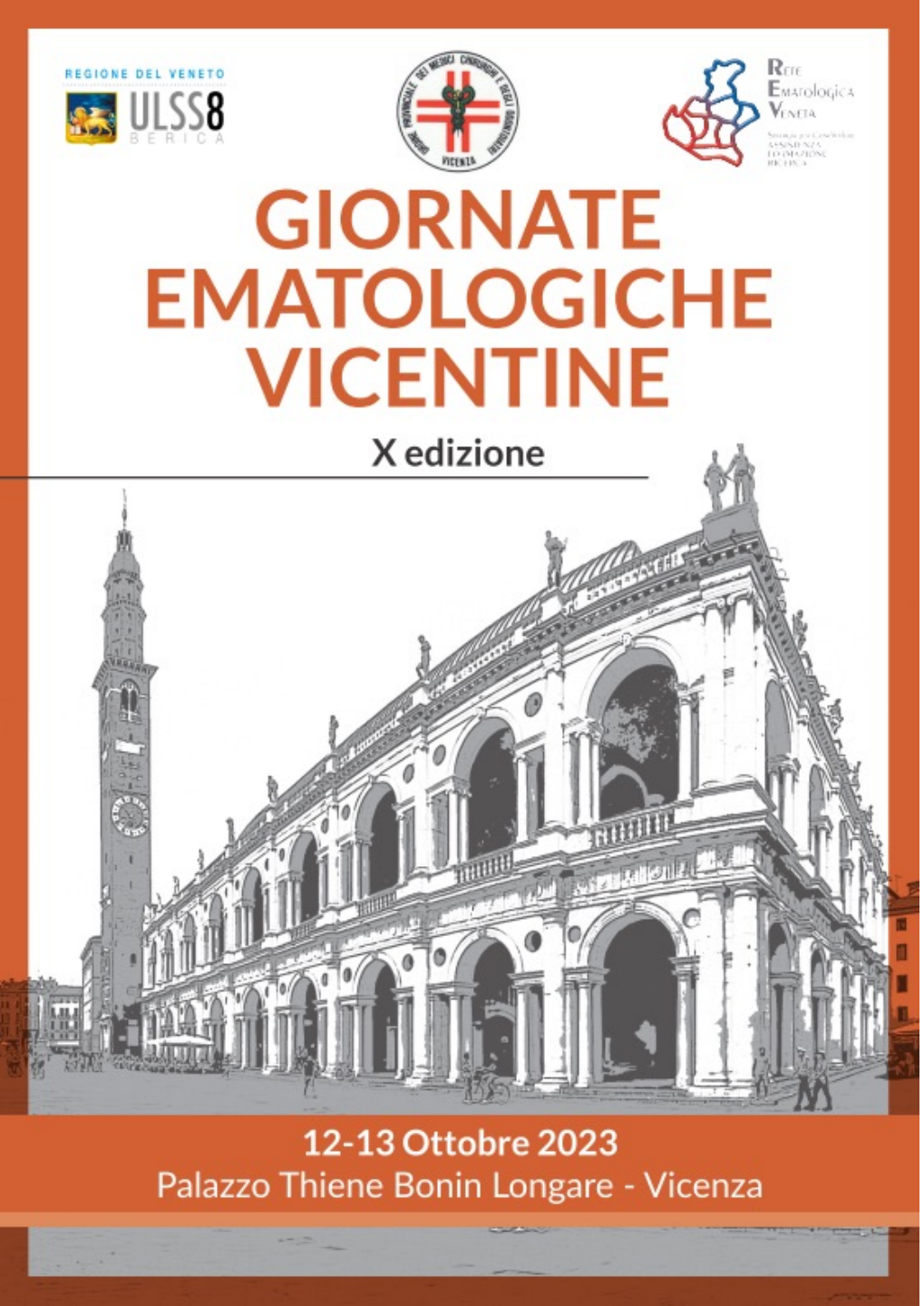


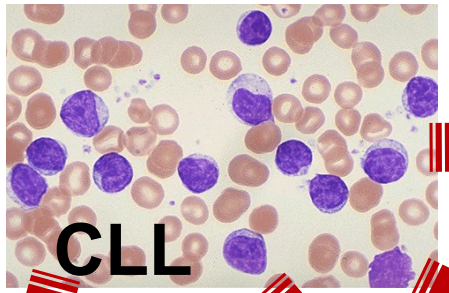
Sindrome di Richter: stato dell'arte e opzioni terapeutiche

Dr. Jacopo Olivieri

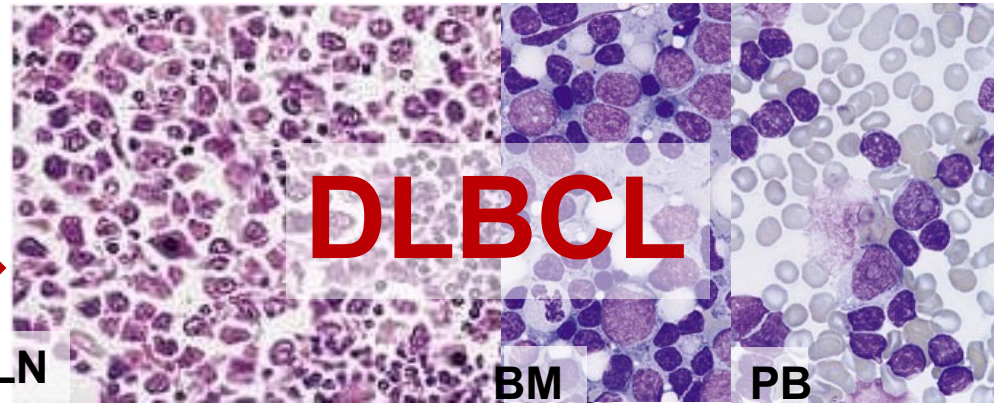
Clinica Ematologica
Centro Trapianti e Terapie Cellulari "Carlo Melzi"
Azienda Sanitaria Universitaria Friuli Centrale, Udine

Definition of Richter syndrome

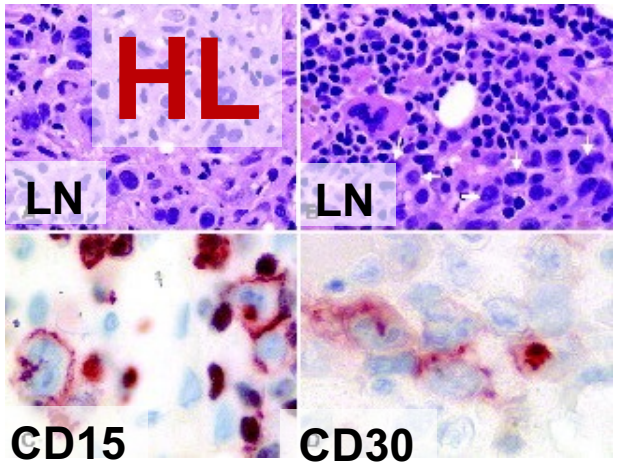
Development of an histologically aggressive lymphoma in a patient with previous or concurrent diagnosis of CLL/SLL



95%



5%



Uncertain

T-cell lymphoma

Exceptional

Plasmablastic lymphoma, Lymphoblastic lymphoma

INCIDENCE

- ✓ 0.5-1%/year
- ✓ Higher if pts exposed to therapy (3-4%) but similar between CHT and novel agents

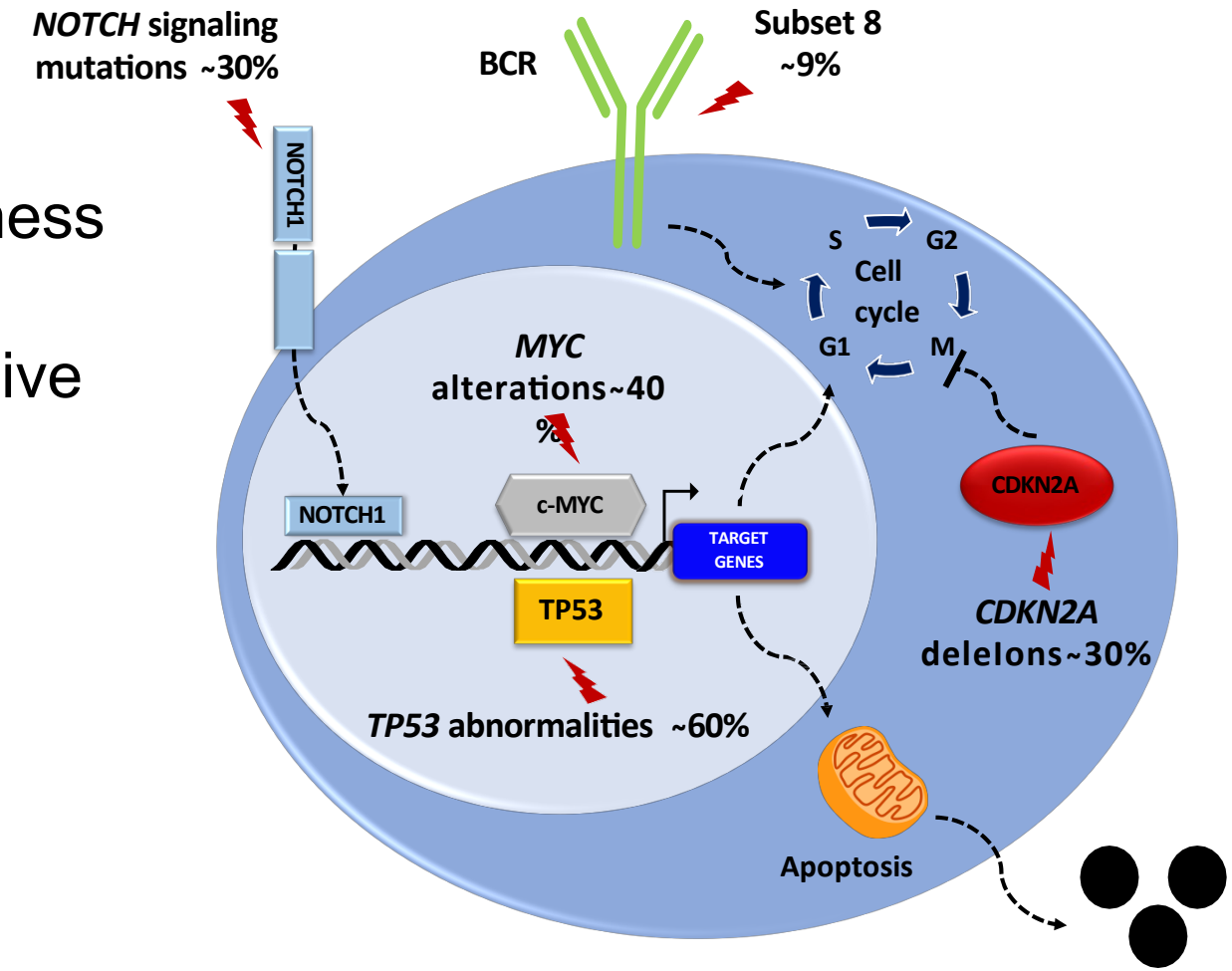
OUTCOME

- ✓ MDACC cohort mOS 8 mo
- ✓ FILO mOS 9.5 mo
- ✓ US real world mOS 3.3 mo

Müller-Hermelink HK, et al, WHO Classification 2008; Al Sawaf, Leukemia 20121, Parikh, BJH 2013 and Blood 2014, Rossi D, Blood 2018

Pathogenesis of Richter syndrome

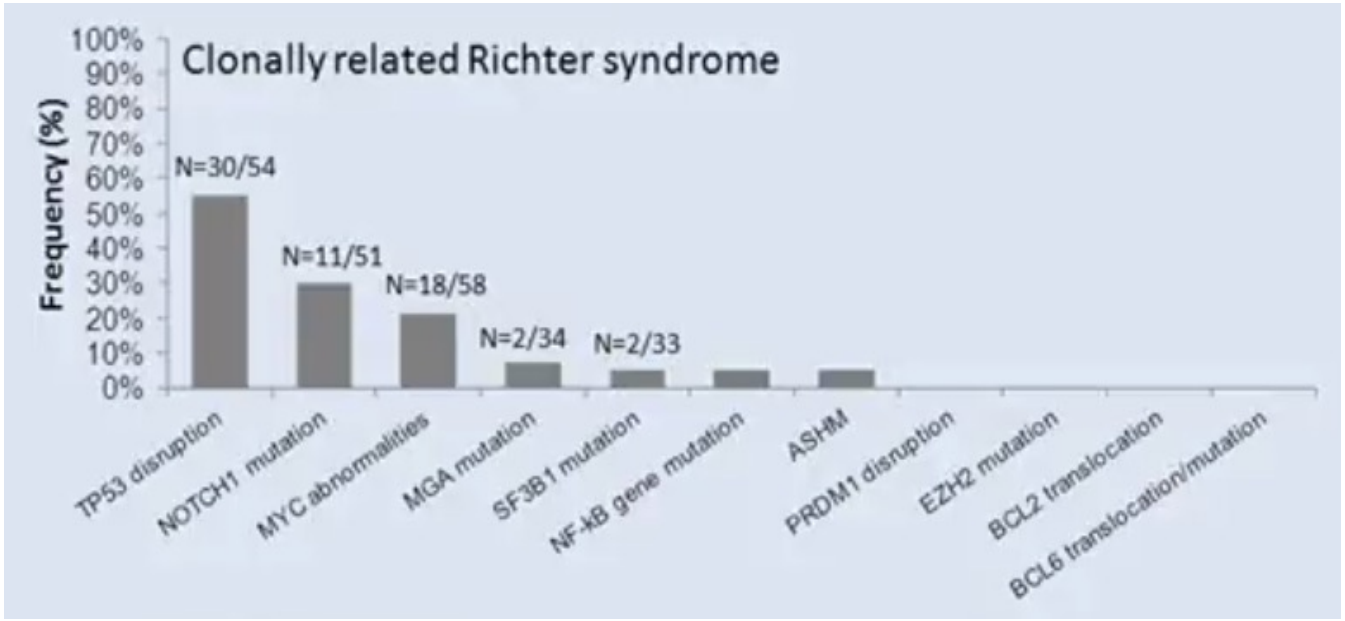
- Chemorefractoriness
- Rapidly progressive kinetics

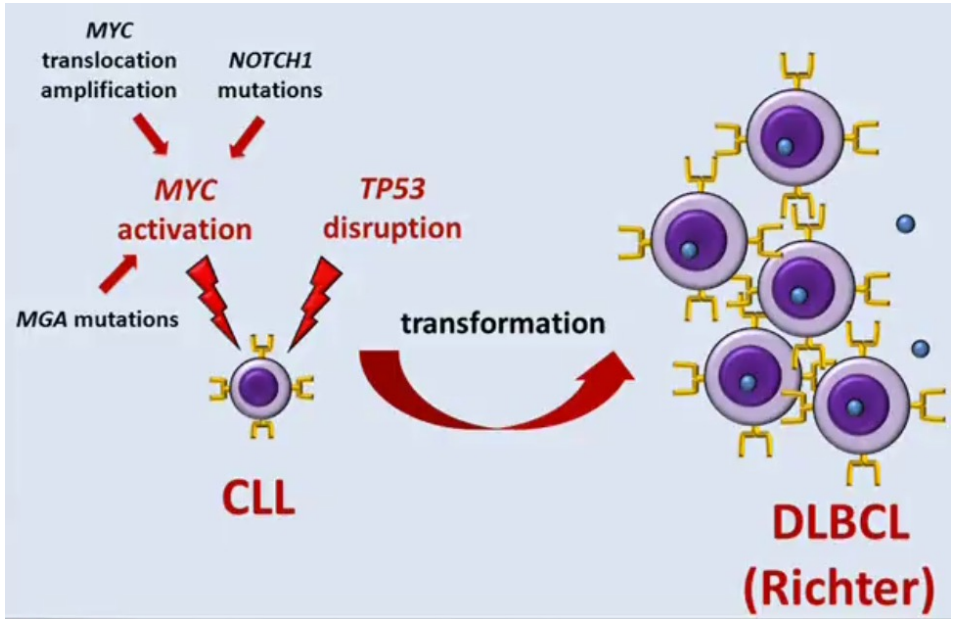


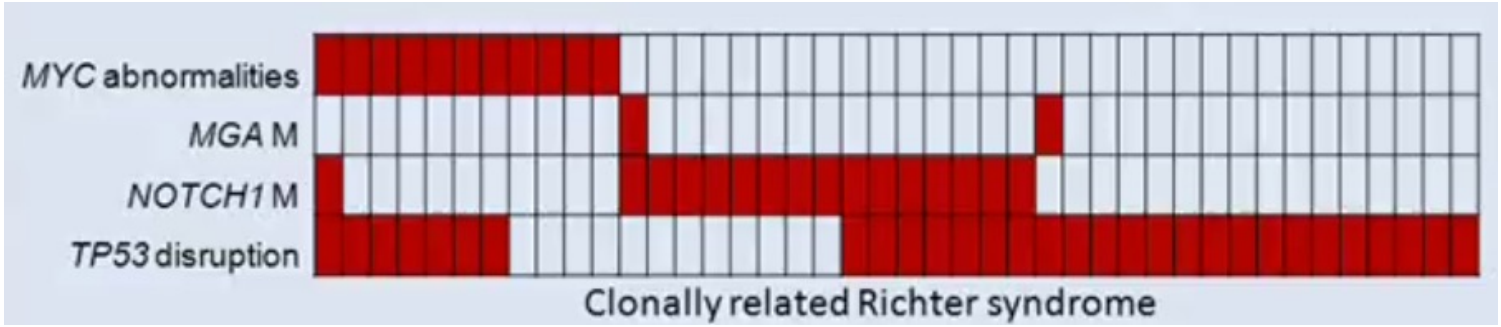
Other pathways:
- BCR-Subset 8
- Akt/NOTCH1
- CDKN2A

Adapted from Rossi D, *et al. Semin Oncol* 2016; 43:311–319.

