XIX CONGRESSO NAZIONALE SIES 2026

FONDAZIONE ITALIANA LINFOMI

Emopoiesi Clonale nel Linfoma Follicolare: Analisi Dello Studio di Fase III FIL FOLL12

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Palazzo degli Affari

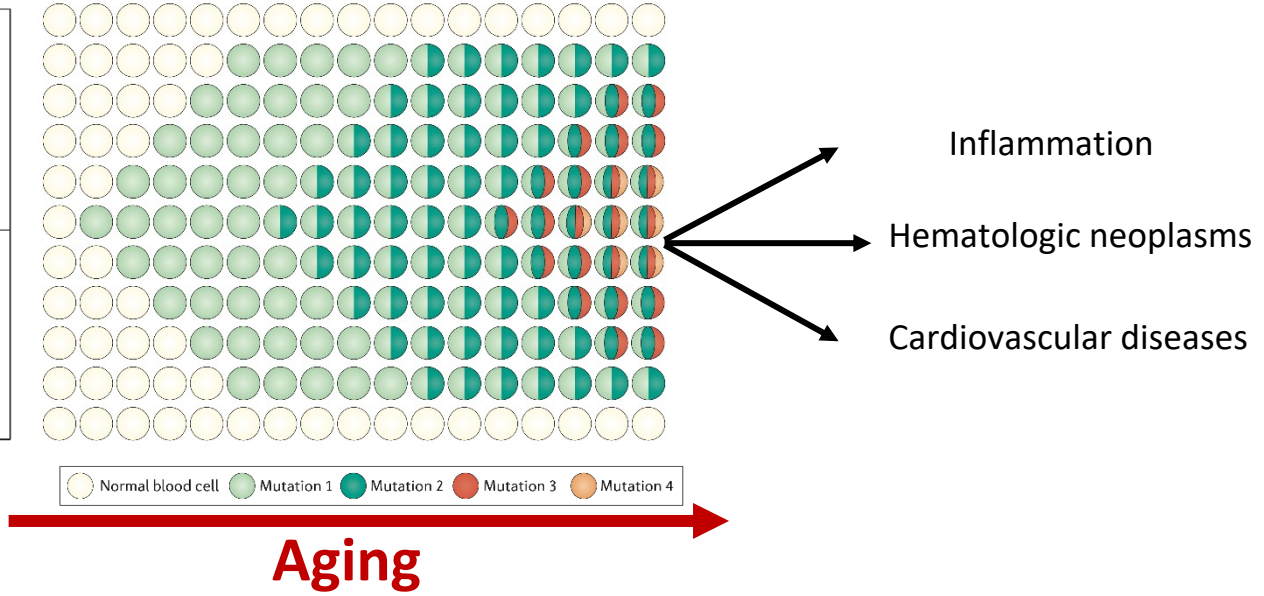
Disclosures of Nawar Maher

Company name	Research support	Employee	Consultant	Stockholder	Speakers bureau	Advisory board	Other
No disclosures							

Clonal hematopoiesis

Clonal hematopoiesis (CH) is an aging-related phenomenon resulting in the accumulation of somatic mutations in hematopoietic stem cells.

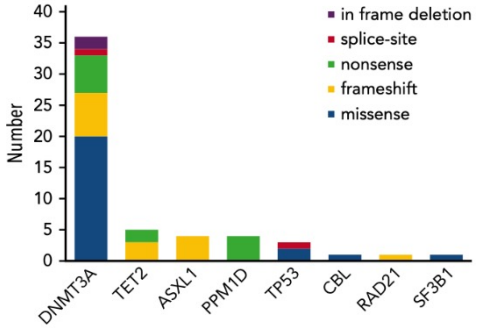
Gene expression regulation	*D*NA *d*amage *r*esponse
DTA: *DNMT3A* *TET2* *ASXL1*	**DDR:** *TP53* *PPM1D* *CHEK2* *RAD21*
Signaling pathways	Splicing
JAK2 *CBL* *GNB1*	*SRSF2* *SF3B1* *U2AF1*

