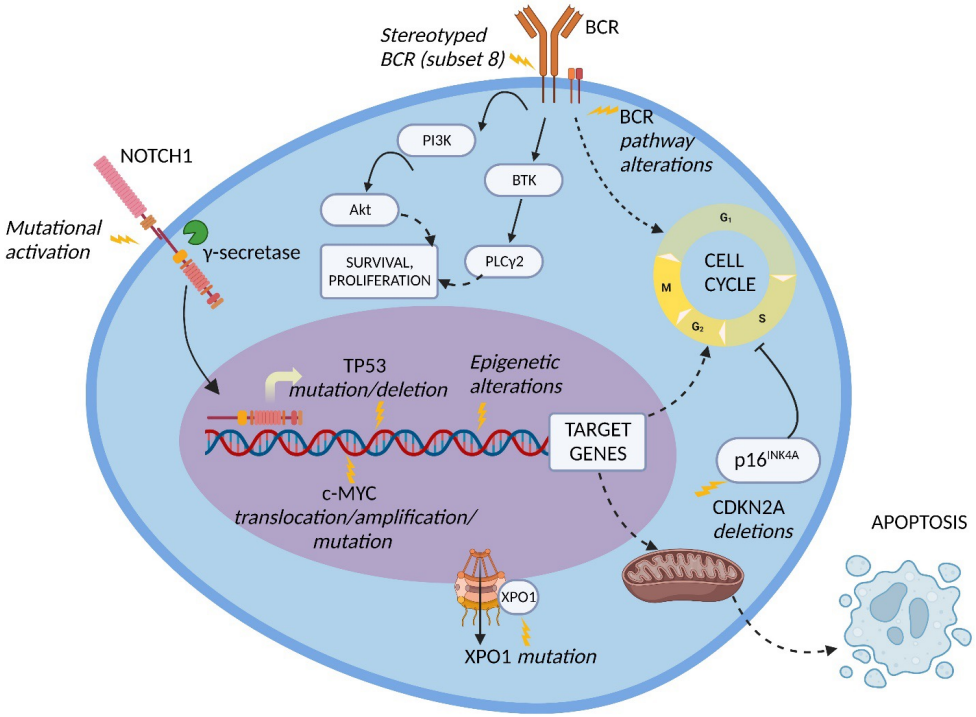
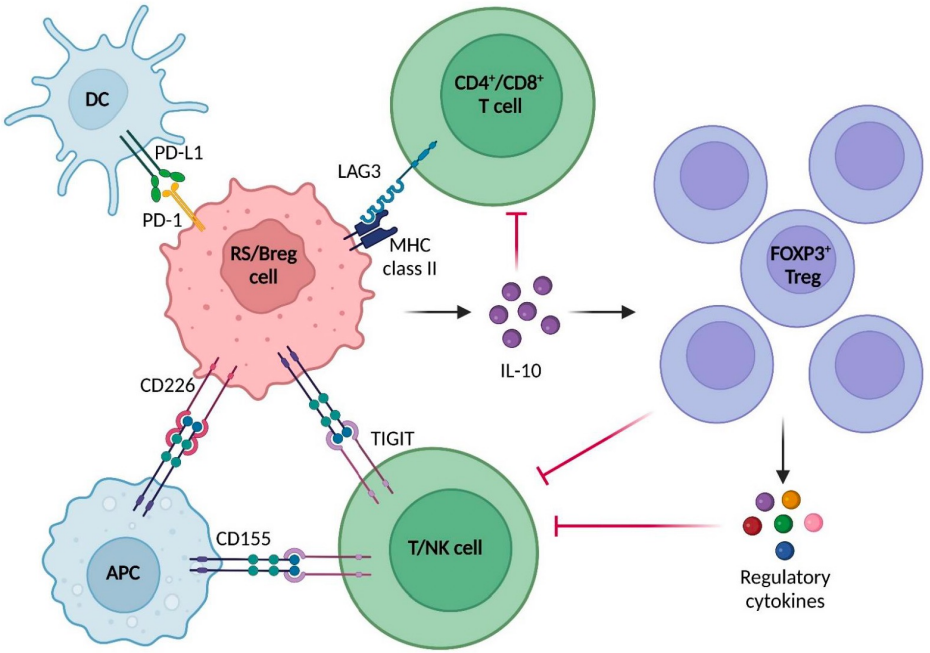
***CDKN2A* loss ➜ Rapidly progressive kinetics**

