POST-SAN DIEGO 2024
Novità dal Meeting della Società Americana di Ematologia

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Bologna
Palazzo Re Enzo
13-15 Febbraio 2025

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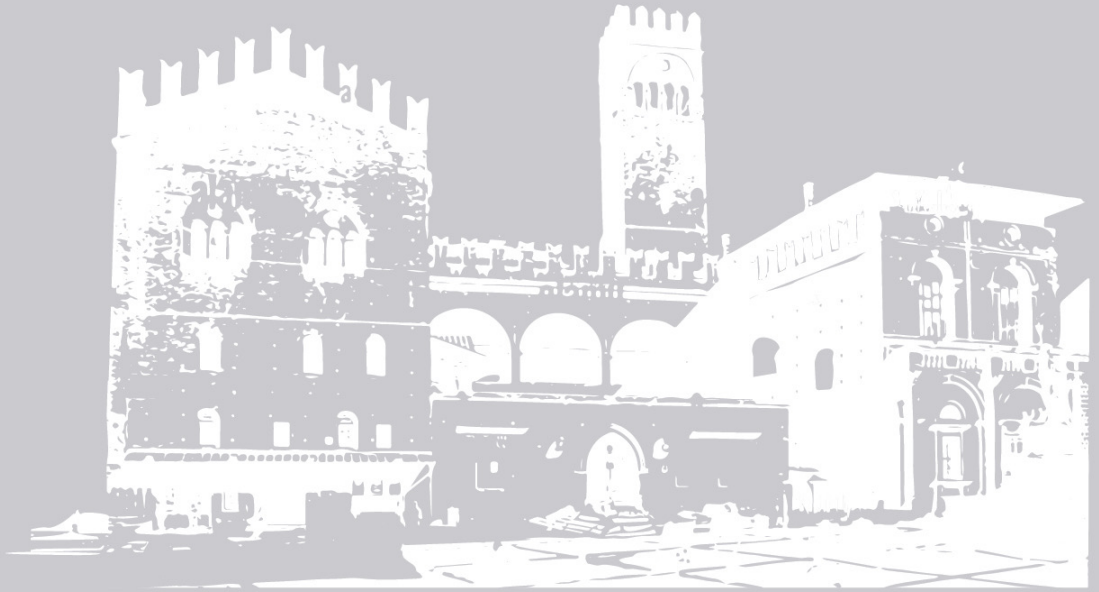

3° SESSIONE – LEUCEMIA LINFATICA CRONICA:
Sindrome (Trasformazione) di Richter

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Disclosures of Name Surname

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
Janssen						X	X
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Abbvie						X	x
AstraZeneca						x	x

ASH 2024, RICHTER TRASFORMATION, AGENDA:

New drivers in RT and potential therapeutic targets

RT prognosis

RT therapy

ASH 2024, RICHTER TRASFORMATION, AGENDA:

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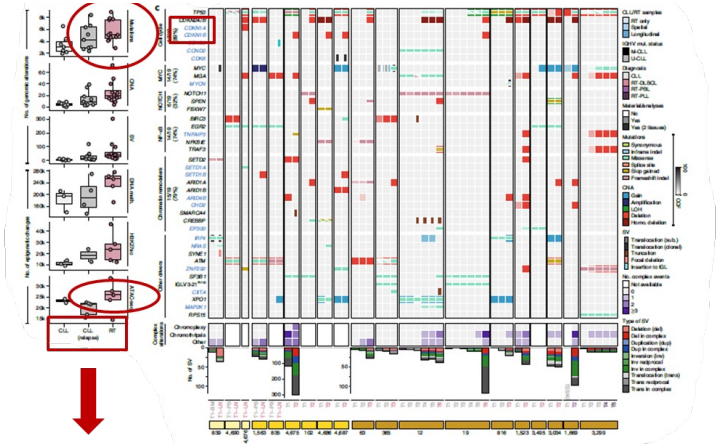
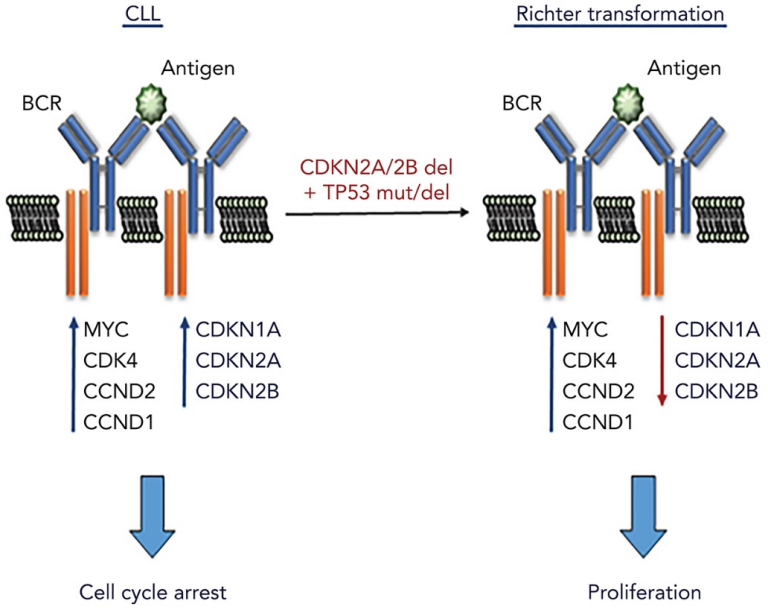
RT therapy