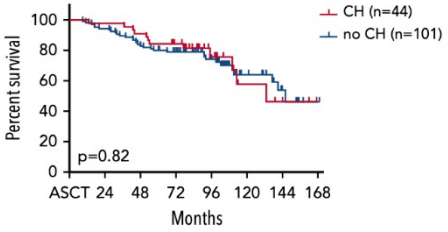


Challen *et al., Blood*. 2020; Jaiswal *et al., N Engl J Med*. 2014

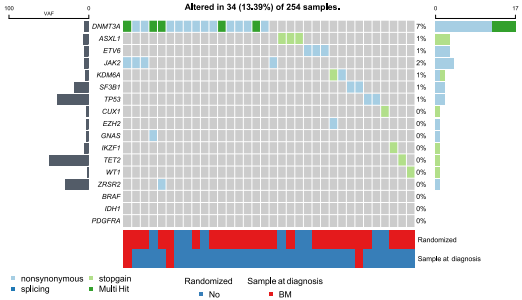
CH in patients with B-cell lymphoma

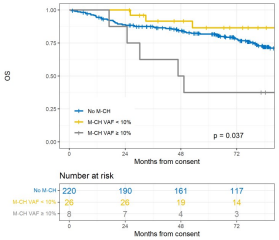
Newly diagnosed MCL patients
(N=149)
CHIP in 30.0% of cases



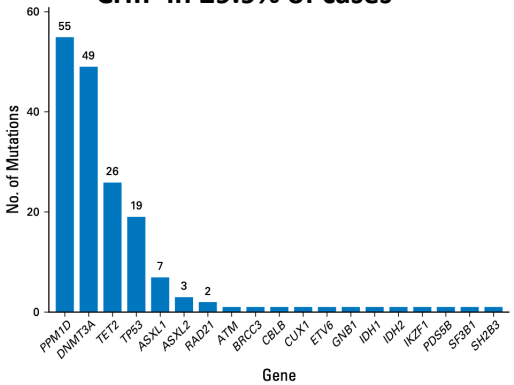


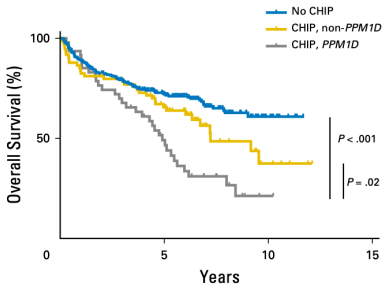
Newly diagnosed MCL patients
in the FIL MCL0208 trial
(N=254)
CHIP in 13.4% of cases