***TP53* disruption ➜ Chemorefractoriness**

High PD1 ➜ Immune evasion

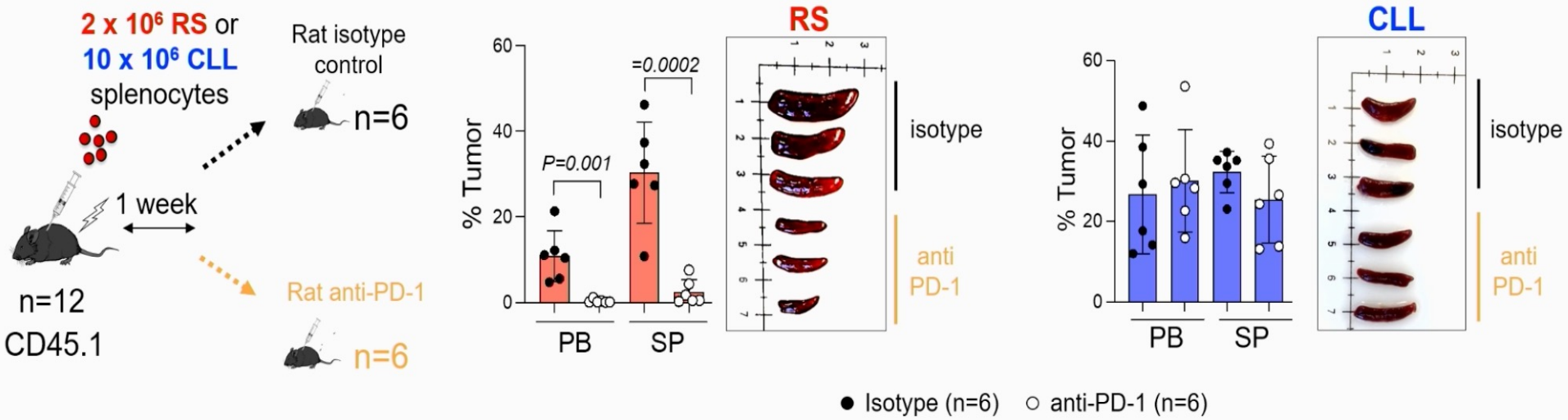
BCR hyperactivation ➜ cell survival





Mouhssine and Gaidano, Cancers, 2022; Mahmoud et al., Cancers 2023

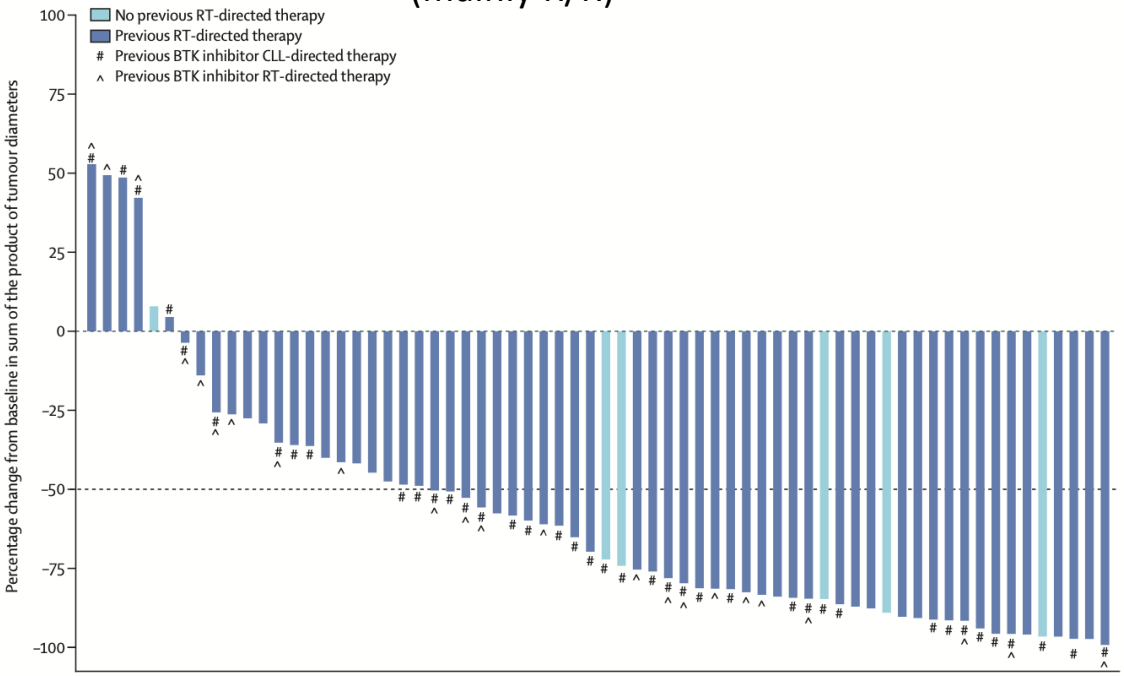
Anti PD-1 therapy is active in mice with Richter but not with CLL