TP53 and MYC alterations are hallmark lesions in Richter syndrome







Rossi, Blood 2011
Rossi, Blood 2012

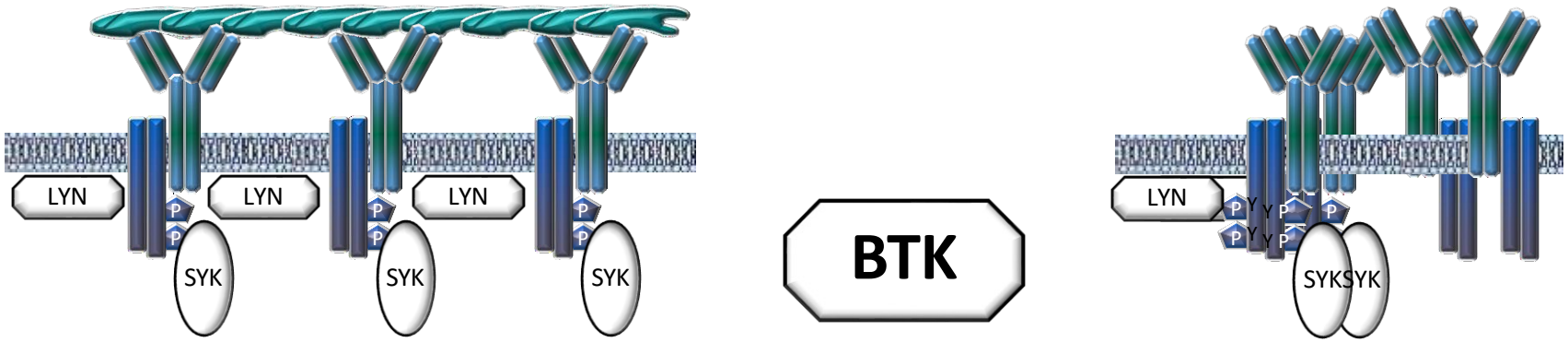
Usage of subset 8 configuration of the BCR is biased in Richter syndrome

External antigens

Autoantigens exposed on apoptotic cells

Cell autonomous BCR signal

Interaction between of one BCR with another BCR that functions as an autoantigen



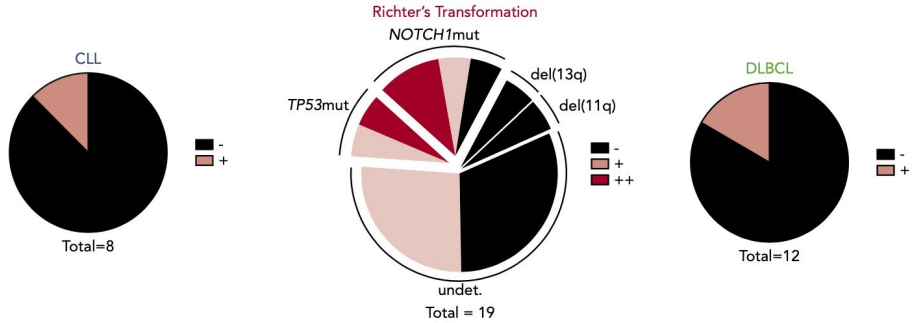
Subset #8

- 0.5% of CLL
- 10% of Richter syndrome
- IGHV unmutated
- Low affinity homotypic interactions
- Extreme antigen polyreactivity
- Strong phosphorylation of PLCγ2 and ERK1/2

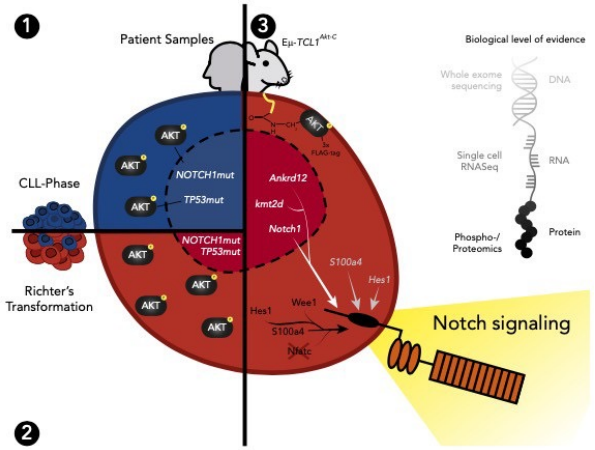
Rossi D, et al, Clin Cancer Res 2009; 15: 4415-22; Chu, et al, Blood 2011; 117:2227-36; Rossi D, et al, Blood 2013; 121: 4902-5; Gounari M, et al, Blood 2015; 125: 3580-7; Minici C, Nat Commun. 2017;8:15746; Jaramillo S, Haematologica. 2019; doi:10.3324/haematol.2019.231027

Akt signaling triggers CLL toward Richter transformation via overactivation of Notch1

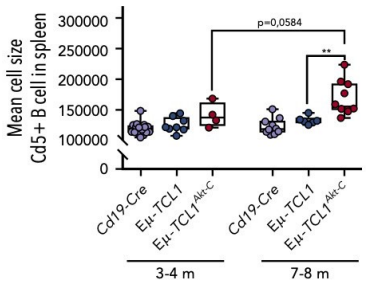
High levels of AKT phosphorylation occur both in high-risk CLL patients as well as in patients with RT

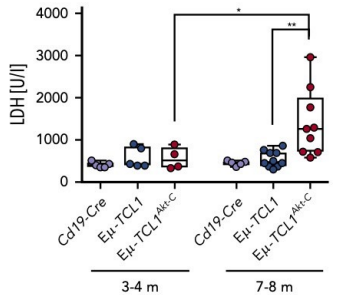


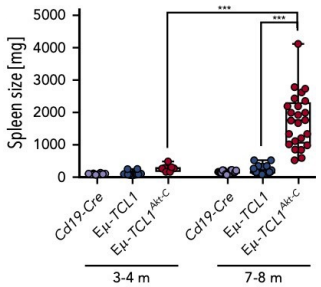
Akt activation was identified as an initiator of CLL transformation toward aggressive lymphoma by inducing Notch signalling

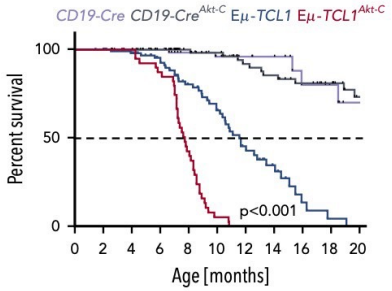


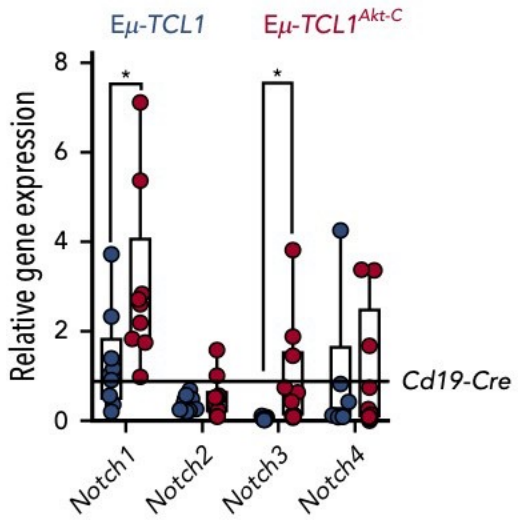
Overactivation of Akt in the murine Eμ-TCL1 CLL mouse model resulted in CLL transformation to RT with significantly reduced survival and an aggressive lymphoma phenotype











Slide by Davide Rossi
Kohlhaas *et al, Blood* 2021

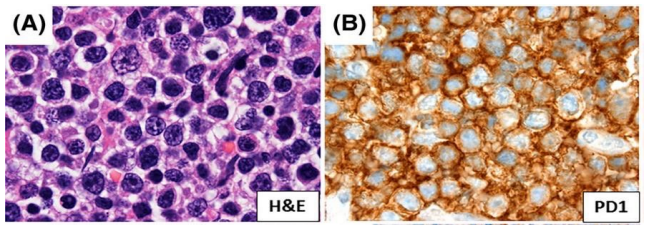
Immune escape in Richter syndrome

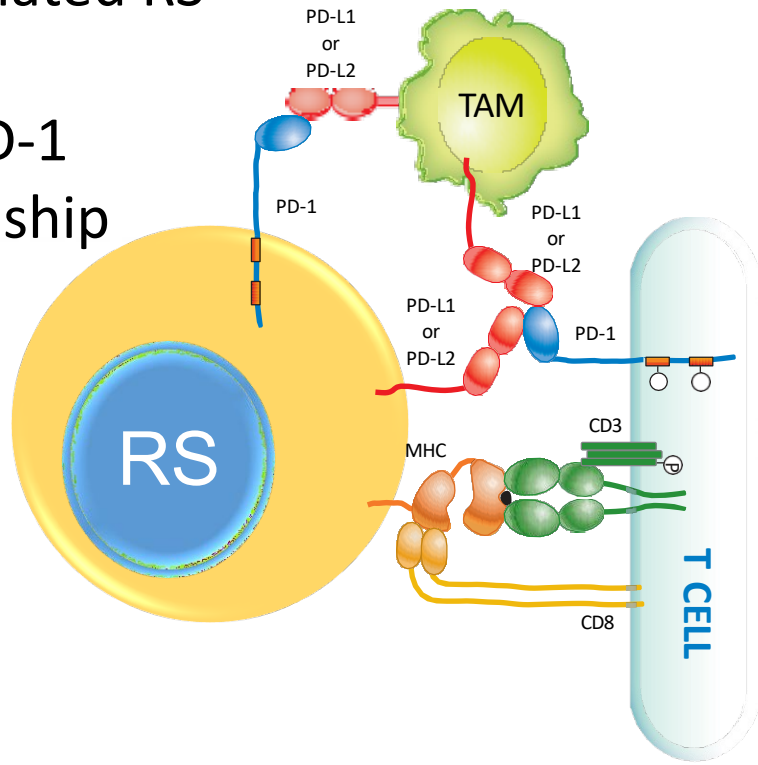
High genomic complexity of Richter syndrome → implication for neoantigens?

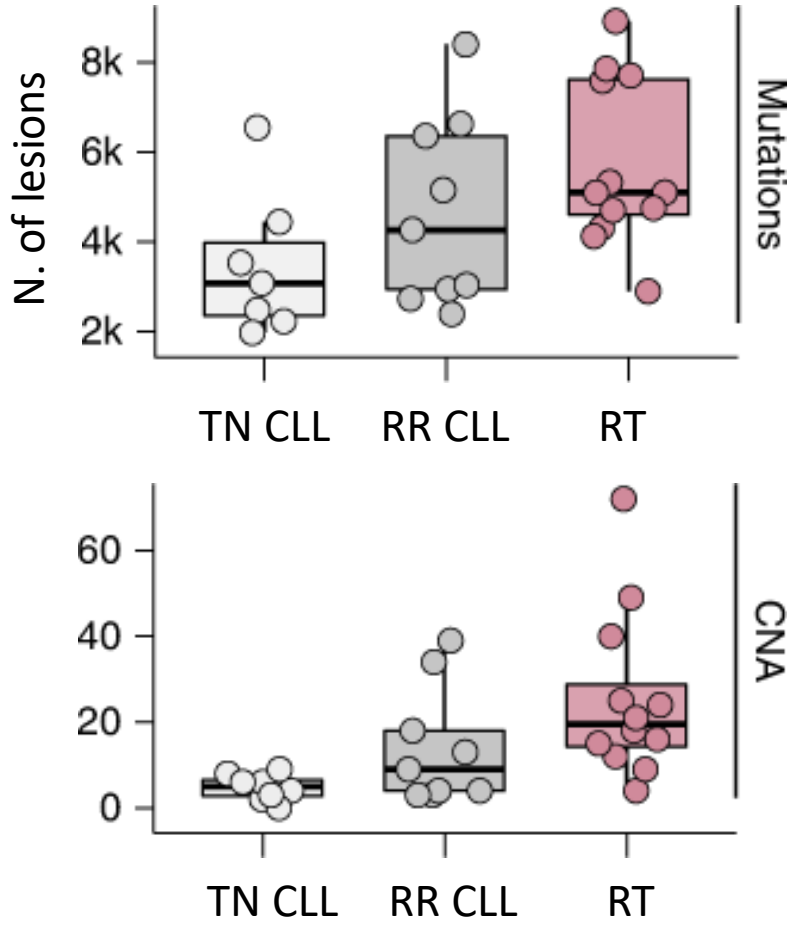
PD-1 expression:
- low in CLL and clonally unrelated RS
- high in clonally related RS

90% concordance between PD-1 expression and clonal relationship

PD-1 81% (26/32)