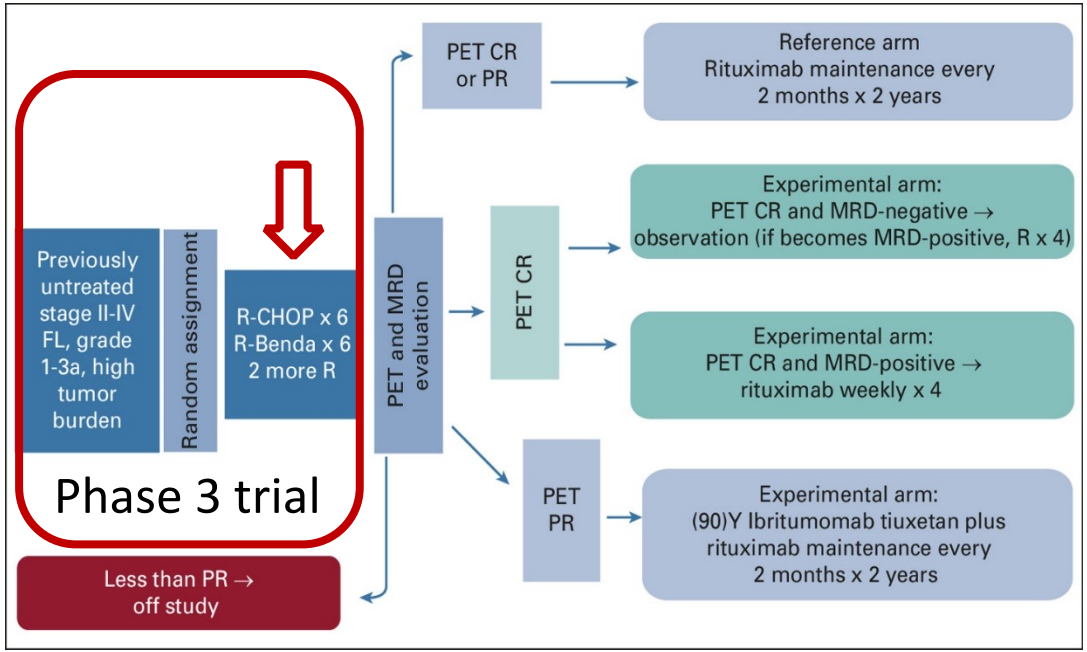


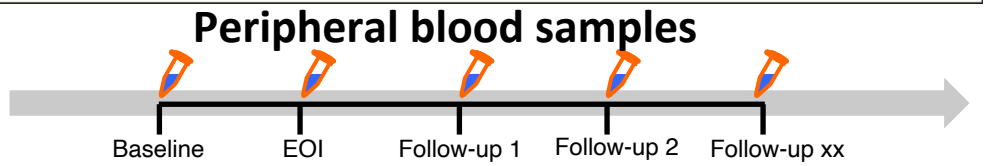
R/R B-cell lymphomas before ASCT
(N=120)
CHIP in 29.9% of cases





FIL FOLL12 Trial

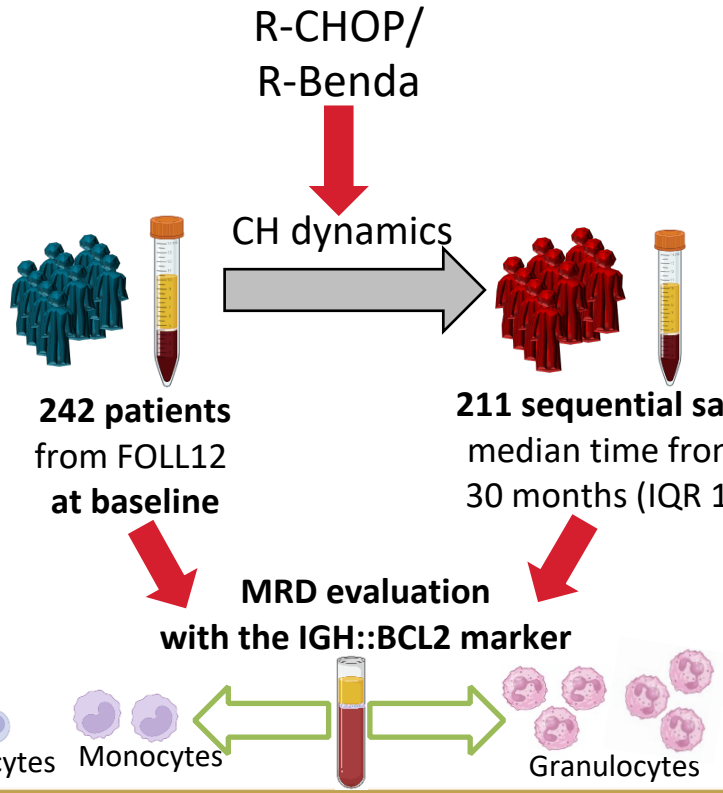




Aims of the study

- To define the prevalence of CH in newly diagnosed FL patients
- To assess the prognostic impact of CH in terms of PFS and OS
- To evaluate whether CH predisposes to a higher frequency of therapy-related toxicities
- To monitor the evolutionary trajectories of CH before and after chemo-immunotherapy

Study design



Targeted Next Generation Sequencing (NGS)