Ten Hacken *et al., ASH 2023.* #636

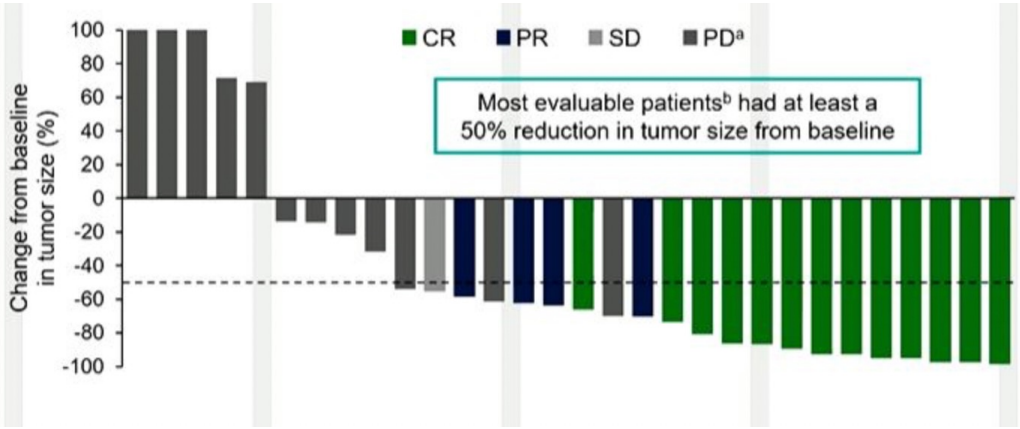
Chemo-free strategies for Richter transformation

Pirtobrutinib in Richter patients
(mainly R/R)



The overall response rate was 50%
13% of patients had a complete response
37% of patients had a partial response

Epcoritamab in R/R Richter patients
(mainly R/R)