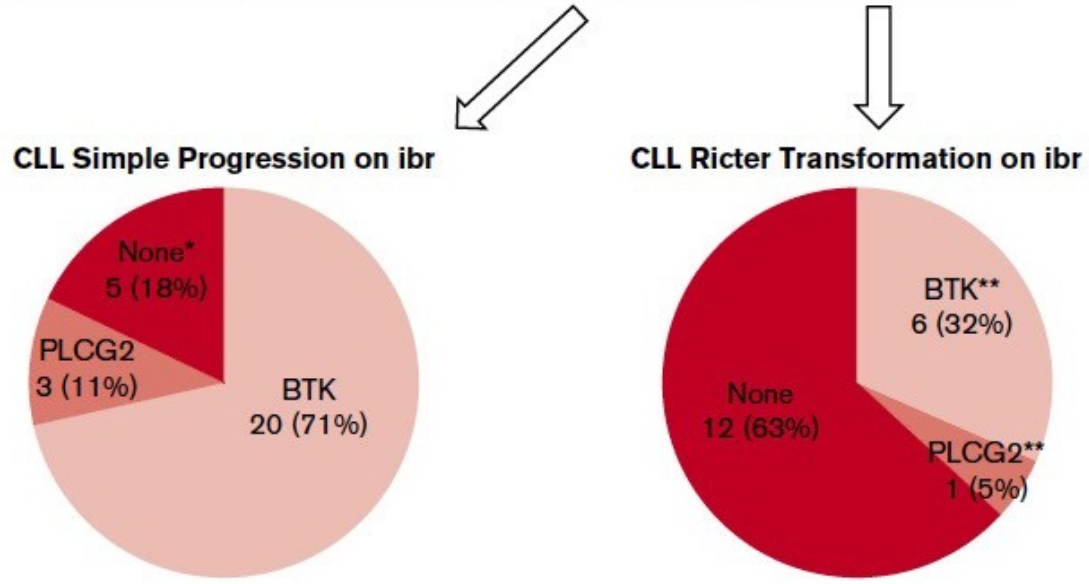


Behdad A, et al. Br J Haematol. 2019;18:370-373; He R, Ding W, et al. PD-1 Am J Surg Pathol. 2018;42:843-854

Nadeu F, Nat Med. 2022

BTK and PLCG2 mutations in Richter syndrome developing under Ibrutinib

	Total pt	CLLPD	RT
Maddocks[6]	20	11	9
Burger[18]	5	5	0
Ahn[43]	12	9	3
Current study	9	3	6
Total	46	28	18



Richter syndrome developing under Ibrutinib hinges on different pathways than BCR signaling

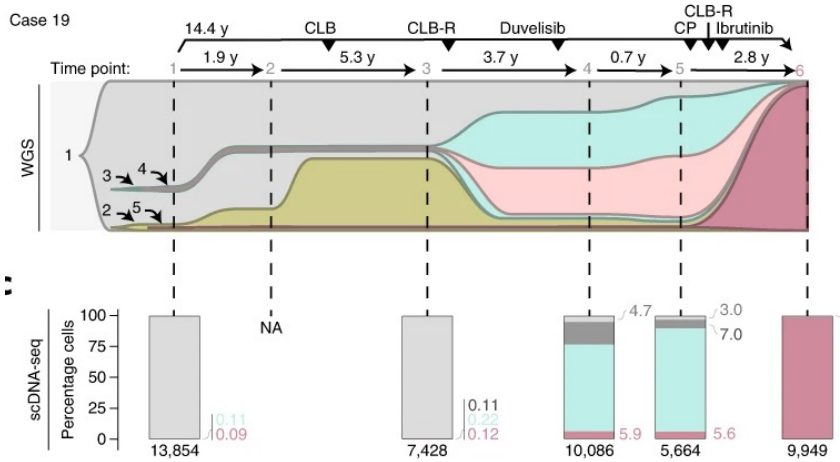
Kadri et al, Blood Adv 2017

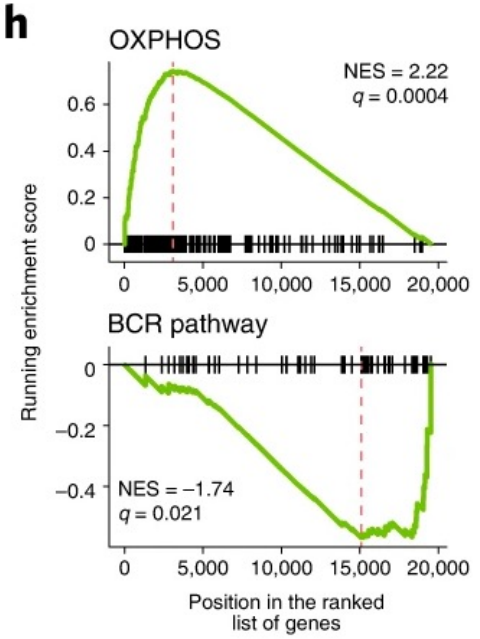
ARTICLES
https://doi.org/10.1038/s41591-022-01927-8
nature medicine

OPEN

Detection of early seeding of Richter transformation in chronic lymphocytic leukemia

- Dormant minute subclones of RS are present 19 years before clinical transformation
- Discovery of new driver alterations and new mutational signatures of RS (SBS-RT)
- RS is characterized by OXPHOS^{high} and BCR^{low} signaling transcriptional axis





Nadeu, Nature Med 2022

Risk factors for developing Richter syndrome

CLL BIOLOGY

- High-risk genomic characteristics of CLL increase the risk of transformation
  - Unmutated IGHV status
  - IGH stereotyped subset number 8 (IGHV4-39-IGHJ5)
  - Activating NOTCH1 mutations
  - TP53 deletion and/or mutation
  - Del11q
- Near tetraploidy has been associated with a high risk of RS in pts receiving Ibrutinib

CLL THERAPY

- No difference in RS risk between treatment arms (CHT vs new agents)
  - Ibrutinib-Rituximab vs FCR (E1912)
  - Chlorambucil-Obinutuzumab vs Venetoclax-Obinutuzumab (CLL14)
  - A lower rate for FCR vs FC (CLL8)
- The risk for RS increases in studies in R/R CLL compared to front-line patients (high-risk biology + clonal evolution during therapy)

Fisher K, Blood 2016; Shanafelt TD, Blood 2022; Al Sawaf, JCO 2021; Chigrinova E, Blood 2013; Rossi D, Blood 2018

Diagnosis of Richter syndrome

Clinical suspicion of transformation

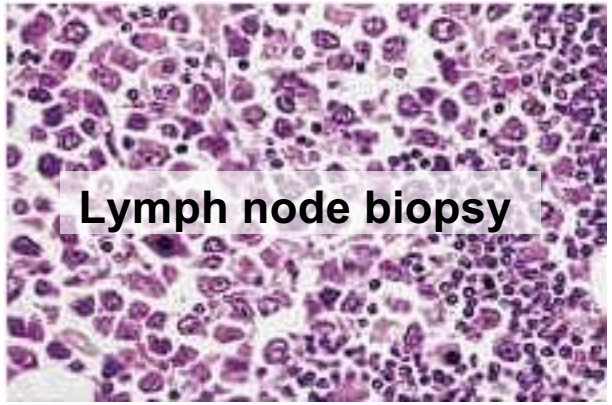
- Asymmetric growth of localized lymph nodes
- Bulky disease
- B symptoms
- Sudden and excessive rise in levels of LDH

PET/CT in Richter syndrome diagnosis

	RS
Sensitivity	91%
Specificity	80%
Positive predictive value	53%
Negative predictive value	**97%**

Max SUV cut off=5

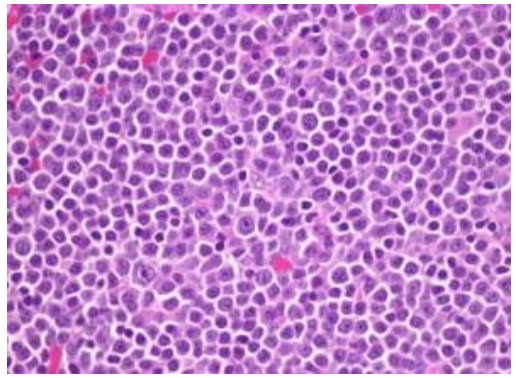
BIOPSY IS MANDATORY (PET-guided)



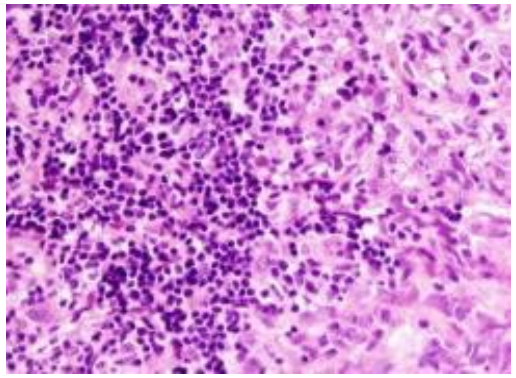
Rossi D et al. Semin Oncol 2016 43:311-9
Gine' E et al. Haematologica. 2010 95:1526-33
Buzzi JF et al. J Nucl Med 2006 47:1267-73
Mauro FR et al. Leukemia 2015 29:1360-5.

Clinical implications of differentiating histologically aggressive CLL vs Richter syndrome

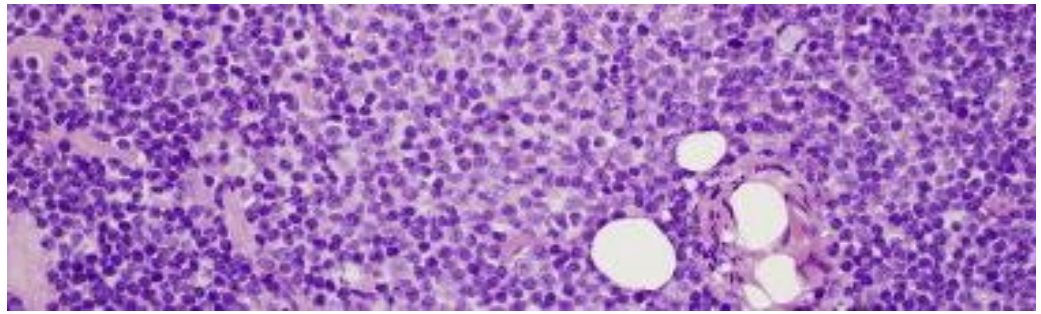
CLL



RS

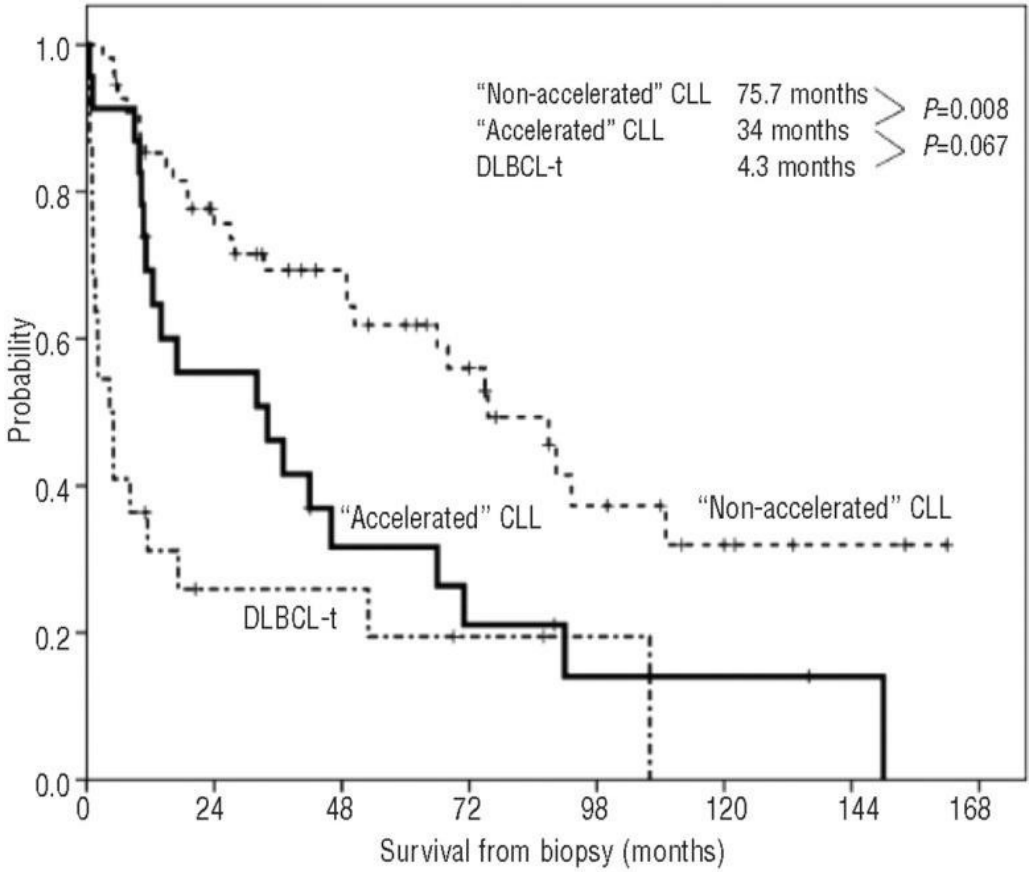


Histologically aggressive CLL



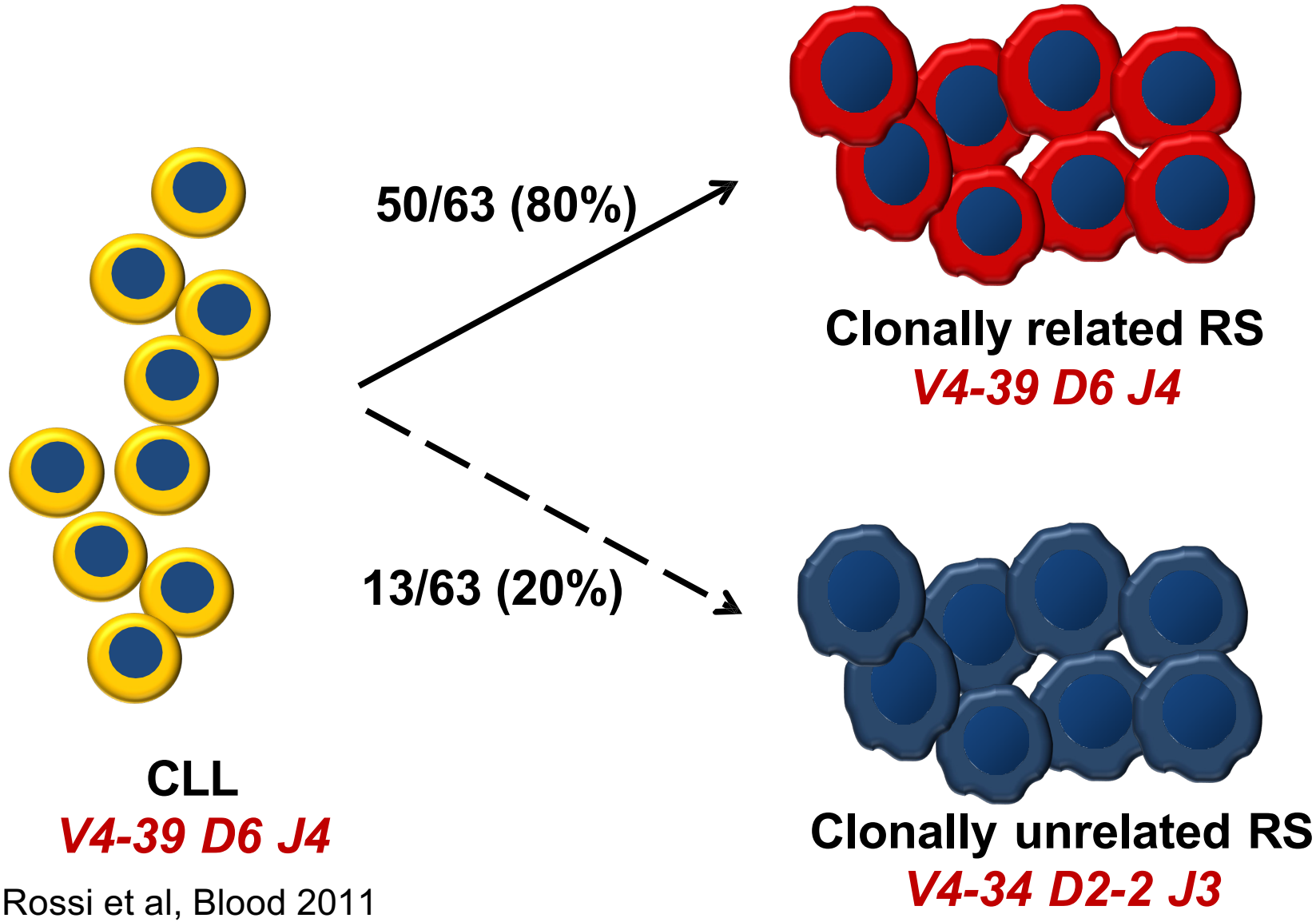
Treat as progressive CLL!