Genes	Exons
ASXL1	12
BRCC3	All exons
CALR	9
CBL	8.9
CHEK2	All exons
CUX1	All exons
DNMT3A	All exons
GNAS	8.9
GNB1	5.6
IDH1	4
IDH2	4
JAK2	12.14
JAK3	13
KDM6A	14

Genes	Exons
KRAS	2.3
MPL	10
NRAS	2.3
PIGA	From 3 to 5
PPM1D	5.6
PTPN11	3.13
RAD21	All exons
RUNX1	All exons
SF3B1	From 13 to 16
SOCS1	All exons
SRSF2	1
TET2	From 3 to 11
TP53	From 2 to 11
U2AF1	2.6

Target region size: 29710 bp

- A CAPP-Seq panel of 28 genes frequently mutated in CH has been used
- CH datasets have been used for comparative purposes (Vlasschaert *et al., Blood*. 2023; Niroula *et al., Nat Med*. 2021)
- A VAF ≥ 1% was set for variant calling

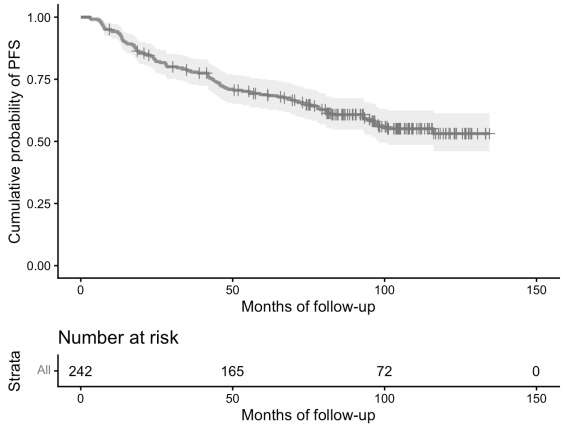
Patient characteristics

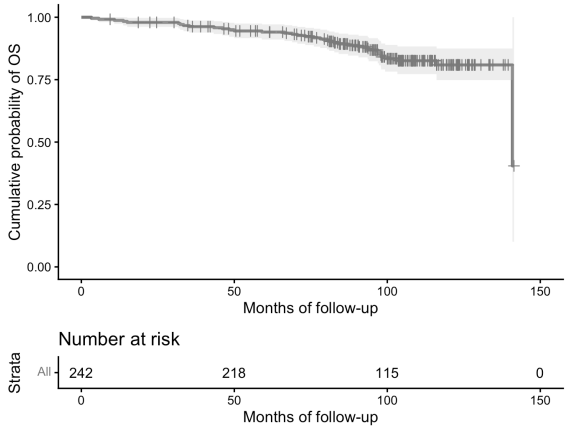
Characteristic		Value No. (%)
Age (years)	median	61.5
	range	51.7-69.0
Gender	male	116 (47.9)
	female	126 (52.1)
Ann Arbor stage	II	29 (12.0)
	III	45 (18.7)
	IV	167 (69.3)
B symptoms	No	207 (85.9)
	Yes	34 (14.1)
β2M	≤ULN	117 (48.3)
	>ULN	125 (51.7)
Grading	grade 1	40 (19.4)
	grade 2	116 (56.3)
	grade 3A	50 (24.3)
Hb	≥12 g/dl	203 (83.9)
	<12 g/dl	39 (16.1)
LDH	≤ULN	176 (75.9)
	>ULN	56 (24.1)
Nodal sites	0-4	151 (63.2)
	>4	88 (36.8)
FLIPI	0-1	59 (25.7)
	2	88 (38.3)
	3-5	83 (36.1)
FLIPI2	1-2	146 (60.3)
	3-5	96 (39.7)
Treatment	R-CHOP	141 (58.3)
	R-Benda	101 (41.7)