Genetic lesions in G1-phase cell-cycle regulators are the most frequent genetic aberrations in clonally related RT



New driver genes of RS transformation were identified, such as downregulation of CDKN1A and CDKN1B expression

Nadeu et al., Nat Med 2022



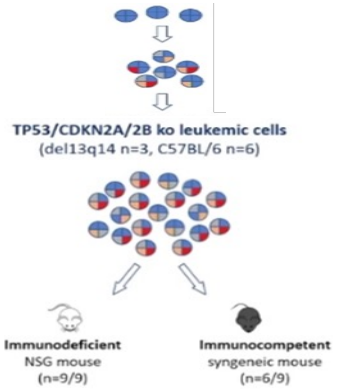
LOF mutations inTP53 and CDKN2A/CDKN2B lead to spontaneous leukemic cell proliferation *in vitro* and histological features of RT *in vivo*

TP53/CDKN2A/2B-ko cells require BCR signals for proliferation

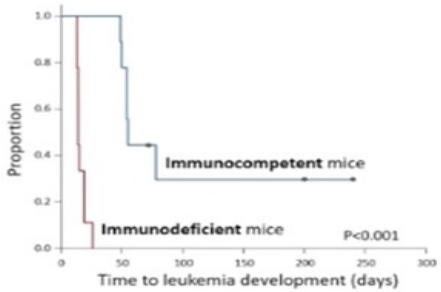
Chakraborty et al., Blood 2021

Driver LOF mutations in transformation of non leukemic B cells from mice with 13q14 deletion or normal B cells

TP53/CDKN2A/2B mutations



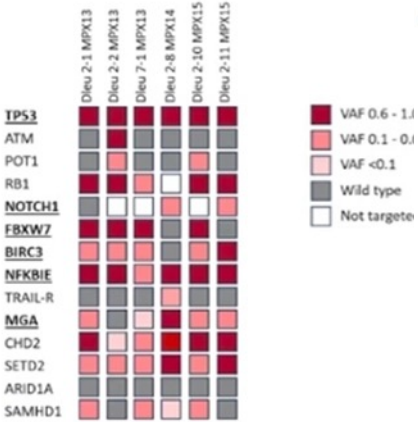
RT in 6/7 RT in 1/3

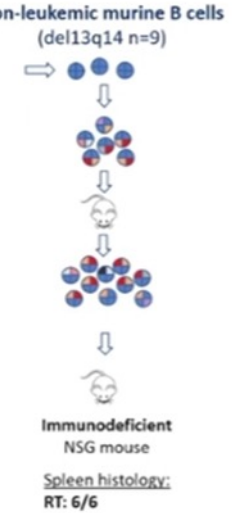


Transformed cells present:

- **Restricted IGHV repertoire**
- **Characterized by autoreactivity**
- **BCR dependance**

Other mutations





Transformed cells present:

- **different IGHV repertoire**
- **not self-reactivity**

Martines at al ASH 2024

Novelty in this study

1) Characterization of a specific CD5+ B-cell subset as target of transformation

- With a **restricted IGHV repertoire** ← strong antigenic selection
- Characterized by **autoreactivity** ← potential role of self-antigens in RT
- **BCR dependency** ← BCR as a therapeutic target