Survival from biopsy according to the histology



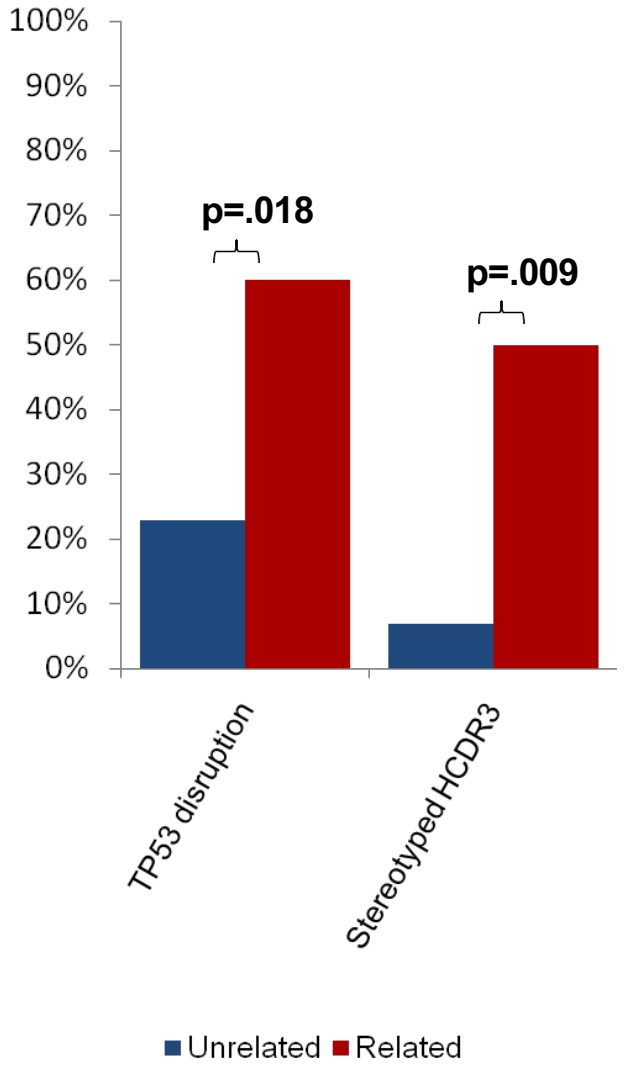
Giné E *et al. Haematologica* 2010; 95 (9): 1526–1533.

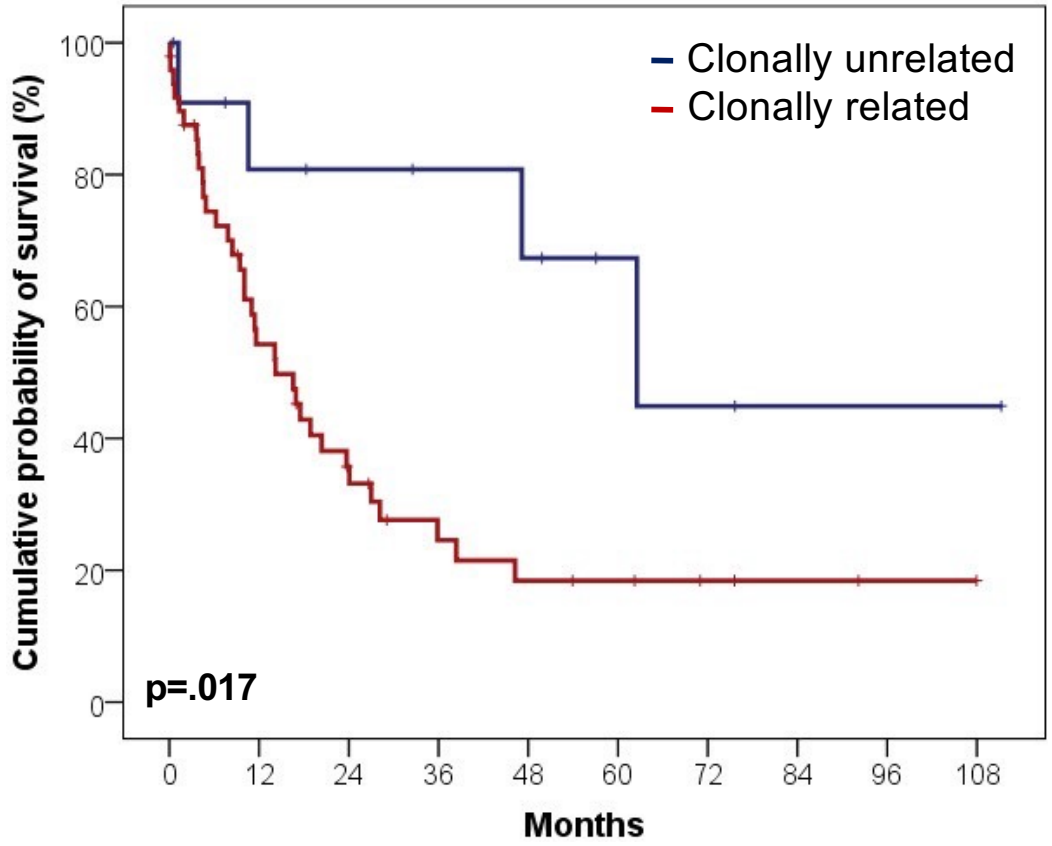
Clonally related vs unrelated Richter syndrome



Rossi et al, Blood 2011

Clonally unrelated Richter syndrome are de novo DLBCL with better outcome

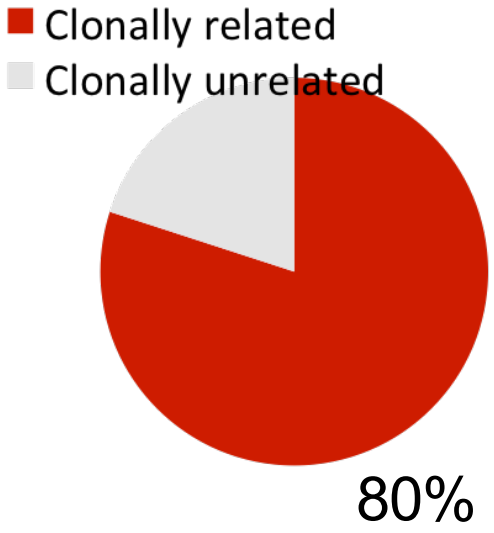


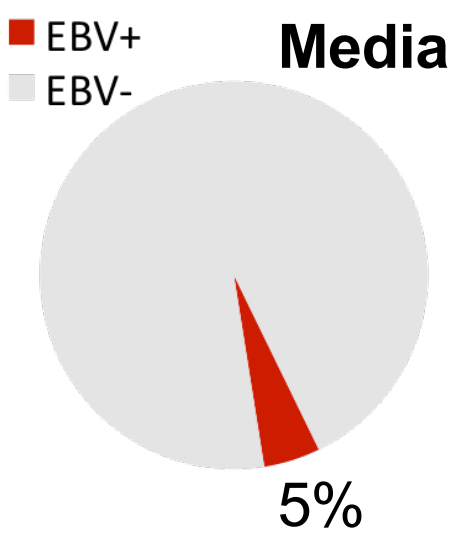


Rossi et al, Blood 2011

Prognosis: importance of histotype

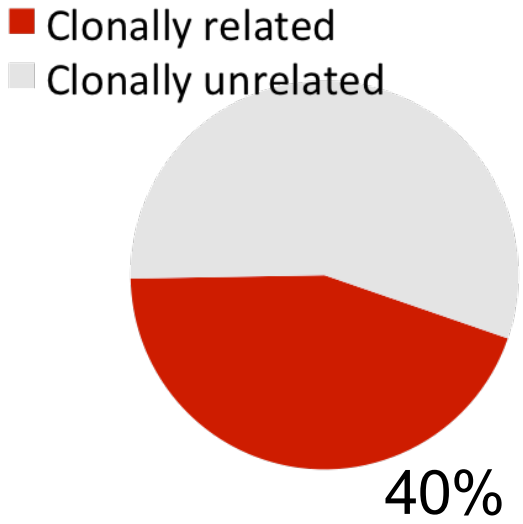
DLBCL variant

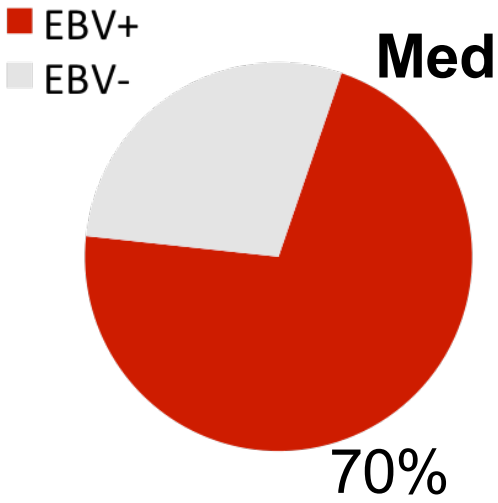




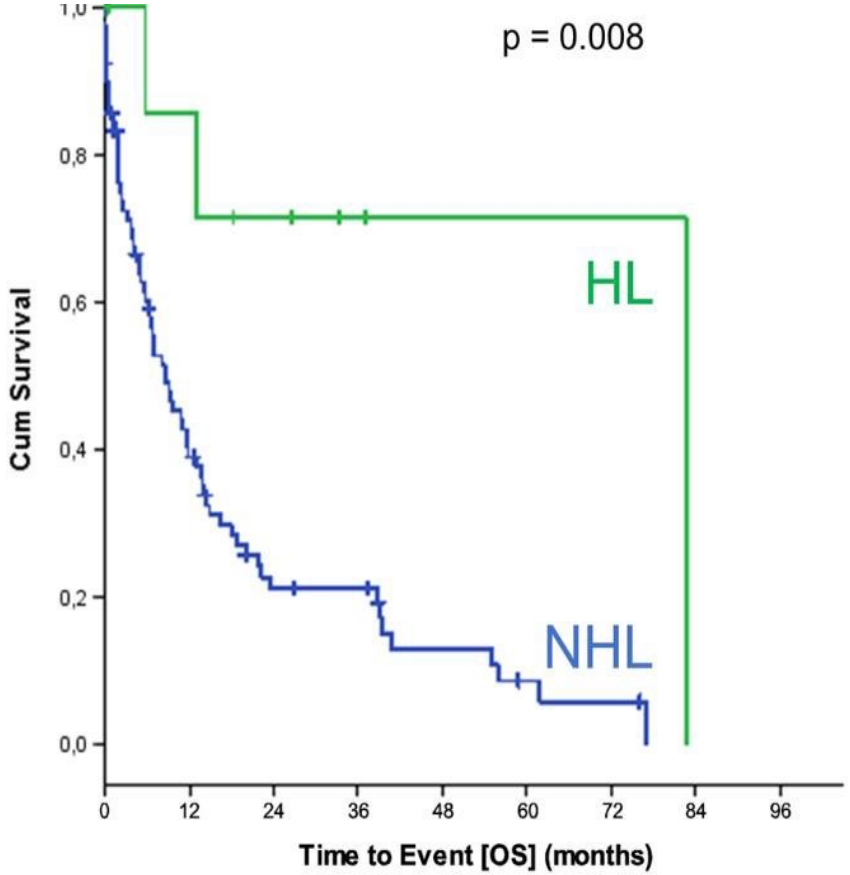
Median OS: <1 y

HL variant





Median OS: 4 y



Abruzzo et al, Am J Surg Pathol 2002; 26: 630-6 O'Brien et al, Cancer 2003; 98: 2657-663 Thornton et al, Leuk Res 2005; 29: 389-95 Ammatuna et al, Leuk Lymphoma 2009; 50:; 857-8 Kanzler et al, Blood 2000; 95:1023-31 Tsimberidou et al, Cancer 2006; 107: 1294-302 Rossi D, et al, Clin Cancer Res 2009; 115: 4415-22, Xiao et al, Hum Pathol 2016;55:108-16

Al-Sawaf O et al. Leukemia 2021

Our experience with HL-RS

	PATIENT 1	PATIENT 2
Features		
Age at diagnosis of CLL	46	60
Age at diagnosis of RS-HL	60	68
Sex	Male	female
Concomitant disease	/	Multiple sclerosis; diverticular perforation with hemicolectomy
CLL stage at the first treatment	II Rai; B Binet	II Rai; B Binet
Molecular features	Unmutated type; 13q deletion	Unmutated type; 13q deletion; 11q22 deletion
Therapies before Ibrutinib	FCR; BR	FCR; BR
Time from start Ibrutinib to RS (months)	40	15
EBV reactivation at the time of RS	Yes	NA
EBV positivity on biopsy	Yes	Yes
Persistence of CLL with RS-HL	No	Yes
Histological type of RS-HL	Type 2	Type 2
Clinical features of RS-HL	Fever; splenomegaly; adenopathies	adenopathies
LDH level (n.v 240-480 UI/L)	629	449
Max SUV of RS-HL	31.4	22.5
Sites of PET uptake	Adenopathies; spleen; skeletal focal lesions	Adenopathies; skeletal focal lesions; pleural thickening
Therapy for RS-HL	2 ABVD; 4 AVD	1 ABVD; 5 MVD
PET-2 response (DS)	2	3
Final PET response (DS)	2	3
Persistence/recurrence of CLL	No	Yes
PFS (for HL, months)	N.R	N.R

2 identical cases of Richter Hodgkin EBV+ occurring in 3° line after FCR and BR, during Ibrutinib

Does Ibrutinib favour to HL-RS?

- Petrackova (Blood Rev 2021) reports that RS-HL incidence during Ibrutinib increases up to > 10%

Why Ibrutinib favour HL-RS?