8-year PFS: 54.8%

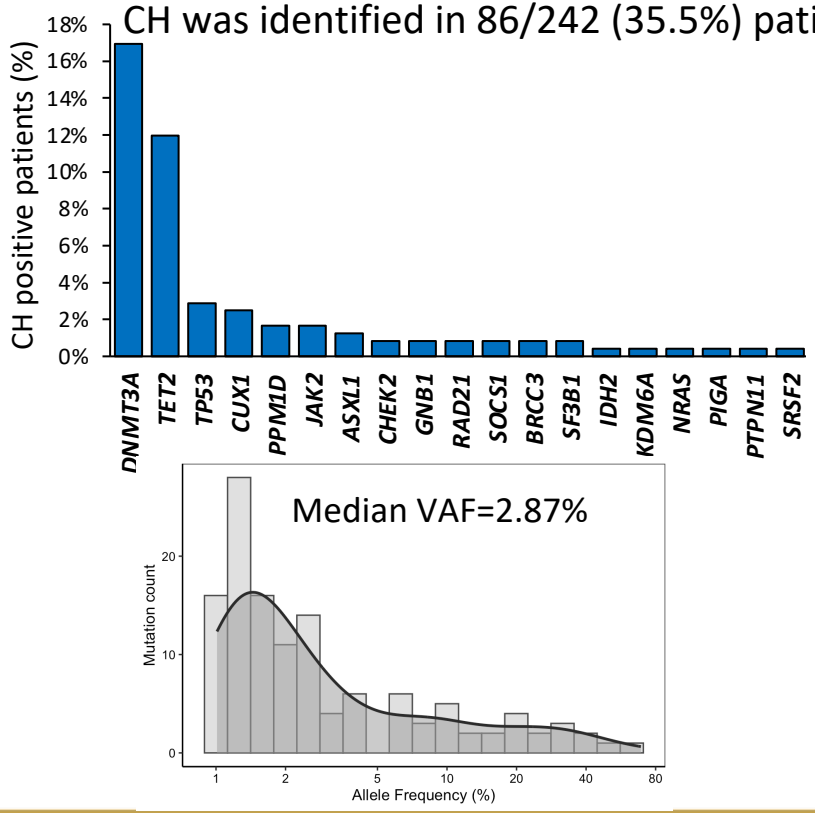
8-year OS: 86.2%

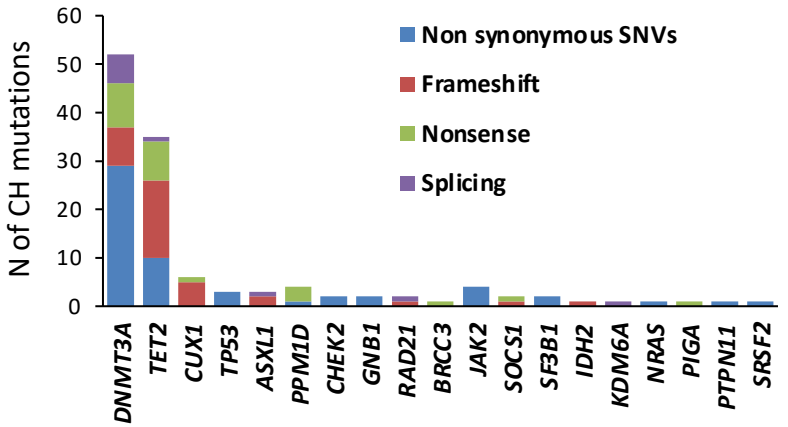
Median follow-up: 98 months





CH prevalence in the studied cohort





	MRD >10^{-3}	MRD ≤10^{-3}	p-value
CH No	32 (56.1%)	37 (58.7%)	0.774
CH Yes	25 (43.9%)	26 (41.3%)	
TP53 wt	54 (94.7%)	62 (98.4%)	0.263
TP53 mut	3 (5.3%)	1 (1.6.0%)	

No significant association between MRD at baseline and CH

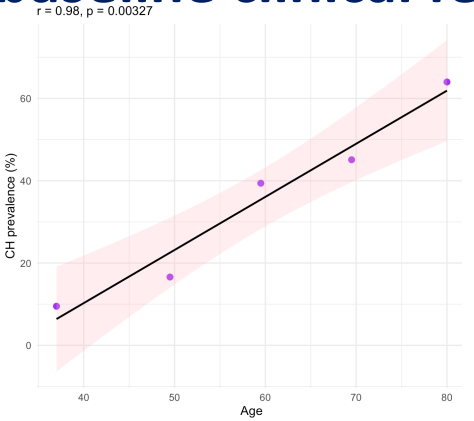
CH correlates with age but not with other baseline clinical features