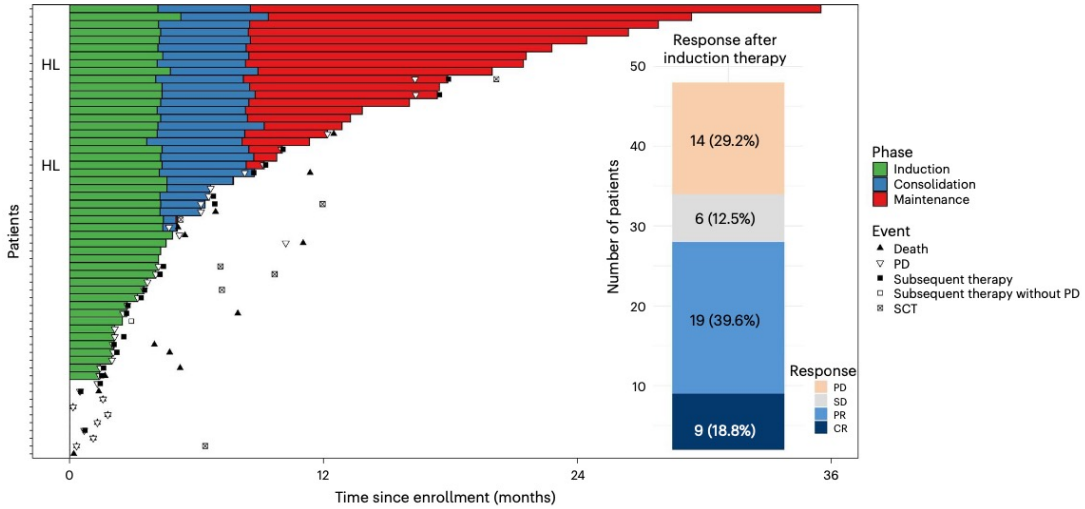


The overall response rate was 50%
35% of patients had a complete response

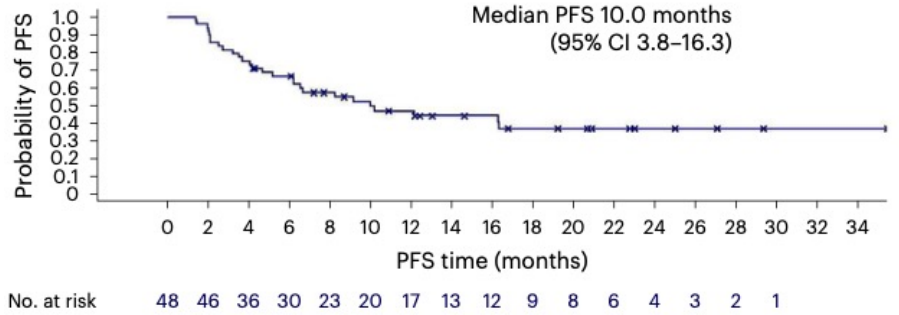
Wierda *et al., Lancet Haematol*. 2024; Kater *et al., EHA* 2024

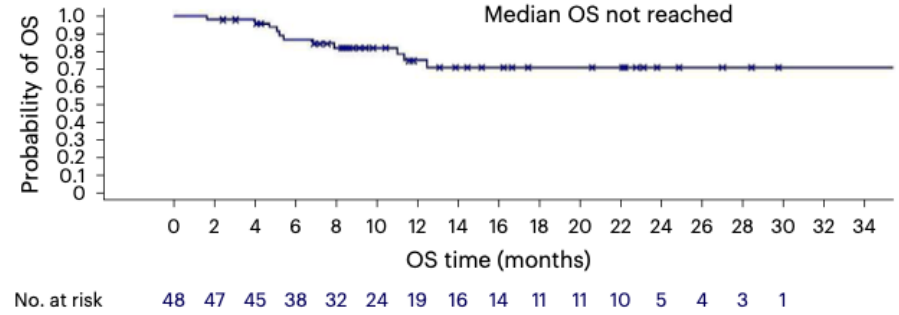
Tislelizumab + zanubrutinib (RT1 trial)

Patient characteristics	
All patients	**48**
Patients with previous CLL-directed therapies, *n* (%)	**36**
Chemo(immuno)therapy	25 (69.4)
SCT	3 (8.3)
BTK/BCL-2 inhibitors	32 (88.9)
BTK inhibitor	24 (66.7)
BCL-2 inhibitor	22 (61.1)
BTK + BCL-2 inhibitor	2 (5.6)
Other	9 (25.0)