Hypothesis:

→ Ibrutinib curbs EBV control favouring development of HL-RS EBV+

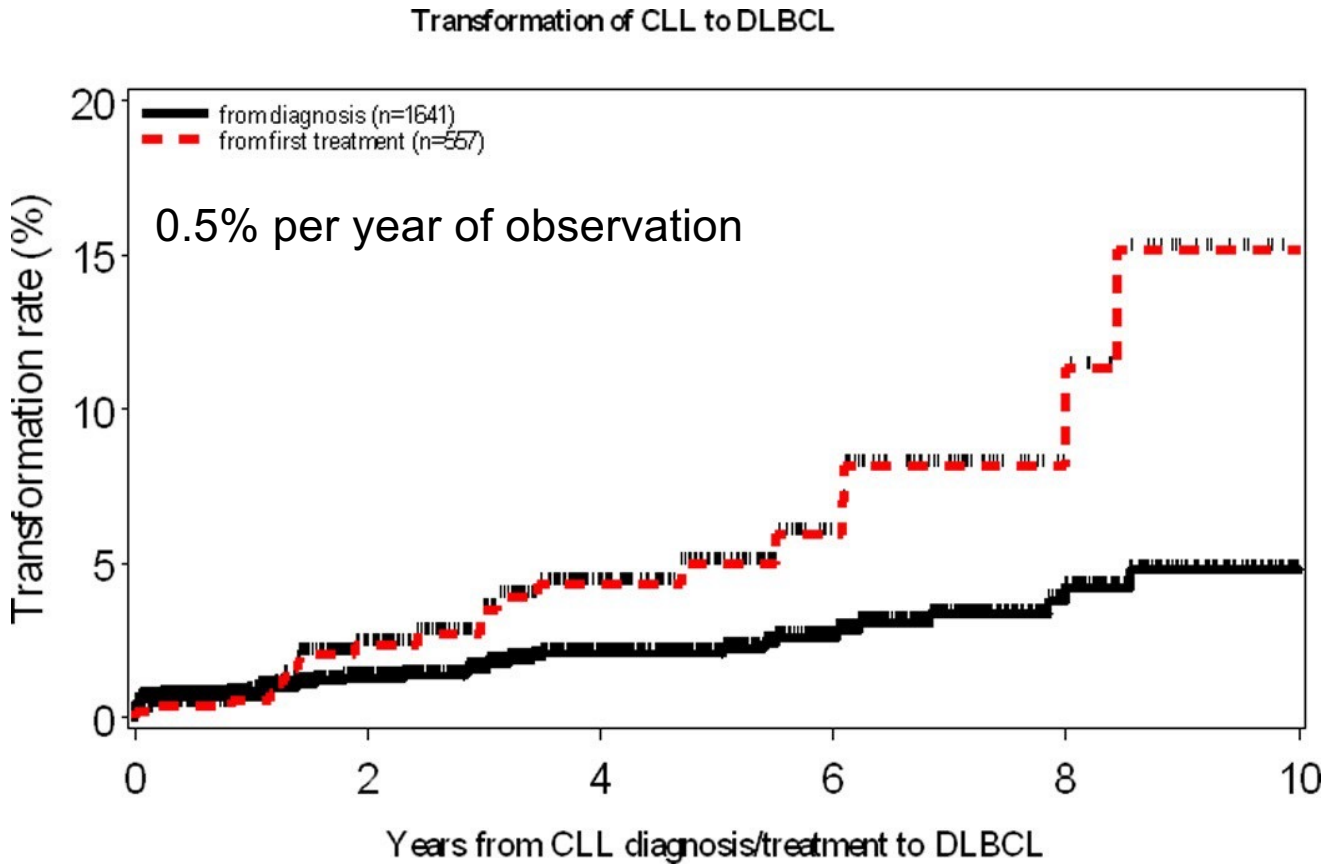
→ Ibrutinib inhibits ITK → ITK deficiency innate immunodeficiency (Tangye Blood 2020) is characterized by frequent EBV reactivation and increased incidence of HL

Why Ibrutinib does not lead to increased EBV reactivation in the clinical practice?

➔ Probably ITK inhibition alone is not enough: however, in the context of an abolished T function after FCR and BR, ITK may be the only guardian left to EBV reactivation

Rosignoli C et al, unpublished

Cumulative incidence of Richter syndrome “then”



Parikh et al Br J Haematol 2013

Incidence of Richter syndrome with new drugs

Reference	Total pts	Study population	Treatment	Pts that developed RS	RS prevalence
Burger, 2015	186	Treatment naive	Ibrutinib	0	0%
Byrd, 2014	391	Relapsed	Ibrutinib	4	1%
O'Brien, 2014	29	Treatment naive	Ibrutinib	1	3%
Jain, 2015	127	Relapsed/Refractory	Ibrutinib	7	5%
Farooqui, 2015	51	17p deleted	Ibrutinib	3	6%
Mato, 2016	178	BCRi treated	Ibrutinib, idelalisib	13	7%
Byrd, 2013	85	Relapsed/Refractory	Ibrutinib	7	8%
Seymour, 2017	49	Relapsed/refractory	Venetoclax-rituximab	5	12%
Roberts, 2015	116	Relapsed/Refractory	Venetoclax	18	16%
Seymour, 2017	49	Relapsed/refractory	Venetoclax-rituximab	5	12%
Strati, 2014	63	17p deleted	Heterogeneous	15	23%

Heterogeneity conceivably due to: case mix, 1st line vs R/R, observation time

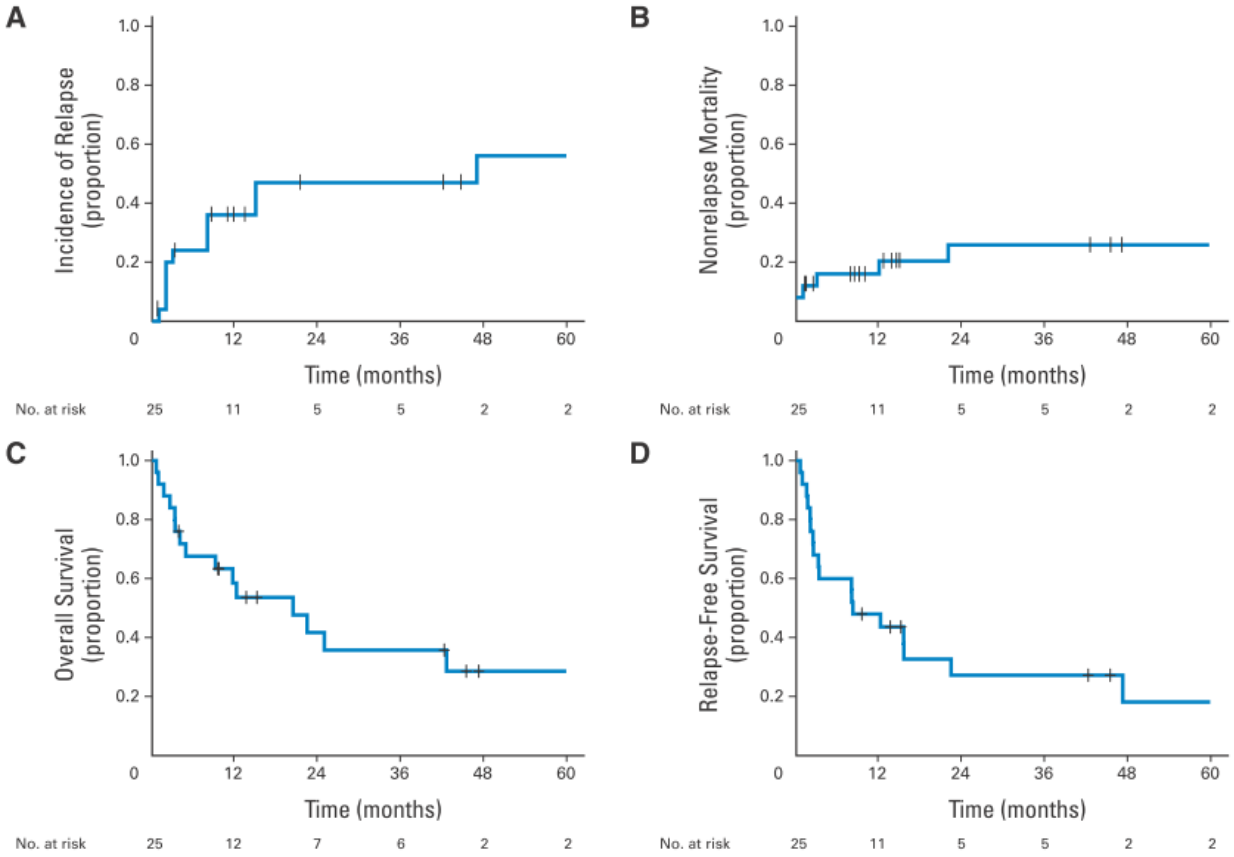
CHEMOTHERAPY IN RICHTER SYNDROME

Study and years of patient recruitment	Regimen	n	Median age (years)	Results		
				ORR	CRR	Median OS
Anthracycline-containing regimens						
Langerbeins et al[16] (2003–2008)	R-CHOP	15	69 (N/A)	67%	7%	21 months
Dabaja et al[17] (published 2000)	HyperCVXD	29	61 (36–75)	41%	38%	10 months
Tsimberidou et al[18] (1999–2001)	Rituximab and GM-CSF with alternating hyperCVAD and MTX/cytarabine	30	59 (27–79)	43%	18%	8.5 months
Rogers et al[19] (2006–2014)	R-EPOCH	46	67 (38–83)	39%	N/A	5.9 months
Platinum-containing regimens						
Tsimberidou et al[20] (2004–2006)	OFAR1	20	59 (34–77)	50%	20%	8 months
Tsimberidou et al[21] (2007–2010)	OFAR2	35	63 (40–81)	43%	8.6%	6.6 months
Fludarabine-containing regimens						
Giles et al[22] (1992-1996)	PFA or CFA	12	59 (49–74)	45%	N/A	17 months
Tsimberidou et al[23] (1997–2001)	FACPGM	15	62 (42–74)	5%	5%	2.2 months

Thompson, ASH Educat 2022

Auto and Allo SCT in Richter Syndrome

ALLOGENEIC



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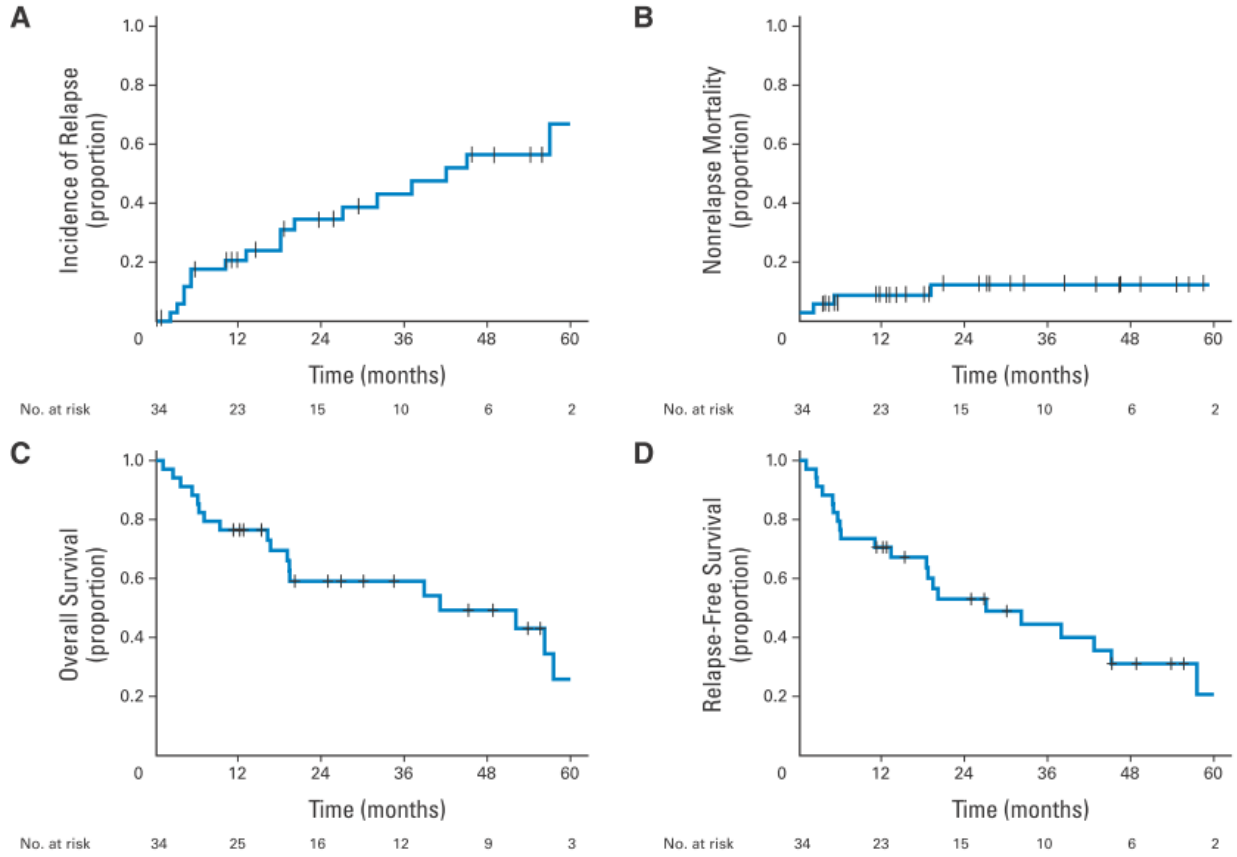

Cwynarsky K, JCO 2012

Auto and Allo SCT in Richter Syndrome

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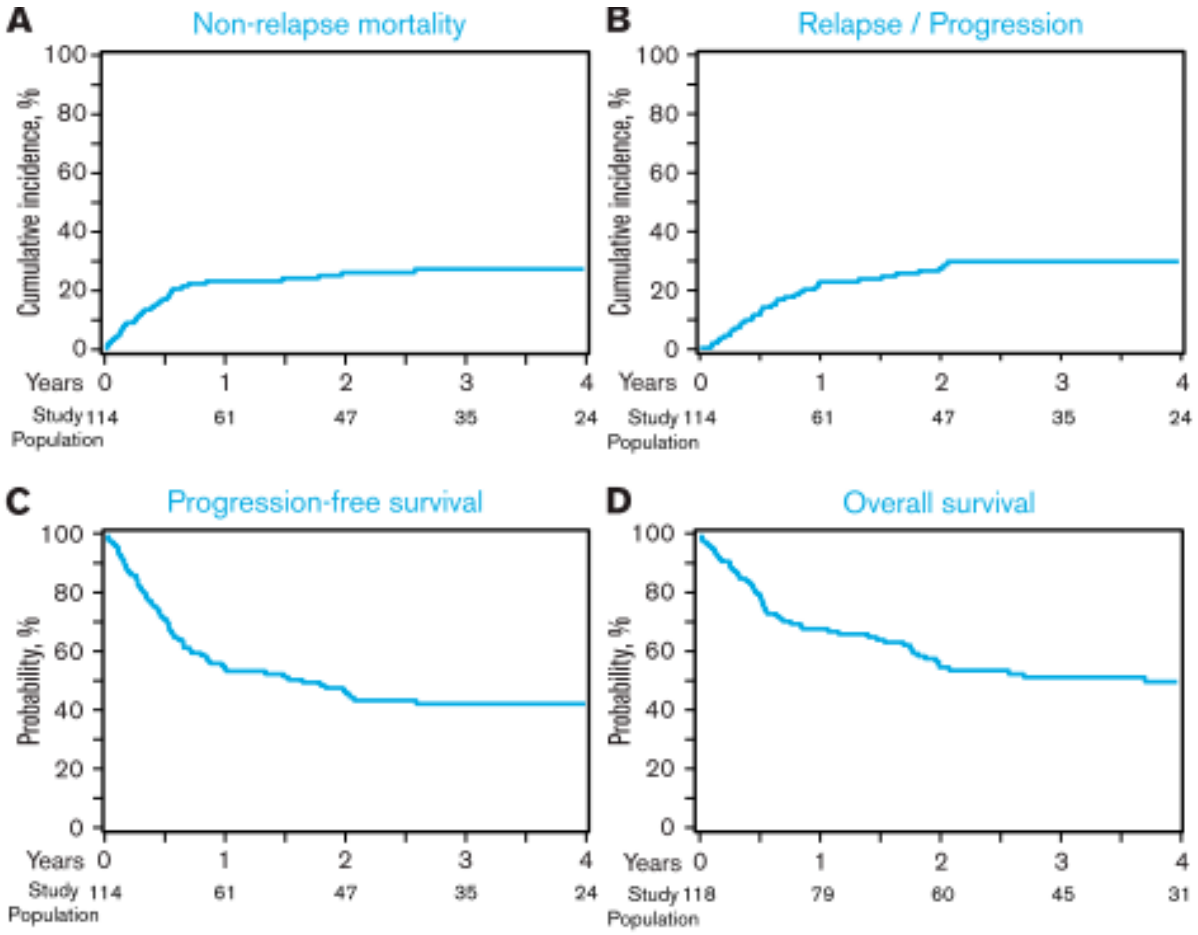