2) Proposal of a new model in RT pathogenesis integrating:

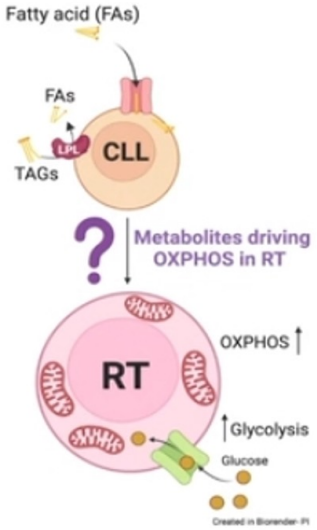
- **Mutations** → TP53 and CDKN2A/B disrupt cell cycle control and DNA damage responses.
- A combination of **autoreactivity and antigenic selection** drives the survival and expansion of the transformed cells
- **NB: TP53 + genetic lesions activating NOTCH1, MYC and NF-kB patways can also induce transformation, but with a different IGHV repertoire and not self-reactive**

3) Therapeutic Implications:

- **Blocking BCR signaling** could be particularly effective for RT
- **Combined strategies targeting both antigenic signaling and mutated pathways** (TP53/CDKN2A/B) might improve clinical outcomes.

Martines at al ASH 2024

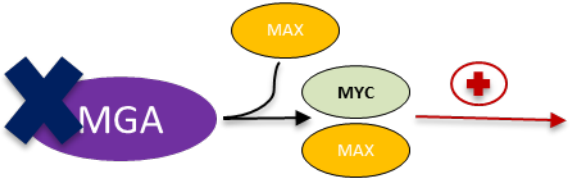
Metabolite changes from CLL to RT



Normal cells – MGA – growth arrest

Arrest growth

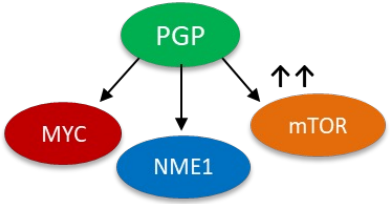
Tumor cells – MGA loss– Promote growth



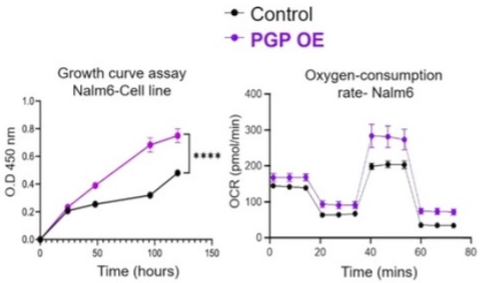
Promote growth

~30% RT
~3% CLL

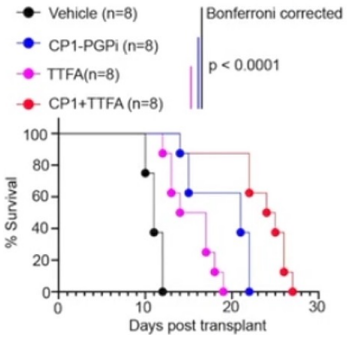
PGP
(Phosphoglycolate phosphatase) is upregulated in murine RT and cell lines with MGA deletion



PGP OE
↑ OXPHOS
and total
NADH-NAD+
levels



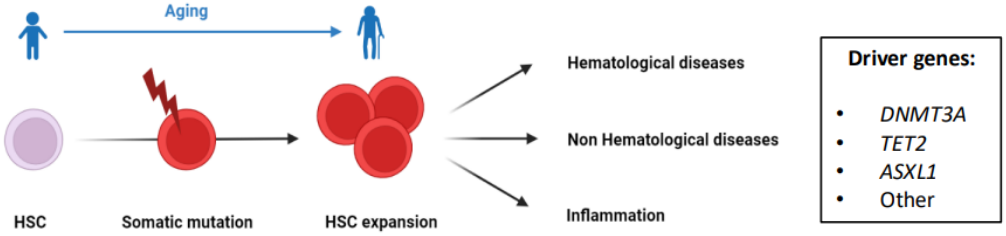
PGPi + OXPHOSi
affect MGAKO cells and
↓ NADH-NAD levels
improving mice survival