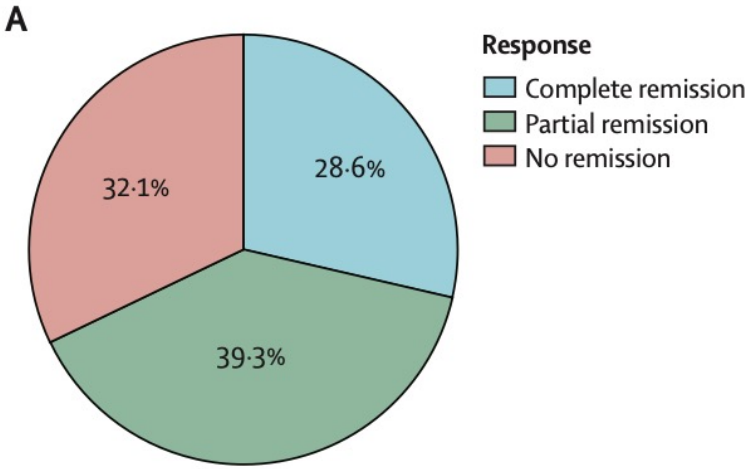
Overall response rate of 58.3%

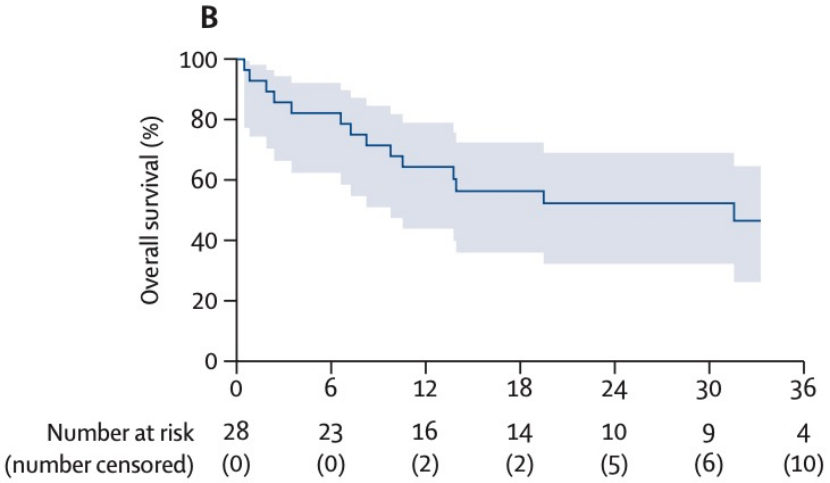




Al-Sawaf *et al., Nat Med*. 2023

Atezolizumab + venetoclax + obinutuzumab (MOLTO trial)





Chronic lymphocytic leukaemia–Richter transformation clonal relationship	
Related	20/24 (83%)
Unrelated	4/24 (17%)

- This combination has limited activity in 3/4 of clonally unrelated RS
- This observation supports that the clonal relationship between DLBCL and CLL might serve as a predictive biomarker for directing patients with clonally unrelated DLBCL-RT to chemoimmunotherapy

Tedeschi, Frustaci *et al., Lancet Haematol. 2024*

International Consensus Statement on Diagnosis, Evaluation, and Research of Richter Transformation

Context of Research

Richter transformation (RT) remains a rare entity and is associated with dismal outcomes. There is no consensus on the study or management of RT currently published.

Aim of This Study

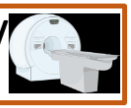
We convened a group of 29 international experts on RT to establish consensus recommendations on the diagnosis, evaluation, and research of RT.

Findings

Diagnosis/ Prognosis

-We strongly recommend attaining an excisional biopsy on the most metabolically active, accessible lymph node for diagnosis.
-Current standard of care treatment with RCHOP-like regimens has poor efficacy.

Prognostication/ Staging



-Clonality should be determined by comparing IG gene rearrangements from the RT tissue and the CLL cells.
-We recommend using a pre-treatment PET-CT to establish the extent of the disease.