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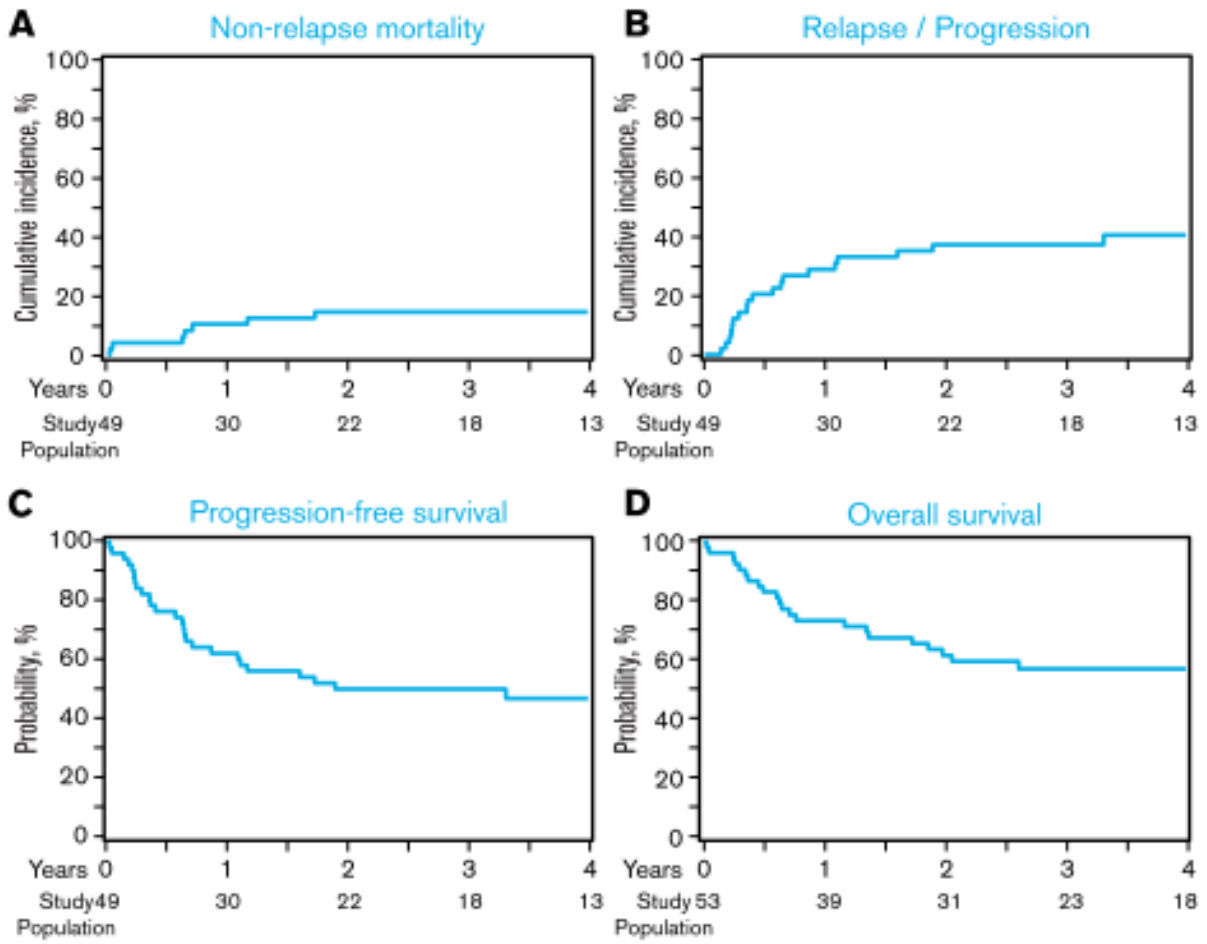
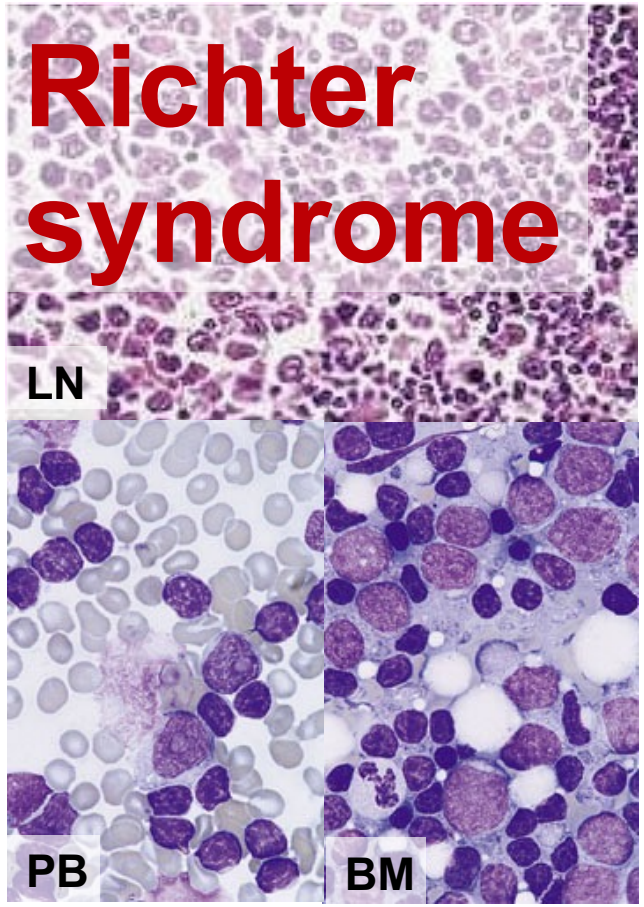


Herrera, Blood Adv 2021

Reasons for treatment failure in Richter syndrome



Biology of the tumor

Patient frailty

Late recognition

Has something changed?

Lack of dedicated treatments

Novel strategies for Richter syndrome

Something has changed…

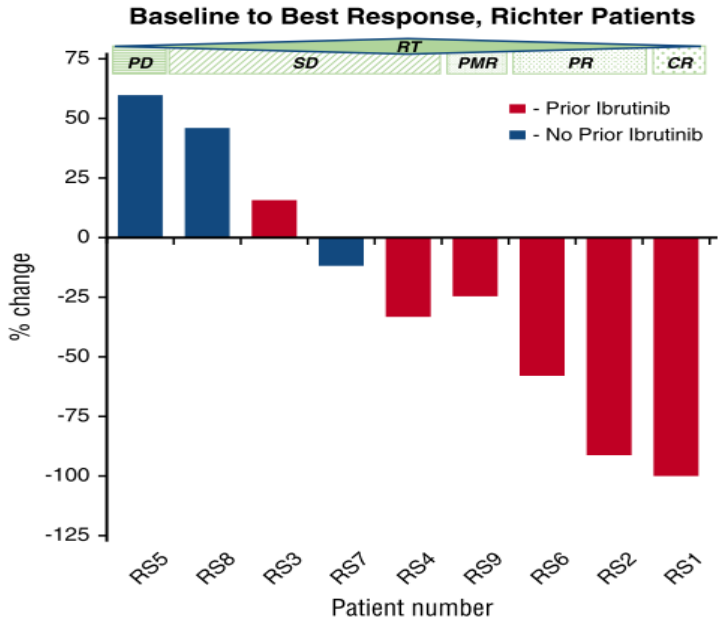
Treatment	Number of patients	Median number prior Rx (CLL + RT)	ORR/CRR (%)	Median PFS/DOR(mo)	Median OS (mo)
Small-molecule targeted agents					
Venetoclax monotherapy[38]	7	NR	43/0	NR/NR	NR
Acalabrutinib monotherapy[25]	25	1 for RT	40/8	3.2/6.2	NR
DTRM-555 (novel BTKi DTRMWXHS-12– everolimus–pomalidomide)[39]	24	5	45/9	NR/NR	NR
Pirtobrutinib[26]	9	6 (including 100% treated with covalent BTKi)	67/NR	NR/NR	NR
CIT + targeted agents					
R-EPOCH–venetoclax[28]	26	1 for CLL, 0 for RT	62/50	10.1/NR	19.6
Checkpoint inhibitors					
Pembrolizumab[30]	9	5	44/0	NR/NR	10.1
Pembrolizumab[31]	23 (2 with CHL)	3 for RT, NR for CLL	5/0 (excluding 2 responders with CHL)	1.6/NR	3.8
Ibrutinib-nivolumab[40]	24	3	43/35	NR/10.	13.8
Ibrutinib- nivolumab[41]	20	2	65/10	5.0/6.9	10.3
Venetoclax-obinutuzumab-atezolizumab[33]	7	NR	100/71	Not reached/not reached	NR
Bispecific antibodies					
Blinatumomab monotherapy (*Leukemia*, in press)	9	4 for CLL +2 for DLBCL-RS	22/11	1.9/NR	10.3
Blinatumomab after R-CHOP[34]	31	2 for CLL	54/39	NR/NR	NR
Antibody-drug conjugates					
Zilovertamab vedotin[36]	6	NR	67/17	NR/NR	NR
CAR T					
CD19 CAR T[42]	6 (DLBCL only)	5	67/67	NR/NR	NR
Axicabtagene ciloleucel[43]	8	4	100/63	NR/NR	NR
Lisocabtagene maraleucel (European Breyanzi label)	4	NR	50/25	NR/2	NR

NR, not reported; RT, Richter's transformation.

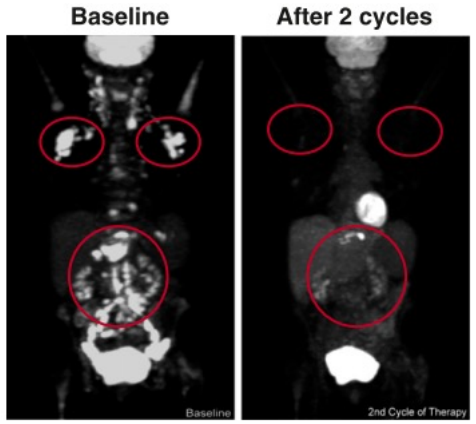
Thompson, ASH Educat 2022

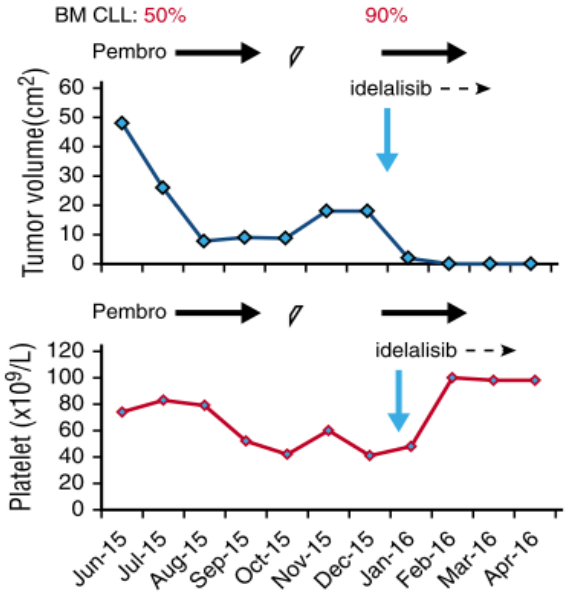
Pembrolizumab for Richter transformation

- 25 pts: 16 relapsed CLL, 9 Richter transformation (DLBCL)
- TP53+ or 17p-: 7/16 RR-CLL, 5/9 RT
- Median previous treatments: 4 (1-10)
- Prior ibrutinib: 9/16 RR-CLL, 6/9 RT
- Pembrolizumab 200 mg q3w (Idelalisib allowed to control CLL)
- ORR: 0% in RR-CLL, 4/9 (44%) in RT (1 CR, 4 PR, 4 SD)
- Biomarkers: responding pts had higher PD-L1; none had 9p24 alterations; no correlation with MSI



#2 had BM progression with CLL after 5mo of Pembro. After addition of Idelalisib he had 2° CR which is ongoing

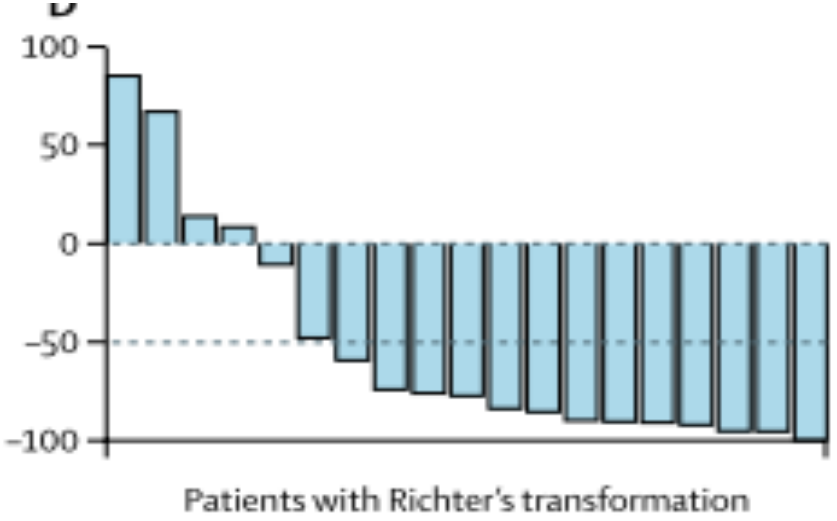




Ding, Blood 2017

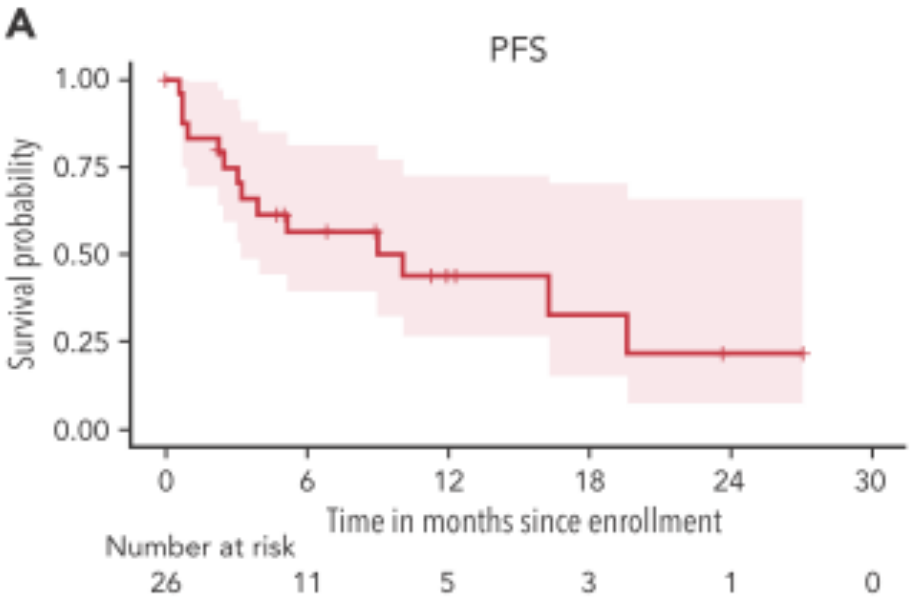
Checkpoint blockade for Richter transformation: other experiences

- Rogers, BJH 2019:
  - 10 pts (7 Nivo, 3 Pembro) treated off-label for DLBCL-RT
  - In 6/10 CPI was 1° treatment for DLBCL-RT
  - 9/10 had treatment failure; 1 maintained NED after surgical resection
- Jain, ASH 2016:
  - 13 pts with RR-CLL or RT treated with Nivolumab + Ibrutinib
  - 4 were RT; 2 had a response (50%)
- Younes, Lancet Hem 2019:
  - 141 pts with B-NHL/CLL treated with Nivolumab + Ibrutinib
  - ORR: 13/20 (65%) pts with RT
  - Previously not exposed to Ibrutinib