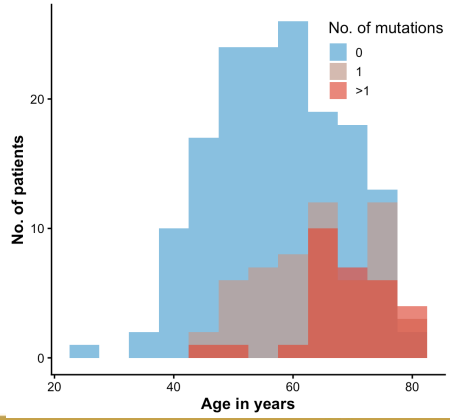
	CH Yes
Age ≥65	
Gender	
Higher grading	
B symptoms	
Higher AA stage	
ECOG PS	
Bone marrow infiltration	
B2M high	
Lymph nodes >6cm	
Lymph node area >4	
FLIPI	
FLIPI2	
MRD positivity EOI	
PET positivity EOI	
Complete response	

Colour scale of -log10 (p)

Positive Correlation

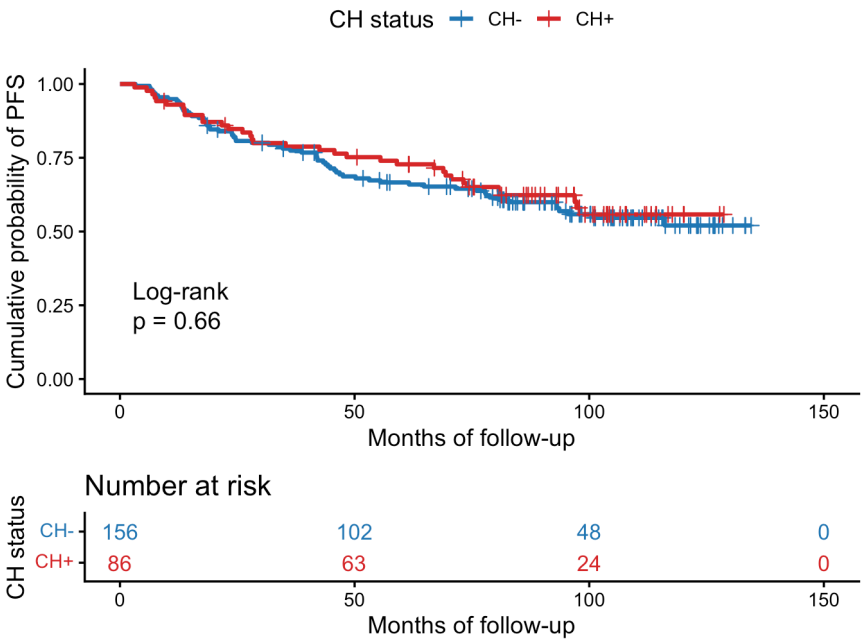
1.4 2 3



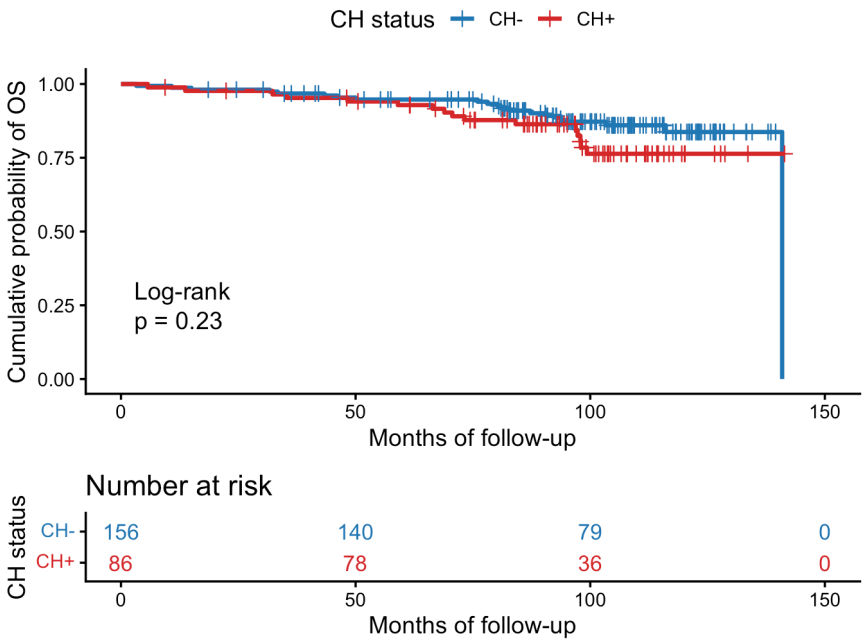


CH at trial enrolment does not impact on PFS and OS

PFS