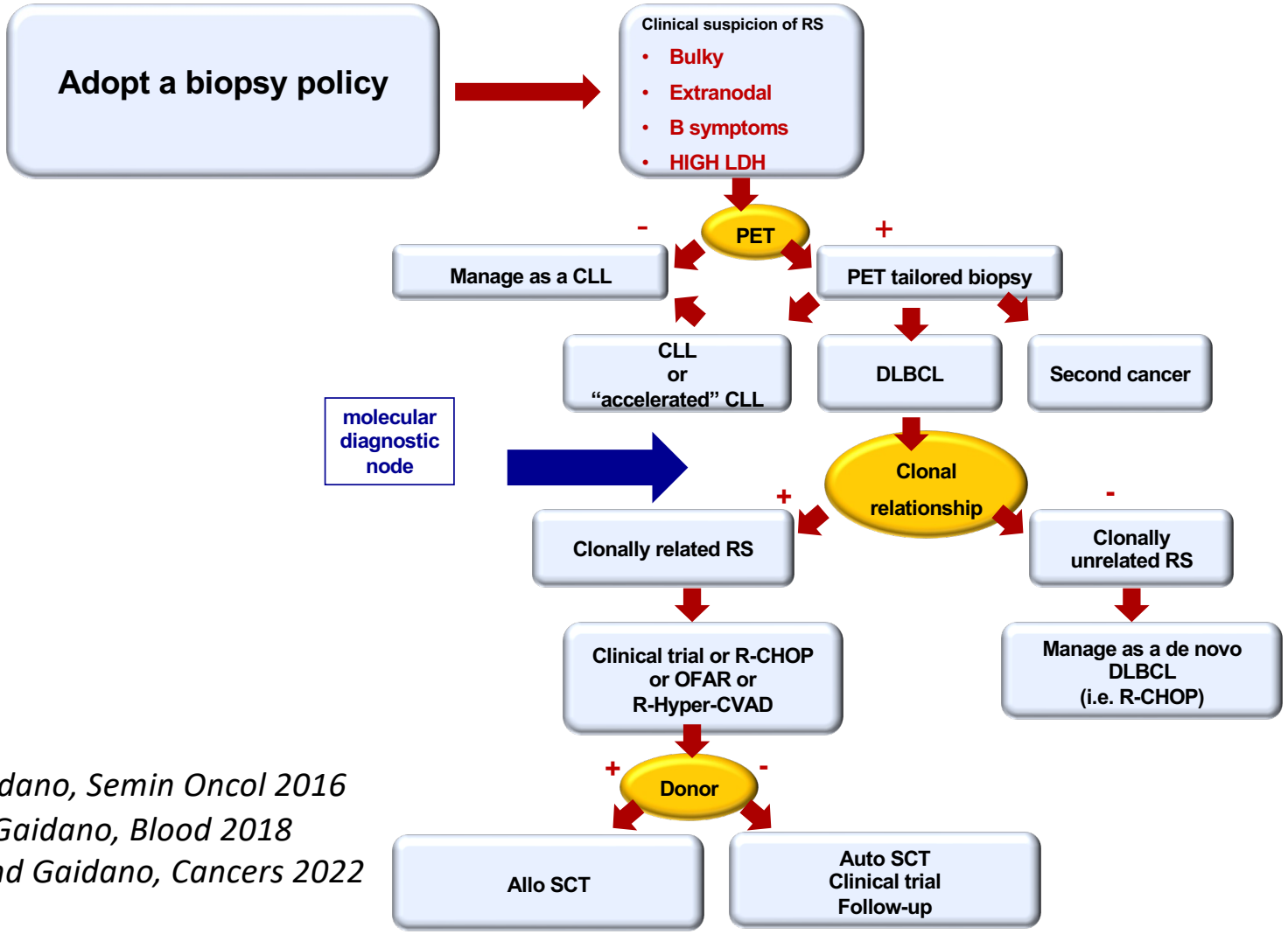
Clinical Trial Recommendations

-If at all possible, patients with RT should be treated on clinical trials.
-Response of RT and CLL should be objectively assessed and reported based on both Lugano criteria as well as iwCLL guidelines.

Conclusions: Given the poor outcomes associated with RT, participation in clinical trials should be encouraged. Prospective clinical studies along with collection of primary longitudinal samples are needed to develop rational therapeutic strategies for this disease.

Kittai A, Marchetti M et al. 2025 Apr 16; doi: 10.1182/blood.2024028064

Clinical algorithm for managing Richter transformation



Rossi and Gaidano, Semin Oncol 2016
Rossi, Spina, Gaidano, Blood 2018
Mouhssine and Gaidano, Cancers 2022

Summing-up

- Richter DLBCL transformation is still present in the era of targeted agents. The prevalence of different histologies (i.e. DLBCL vs Hodgkin lymphoma) after targeted agents is still to be clarified

- Clonal relationship analysis should be included in the staging work-up for all Richter DLBCL transformation since its predictive value for choosing therapy

- The therapeutic landscape of Richter DLBCL transformation is moving towards chemo-free strategies. Randomized clinical trials will be pivotal to define the optimal combination regimen

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