Venetoclax plus dose-adjusted R-EPOCH for Richter syndrome

Matthew S. Davids,[1,*] Kerry A. Rogers,[2,*] Svitlana Tyekucheva,[3] Zixu Wang,[3] Samantha Pazienza,[1] Sarah K. Renner,[4] Josie Montegaard,[1] Udochukwu Ihuoma,[1] Timothy Z. Lehmberg,[1] Erin M. Parry,[1] Catherine J. Wu,[1,5] Caron A. Jacobson,[1] David C. Fisher,[1] Philip A. Thompson,[4,†] and Jennifer R. Brown[1,†]



Venetoclax plus dose-adjusted R-EPOCH (VR-EPOCH) for Richter's syndrome

Patients (n=26 treated)

Biopsy-proven RS

Median age 63 years

78% with prior CLL treatment

52% with complex karyotype

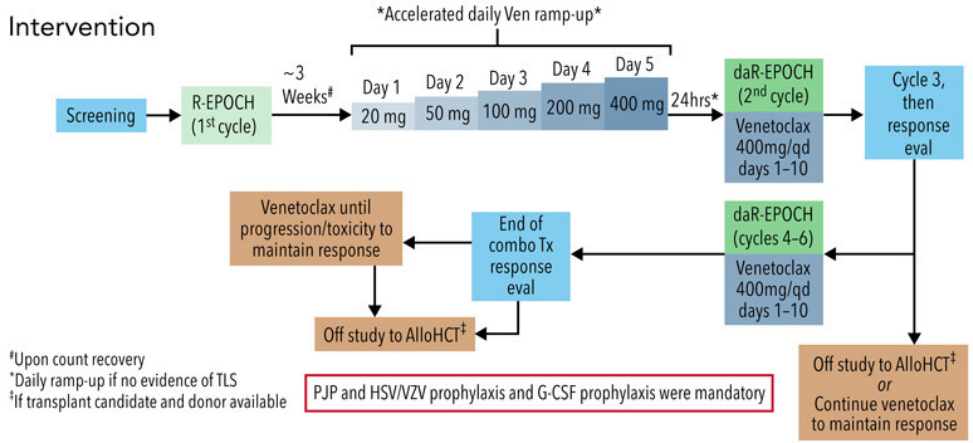
42% with *TP53* aberrancy

41% post-ibrutinib

22% post-venetoclax

15% post-PI3Ki

Intervention



Outcomes

Efficacy

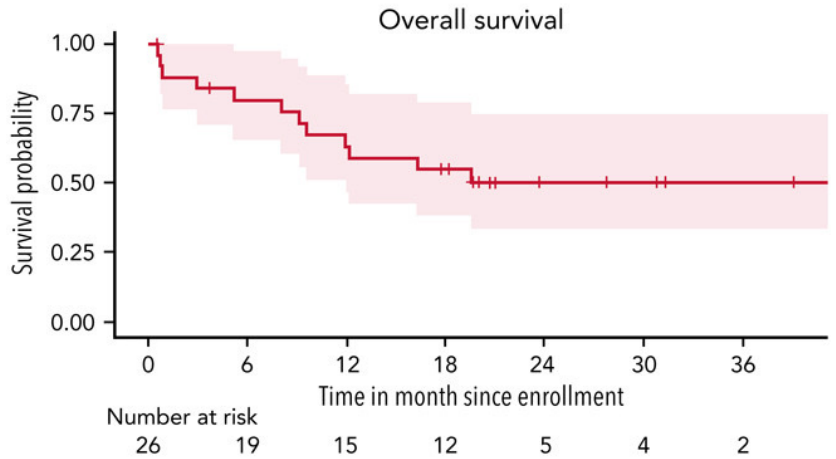
50% CR rate by ITT analysis

11 patients with CLL BM-uMRD

Median follow-up 17 months

Median PFS 10.1 months

Median OS 19.6 months



Safety

Heme tox:

-gr ≥3 neutropenia (65%)

-thrombocytopenia (50%)

-febrile neutropenia (38%)

Infections: pneumonia, sepsis, and enterocolitis (n=3 each)

No patients experienced TLS with daily venetoclax ramp-up

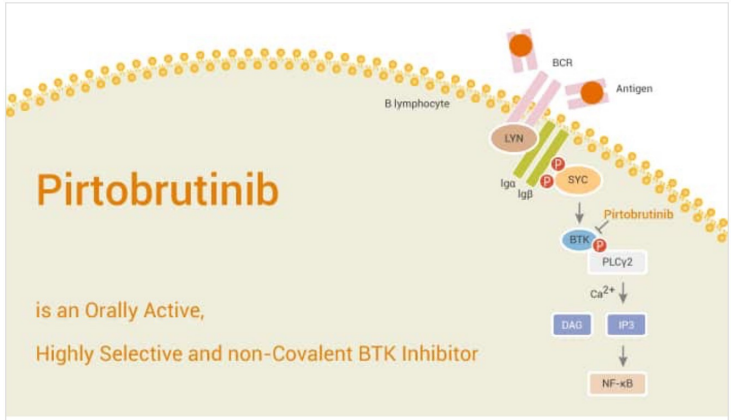
Conclusion

Chemosensitization with venetoclax plus dose-adjusted R-EPOCH led to a high rate of durable CR for Richter's syndrome, with toxicities including cytopenias and infection

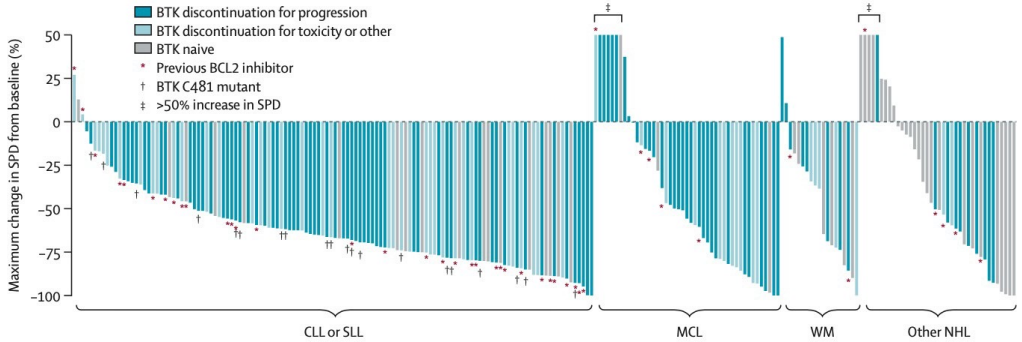
Our experience with DA-EPOCH-R + Ven in RS

Sex	Age	CLL: last therapy	RS: line of therapy	N° of cycles	Best response	Outcome
M	65	Ibrutinib	2	1	PD	Death (cause: PD)
F	57	Ibrutinib	1	4	PR	Death (cause: PD)
F	68	Ibrutinib	1	1	NV	Death (cause: toxicity)
F	67	Ibrutinib	2	1	PR	AlloSCT→PD
M	64	BR (relapsed)	1	4 (ongoing)	CR	ongoing
F	58	Ibrutinib (relapsed)	1	2	PR	ongoing

Pirtobrutinib in relapsed or refractory B-cell malignancies
BRUIN: a phase 1/2 study



Pirtobrutinib is an Orally Active, Highly Selective and non-Covalent BTK Inhibitor



ORR was 62% in CLL/SLL, and 52% in MCL

Pirtobrutinib in Richter syndrome

	Median lines of prior systemic therapy, n (IQR)	Treated, n	Efficacy-Evaluable*, n	Responders, n	ORR#, % (95% CI)	Best Response#, %
DLBCL	4 (3-5)	26	25	6	24 (9-45)	CR: 4 (16)
						PR: 2 (8)
						SD: 2 (8)
						PD: 12 (48)
						NE: 5 (20)
MZL	3 (2-5)	13	9	2	22 (3-60)	PR: 2 (22)
						SD: 7 (78)
Richter's transformation	6 (4-7)	9	8	6	75 (35-97)	PR: 6 (75)
						SD: 1 (13)
						NE: 1 (13)
B-PLL	5 (2-7)	2	2	0	0 (0-84)	SD: 1 (50)
						NE: 1 (50)
Other transformation	5 (4-8)	3	3	0	0 (0-71)	PD: 2 (67)
						NE: 1 (33)
HCL	10 (10-10)	1	0	0	0	NA

Primary Tumor Type	Prior Lines of Therapy	Prior BTK Inhibitor	Best Overall Response	Time on Treatment (months)	Treatment Status
Richter's Transformation	6	Yes	PR	2.3	Discontinued
Richter's Transformation	2	Yes	PR	7.1	Ongoing
Richter's Transformation	3	Yes	PR	6.4	Ongoing
Richter's Transformation	6	Yes	PR	2.9	Ongoing
Richter's Transformation	7	Yes	PR	3.2	Ongoing
Richter's Transformation	4	Yes	PR	2.9	Ongoing

Mato *et al, Lancet* 2021

MOLTO

ObinutuzuMab AtezOlizumab and VenetocLax in RichTer transfOrmation

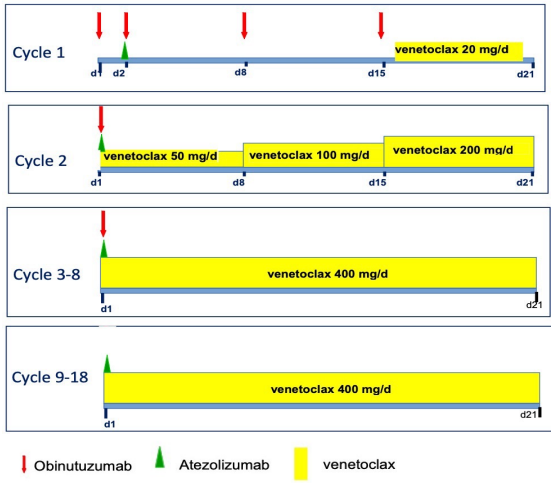
A multi-center, open label, uncontrolled, phase II clinical trial evaluating the safety and efficacy of **atezolizumab (PD-L1 inhibitor)** in combination with **venetoclax** and **obinutuzumab** in DLBCL Richter transformation of CLL

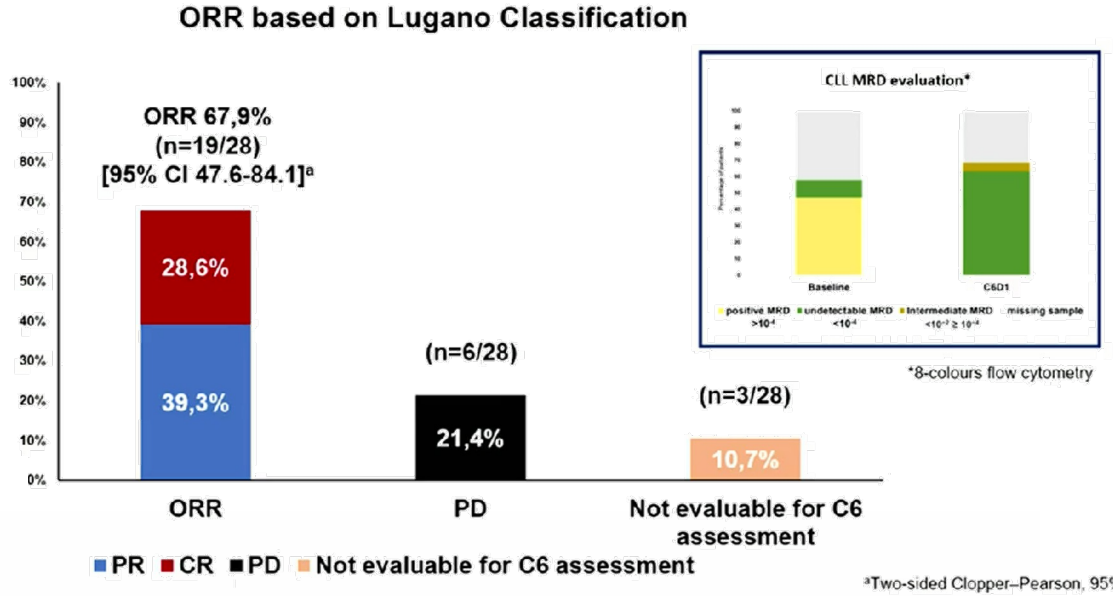
Overall Safety Summary	N=28 n (%)
Median number of cycles/pt administered: 10.5 (range 1-35)	
Pts with serious TEAE	6 (21.4)
Pts with TEAE leading to dose interruption (at least one drug)	8 (28.6)
TEAE leading to study drug discontinuation	1 (3.6)*
TEAE leading to death	2 (7.1)**
TEAE leading to dose reduction	0

*1 MDS in a pts previously treated with CIT
**1 G5 sepsis; 1 G5 pneumonia

- NO TLS recorded
- Accelerated ramp-up in 3 pts

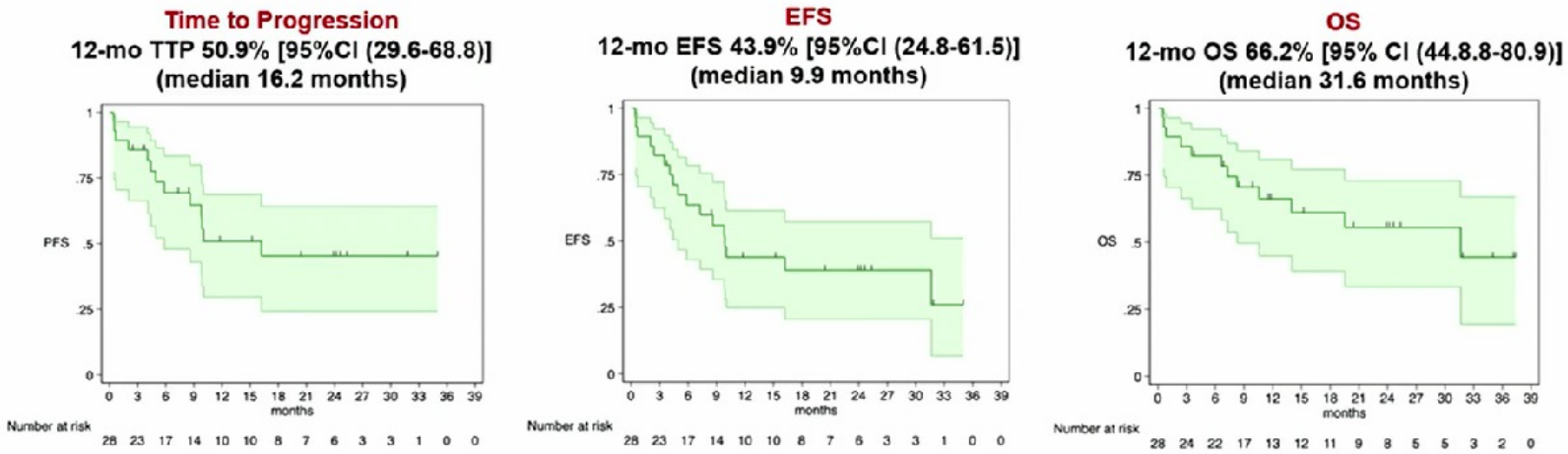
Treatment response at Cycle 6 (ITT)





Survival outcomes

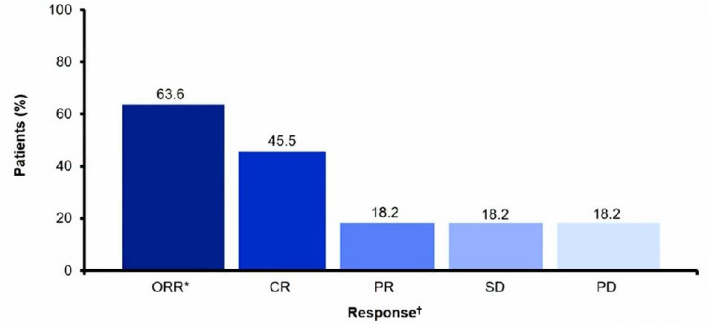
Median follow-up: 11.6 months (range 0.5-37.3 months)