Iyer at al ASH 2024

Clinical impact of clonal hemopoiesis of indeterminate potential in RT

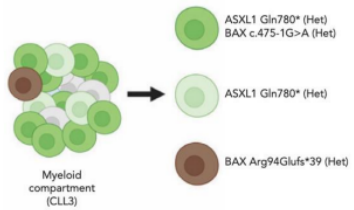
CHIP is an aging phenomenon resulting in the accumulation of somatic mutations in hematopoietic stem cells

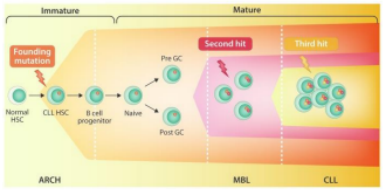


Driver genes:

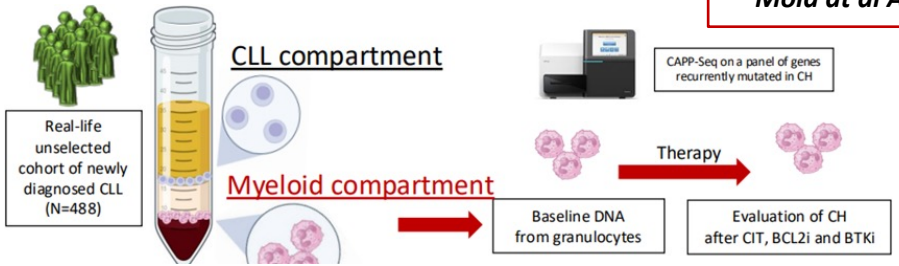
- *DNMT3A*
- *TET2*
- *ASXL1*
- Other

Potential interaction between CH and CLL





Moia at al ASH 2024



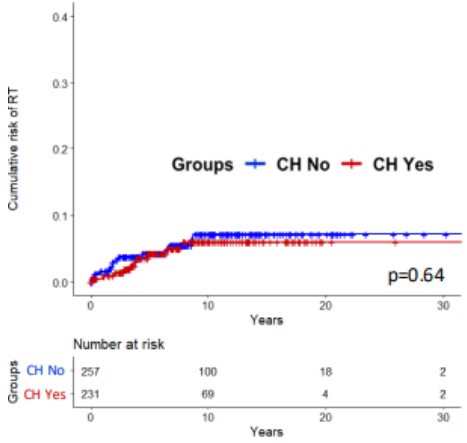
Correlation of CH with:

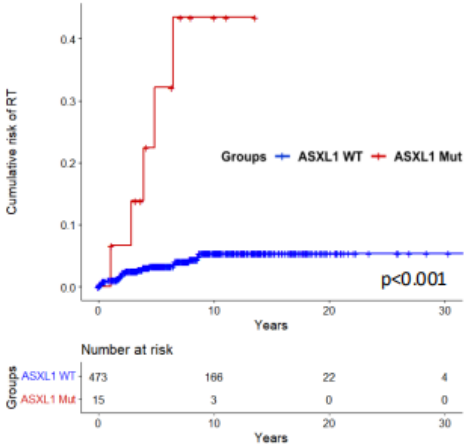
- CLL baseline characteristics
- Survival
- Richter transformation
- Therapy toxicities

- ❑ Most frequently mutated gene DNMT3A, then TET2 and ASXL1
- ❑ ASXL1 mutations associated with:
  - uIGHV
  - Multiple LN
  - AIHA

Jaiswal, NEGM 2014;
Blombery Blood 2022;
Agathangelidis Haematologica 2018;
Condoluci Haematologica 2018

ASXL1 mutations associate with higher risk of RT





Multivariate analysis for Richter Transformation

Variable	Hazard ratio	HR, 95% C.I.	P
NOTCH1 Mut		1.96 (0.56, 6.91)	0.29
TP53 Mut/Del		3.97 (1.27, 12.43)	0.02
ASXL1 Mut		6.80 (1.54, 30.14)	0.01

- CH 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

ASXL1 mutations may represent a novel biomarker of shorter time to RT

Moia at al ASH 2024

ASH 2024, RICHTER TRASFORMATION, AGENDA:

New drivers in RT and potential therapeutic targets

RT prognosis

RT therapy

A MULTI-CENTER RETROSPECTIVE STUDY ON COMPLEX KARYOTYPE IN PATIENTS WITH RICHTER TRANSFORMATION WHO RECEIVED NO CHEMOIMMUNOTHERAPY FOR THEIR CLL

- CK is an **adverse prognostic indicator in CLL**
- CK **at diagnosis** (exp major chromosome abnormalities) is associate with ↑ **risk of RT**
- R/R treated **with ibrutinib** CK and polyploidy are **independent predictors for RT**
- CK is common at transformation and high CK **associates with short survival in RT**

Aim:
To understand the **prognostic significance of CK in RT** treated with targeted agents and **not previously exposed to CIT**

Miller et al. ASH 2024

Pts and disease characteristics of CLL at CLL baseline, of CLL at the time of transformation and of RT

Baseline CLL pts and disease characteristics

N=64	
uIGHV	79.6%
Median prior CLL treatments	1 (1-5)
Prior tratments BTKi BCL2i Both	 59.4% 4.7% 26.6%

Pts and disease characteristics at RT

N=64	
Median age	65.8
ABC subtype	84.6%
Clonally related	96.6%
Ki67 % median	80%

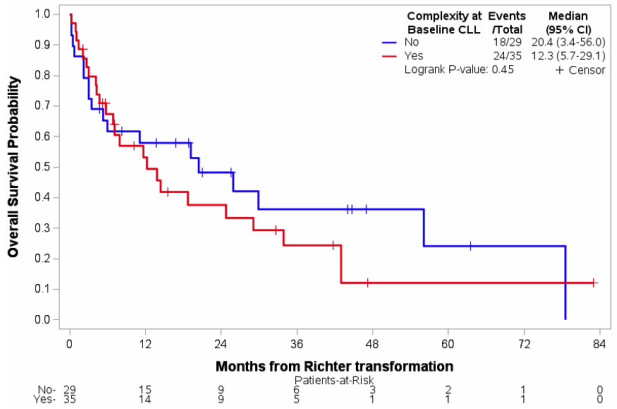
N of deaths: 42
Median FU 17.8 months

	At CLL baseline	CLL tissue at RT diagnosis	RT tissue
CLL CK	55%	79%	70%
Median N of abnormalities	3	8	8
CK2	97%	96%	92%
Polyploidy	6.3%	30%	33%
17p-/*TP53* mut	46%	52%	
Karyotype evolution		(from baseline) 74%	(from CLL tissue) 37.5%

Miller et al. ASH 2024

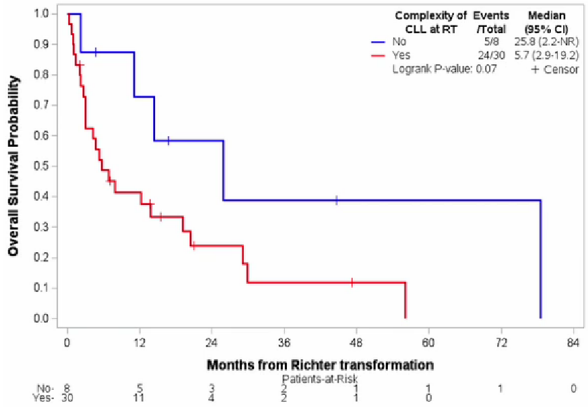
Survival according to complexity and karyotype evolution on CLL, CLL at transformation, and RT

CLL karyotype at CLL baseline



OS at RT
by complexity of CLL at baseline
P .45

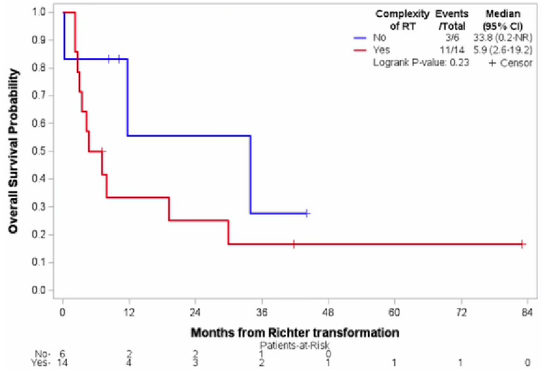
CLL karyotype at RT



OS at RT
by CLL Karyotype evolution from baseline at RT
p .05

RT karyotype

OS at RT
by complexity of RT tissue
P .03



- ✓ **Worse OS in increased complexity at RT in pts not treated with CIT**
- ✓ **Clinical utility of karyotype evaluation in the modern era**