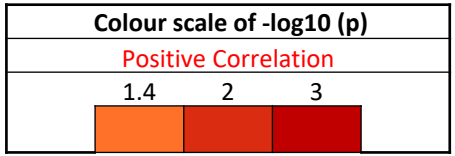


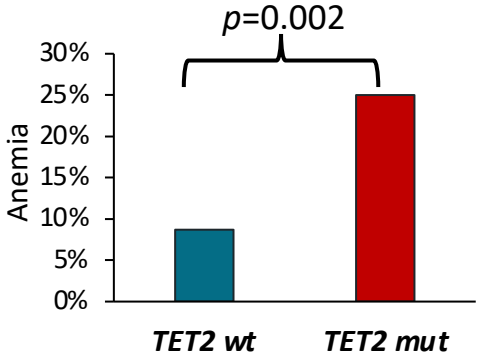
OS

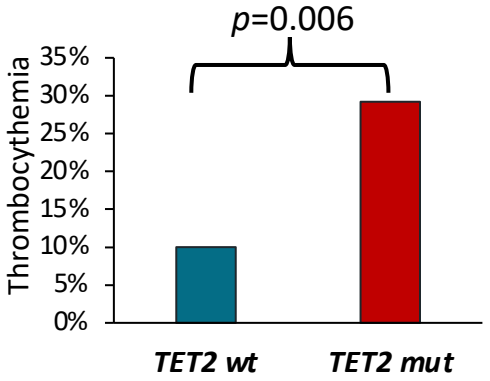


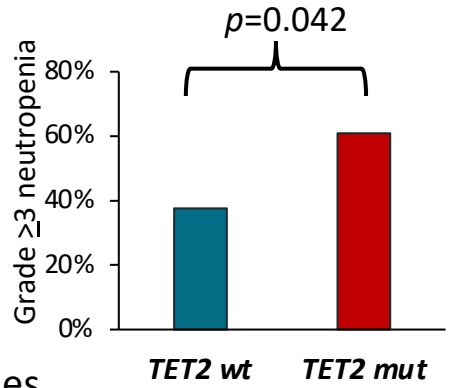
CH associates with short and long-term toxicities

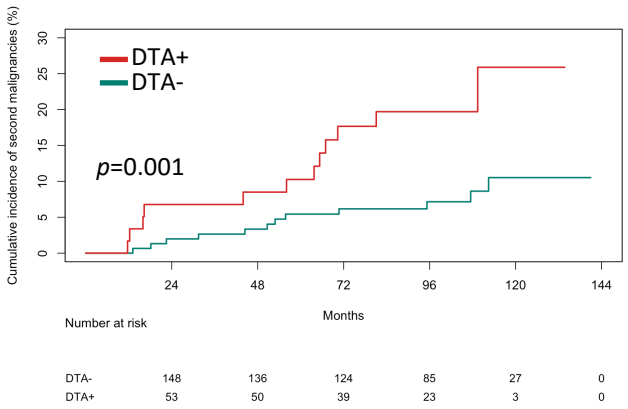
	CH	DNMT3A	TET2	TET2 + DNMT3A
Hematological toxicity				
Anemia				
Thrombocitemia				
Neutropenia grade ≥3				
Kidney toxicity				
Cardiological toxicity				
Vascular toxicity				
Gastrointestinal toxicity				
Respiratory toxicity				