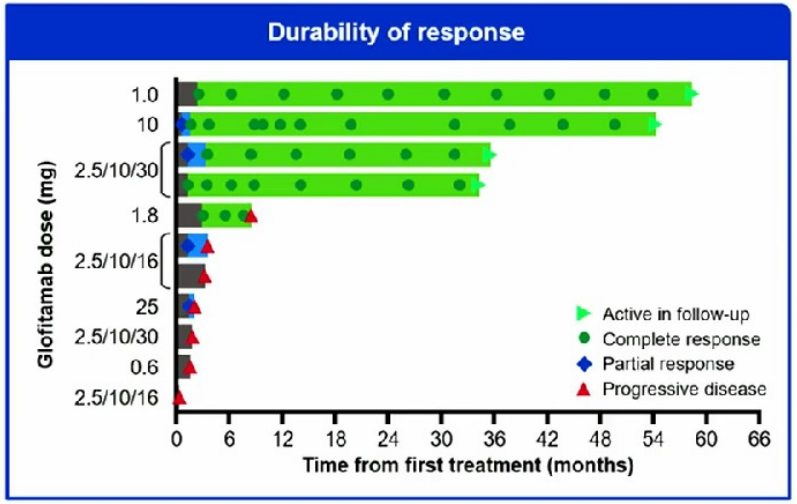


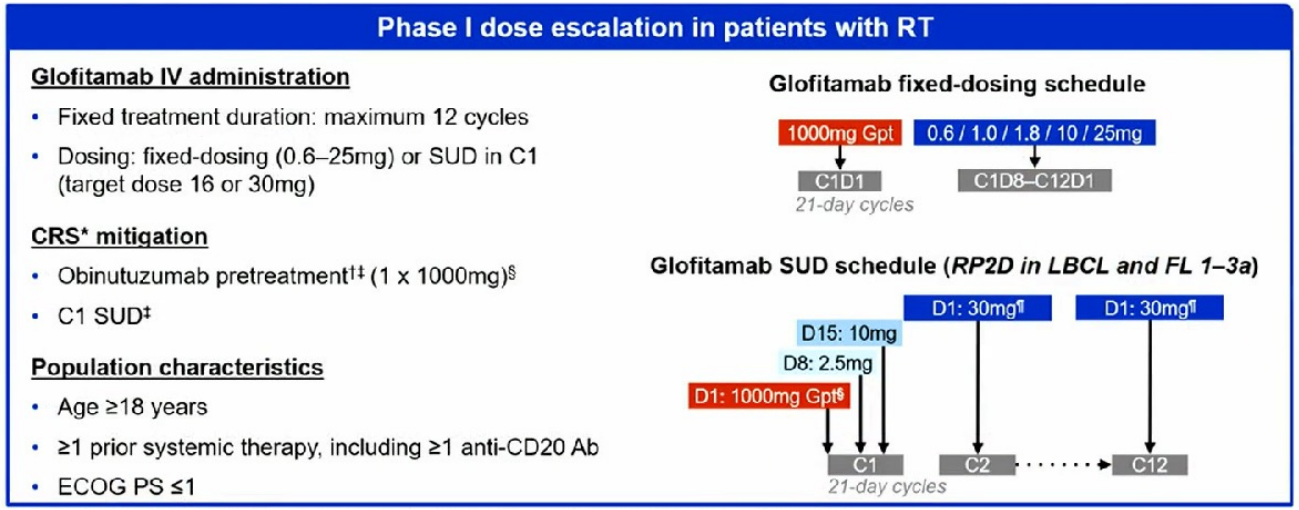
Frustaci, ICML 2023

Glofitamab in RS

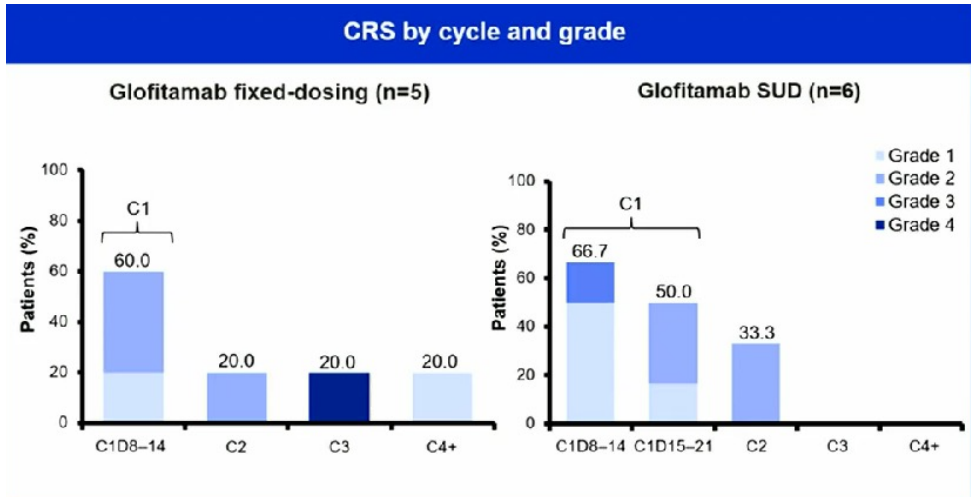
- 11 pts, age 48-77y
- Median lines of prior therapy=3
- Bulky disease in 64%
- 100% refractory to any prior therapy







- ORR 64%, CR 46%
- CR were durable: 4/5 were ongoing at data cutoff after 33mo
- CRS was mostly low grade and occurred in C1-C2 with step-up dosing



Carlo-Stella, ICML 2023

Epcoritamab: Epcore CLL-1 RS expansion cohort

Study Design: EPCORE CLL-1 RS Expansion Cohort

Dose escalation → **Median follow-up: 4.9 mo (range, 0.6–9.3)**

CLL[1]
- ✓ No DLTs
- ✓ MTD not reached
- ✓ RP2D identified
- ✓ Manageable safety profile
- ✓ Encouraging antitumor activity

Key RS inclusion criteria
- Ineligible for or voluntarily declined chemotherapy
- ≤1 prior line of therapy for RS-DLBCL
- Biopsy-proven transformation to CD20+ RS-DLBCL
- Prior clinical history of CLL or SLL
- ECOG PS 0–2
- Measurable disease by PET and/or CT/MRI

RS-DLBCL expansion, N=10

Step-up dosing[a] → **Epcoritamab (SC) 48 mg** QW C1–3, Q2W C4–9, Q4W C10+ → Efficacy assessment by PET-CT obtained Q6W until C6, and then Q24W thereafter → Treatment until disease progression

- To ensure patient safety and better characterize CRS, inpatient monitoring was required at first 4 doses of epcoritamab
- **Primary endpoint:** Overall response rate (ORR)
- **Key secondary endpoints:** Complete metabolic response (CMR) rate, time to response (TTR), and safety/tolerability

Data cutoffs: September 8, 2022 (efficacy); September 16, 2022 (safety). Epcoritamab was administered in 28-d cycles as shown. [a]Patients received SC epcoritamab with step-up dosing (ie, 0.16 mg priming and 0.8 mg intermediate doses before first full dose) and corticosteroid prophylaxis as previously described to mitigate CRS. **1.** Kater AP, et al. ASH 2021. Abstract 2627.

EPCORE NHL-1 Clinical Case Study: RS-DLBCL

Patient history
- 76-year-old male
- Diagnosed with SLL in Jul 2019, started on ibrutinib
- Transformed to RS-DLBCL in Oct 2020
- RS-DLBCL treated with 3 cycles of R-CHOP, mixed response

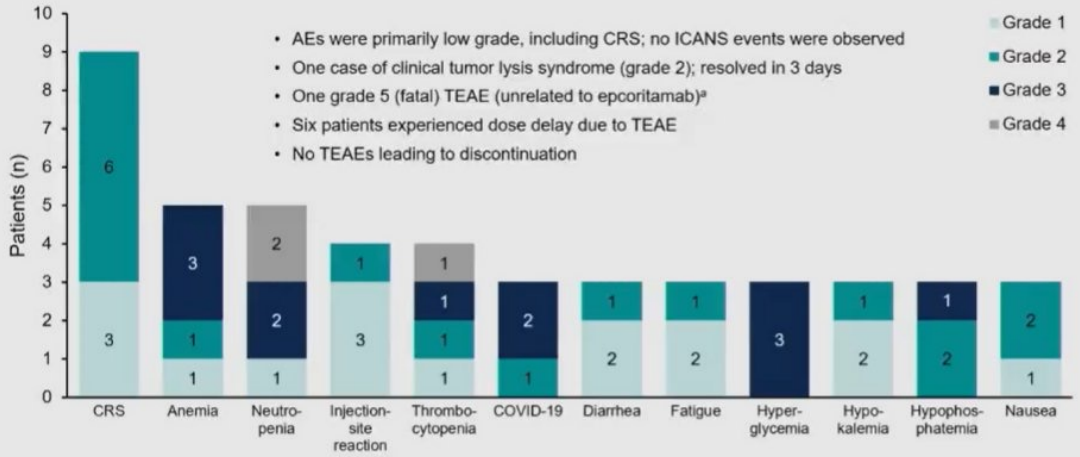
Epcoritamab treatment
- First dose: Feb 2021 (SPD = 105 cm^2)
- CR at week 6, 12, 17, 23, 36, 48, 62, 76 (DS = 1, SPD = 2.8 cm^2)
- Patient has been in sustained CR for over 70 weeks and is still on treatment (last dose C22D1)

Baseline PET/CT scan	12-week PET/CT scan	76-week PET/CT scan
Mesenteric mass: 11.6 x 7.2 cm	Mesenteric mass: 0.5 x 0.5 cm	Mesenteric mass: 0.5 x 0.5 cm
SUV max 6.3 in abdominal/ pelvic mass	SUV max 2.0 in abdominal/ pelvic mass	Background uptake only

Courtesy of Dr. Yasmin H. Karimi.

Treatment-Emergent AEs (≥30%)

- AEs were primarily low grade, including CRS; no ICANS events were observed
- One case of clinical tumor lysis syndrome (grade 2); resolved in 3 days
- One grade 5 (fatal) TEAE (unrelated to epcoritamab)[a]
- Six patients experienced dose delay due to TEAE
- No TEAEs leading to discontinuation



10 pts: 6 naive, 4 R/R

Conclusions
- Response rates: ORR 60%, CMR 50%
- Only low-grade CRS: all resolved
- No ICANS events
- No discontinuation due to TEAEs

EPCORE CLL-1 study is ongoing and recruiting

Kater, ASH 2022; Eichorst, ICML 2023

CAR-T in RS

LYSA study from DESCARTES registry

- 14 pts planned, 12 infused (1 refused, 1 PD)
- 25% had 17p, TP 53 in 57%
- 3 TN for CLL, 7 received Ibr, 5 Ibr and Ven
- Median no of therapies for RS=3
- Bridging therapy for 11/12
- Axi-cel=5, Tisa-cel=7
- ORR=50%, 4 early deaths (2 PD, 2 CRS)
- CRS≥G3 in 25%, ICANS in 42%, 1 MAS

Bensaber, ASH 2022

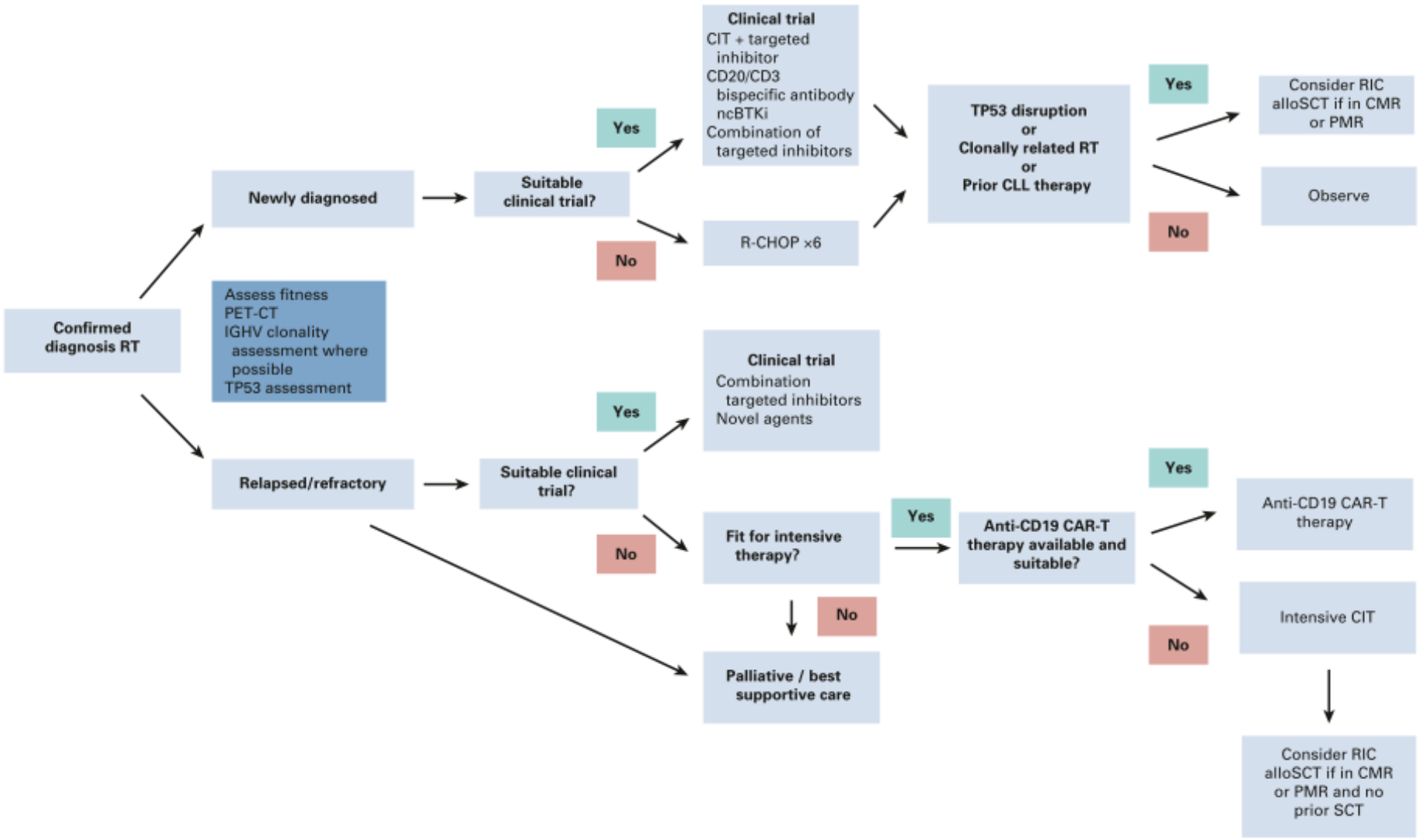
Tel Hashomer single centre study

- 8 CLL pts with disease transformation after CIT and BTKi or BCL2i
- Academic anti-CD19 CAR-T (CD28)
- Del17p/TP53mut in 83%
- 6 RS, 1 accelerated CLL, 1 PLL
- Median no of 3 therapies for CLL, 2 for RS
- CRS G3-4 in 37%, ICANS in 37%
- ORR 71%, CMR 71%
- 2 deaths for PD, no toxicity deaths

Benjamini ASH 2022

Smyth, JCO 2023

Algorithm



GRAZIE PER L’ATTENZIONE