Miller et al. ASH 2024

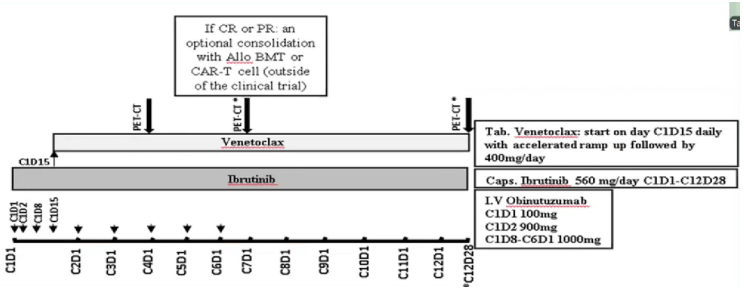
ASH 2024, RICHTER TRASFORMATION, AGENDA:

New drivers in RT and potential therapeutic targets

RT prognosis

RT therapy

Phase II prospective trial of FD obinutuzumab, ibrutinib and venetoclax in elderly pts with RT



12 pts
M age 78 yrs
67% TN

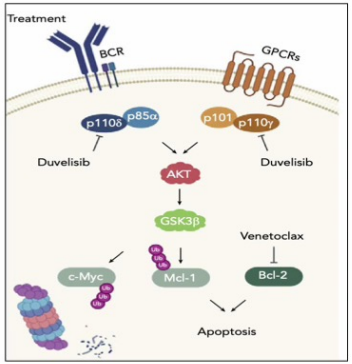
<u>10 evaluable for response</u>:
3 mo **ORR 70% (CRR 40%)**
6 mo ORR 37.5% (CRR 25%)

median PFS 4.4 months
median OS 7.8 months

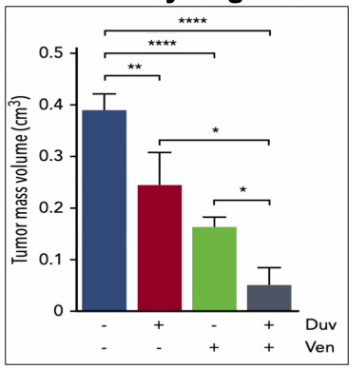
Tadmor et al. ASH 2024

Phase II prospective trial of duvelisib and venetoclax in CLL and RT

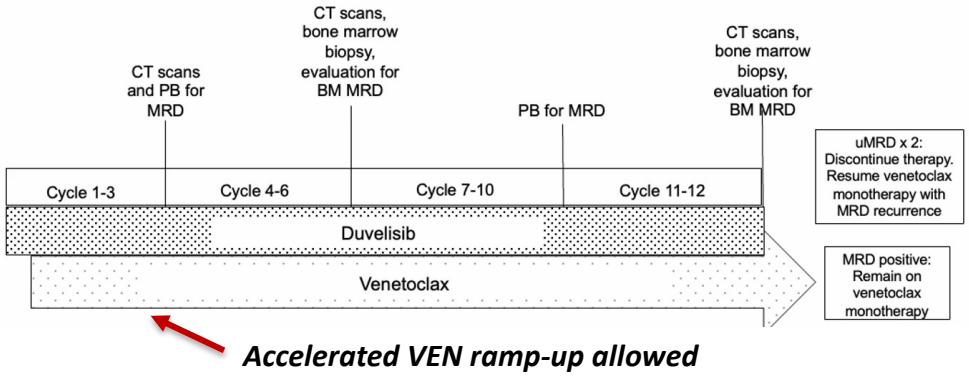
Mechanism of VEN + DUV



VEN + DUV Synergistic in RS



Davids Blood 2012; Patel Leukemia 2017; Iannello Blood 2021



Accelerated VEN ramp-up allowed

Key inclusion:

- TN and RR for RT
- <1 year of venetoclax, no prior DUV

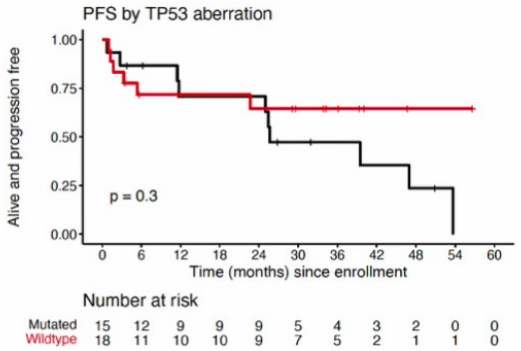
Characteristic	RS Cohort (n=9)
Median age (range, years)	64 (55-72)
Male	7 (77.8%)
Rai Stage 3 or 4	N/A
IGHV Status Unmutated	4 (44.4%)
ZAP-70 Positive	3 (33.3%)
FISH Cytogenetics	
17p deletion	1 (11.1%)
11q deletion	0
Trisomy 12	2 (25.0%)
Complex karyotype*	3 (33.3%)
TP53 Mutation	2 (22.2%)
NOTCH1 Mutation	3 (33.3%)
Median # of prior therapies (range)	2 (1-4)
Prior BTK inhibitor (BTKi)	3 (33.3%)

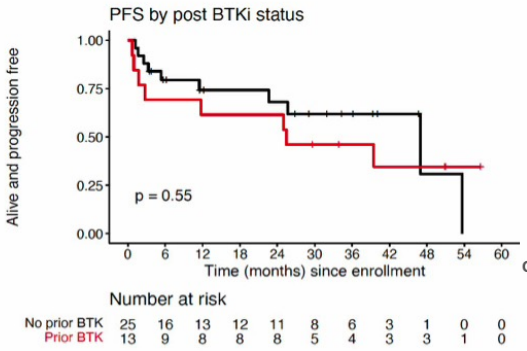
Crombie et al. ASH 2024

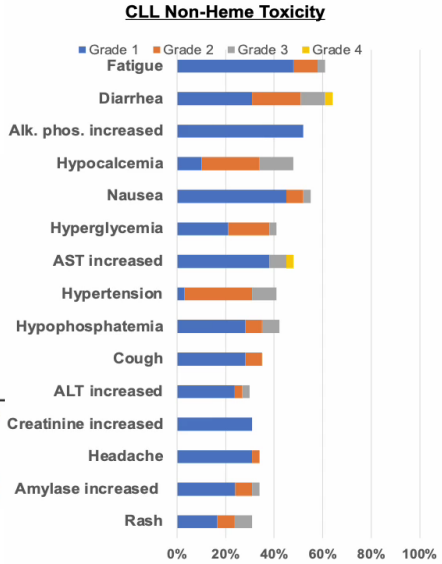
Phase II prospective trial of duvelisib and venetoclax in CLL and RT

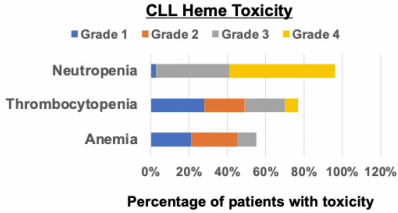
3/9 CR in RT → 1 CR proceeding to alloSCT

All pts









Crombie et al. ASH 2024

Outcomes of therapies following Non-covalent BTKi for patients with RT

Median treatment prior to ncBTKi (whole CLL+RT population): 4

Prior treatment	RT patients (n=32)
CIT	84.4%
cBTKi	87.5%
venetoclax	53.1%

- **ORR to ncBTKi**: 31.3%
- **Median duration of ncBTKi exposure**: 3 months
- **Reasons for ncBTKi dc**
  - PD 75%
  - SCT 3.1%
  - CAR-T 3.1%

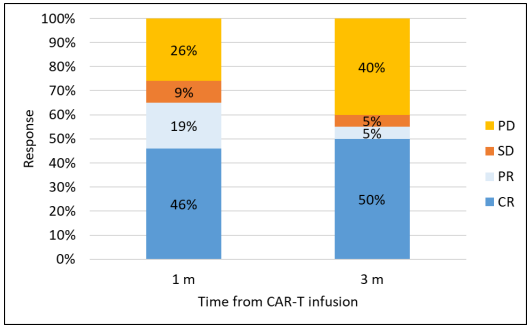
THERAPY	# PTS	OVERALL RESPONSE RATE[1]
CAR T-cell therapy	10	66.7% (CR 6, PR 1, PD 2, uk 1)
CIT	10	11.1% (CR 1, SD 1, PD 7, uk 1)
Stem cell transplant	2	100% (CR 2)
Other treatment or unknown	16	

- **13 pts received 2 treatments post ncBTKi**
- **m PFS at first tx post ncBTKi: 2 months**

Thompson et al. ASH 2024

CD19 CAR-T Cell Therapy in Richter Transformation

	N=54
Age at CAR T	63 y
Prior lines for CLL	2
Prior BTKi	67%
Prior Bcl2	44%
Prior lines for RT	2
Bridging therapy	67%
Disease status pre CAR T	
CR	19%
PR	23%
Stable	9%
Progressive	49%
ECOG PS ≥2	
CAR T product	
Tisagenlecleucel	37%
Acicabtagene ciloleucel	7%
Lisocabtagene maraleucel	2%
Academic	54%



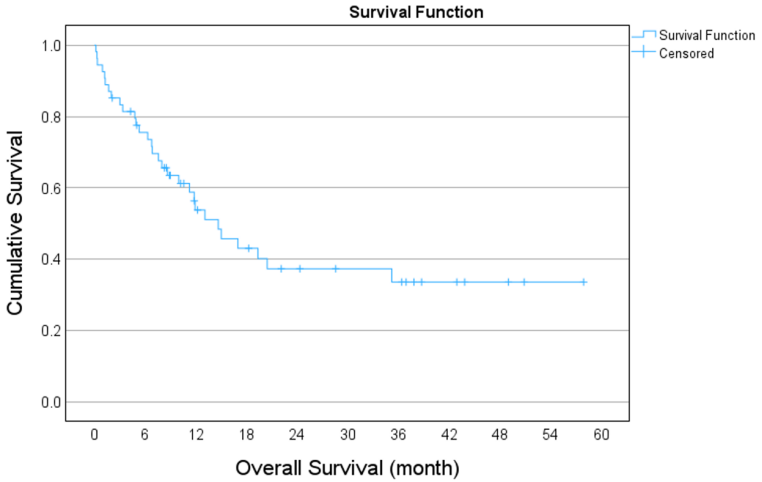
ORR:
1 mo 65%
3 mo 55%

CRS 87% → 86% G1-2
ICANS 22% → 42% G3-4
Infections 41%

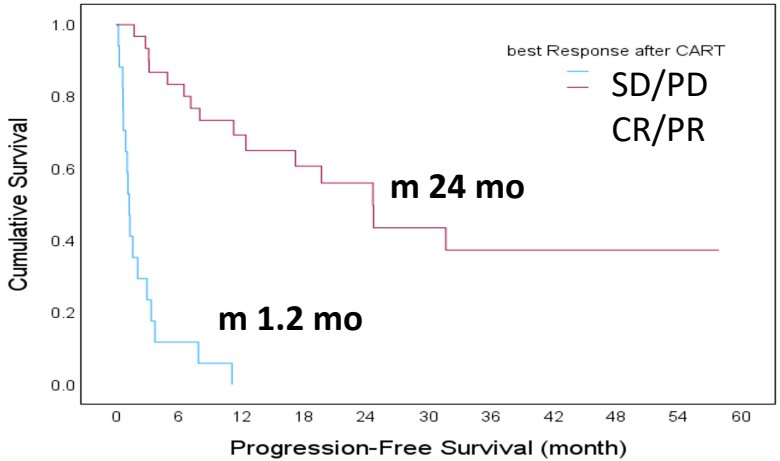
Beyar-Katz et al. ASH 2024

CD19 CAR-T Cell Therapy in Richter Transformation

median OS 14.4 months



PFS at 6 and 12 months 56% and 41%



Mortality independently associated to:
no response to CAR T and ICANS development

Beyar-Katz et al. ASH 2024

ASH 2024, Richter Transformation: key messages

- **New insight from basic research**:
  - characterization of a specific CD5+ B-cell subset as target of transformation and proposal of a new model for RT pathogenesis
  - PGA and OXPHOS inhibition as a possible future therapeutic target

- **Prognostic value of CK (complexity and evolution) for RT even in the modern chemo-free era**

- **Despite improving responses with novel combinations, survival remains poor**
  - Encorauging responses and survival with CD19 CAR T