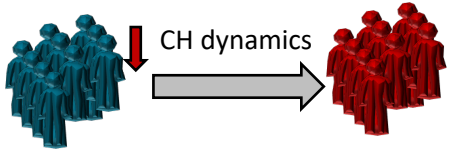




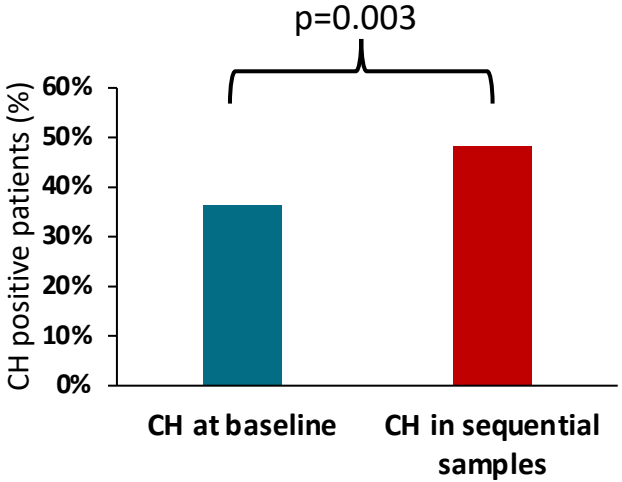


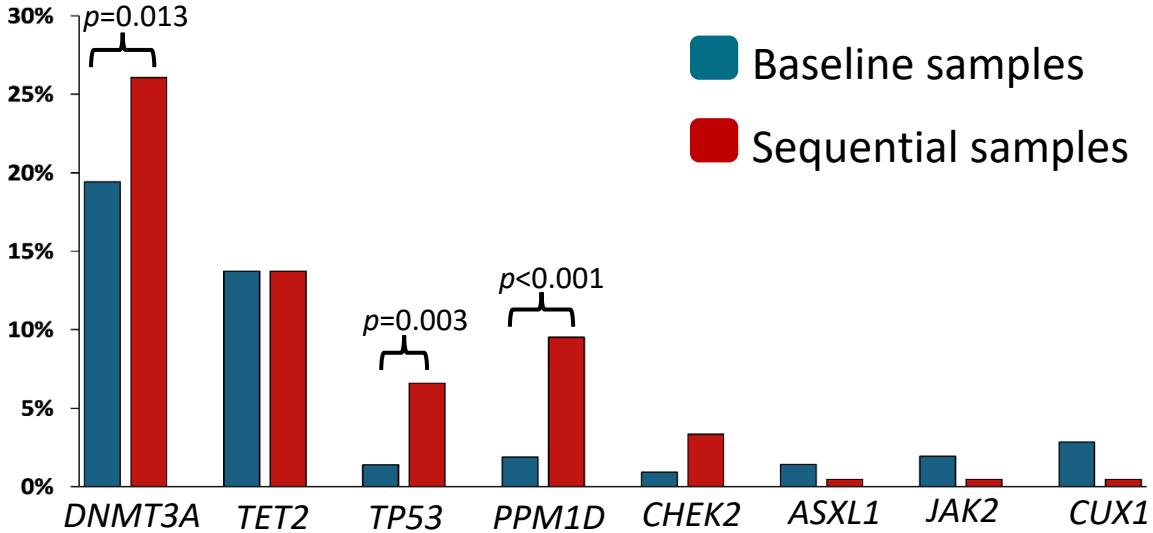
- *TET2* mutations associate with anemia, thrombocythemia, and grade ≥3 neutropenia
- Baseline DTA mutations associate with increased risk of second primary malignancies

Chemo-immunotherapy shapes the CH landscape

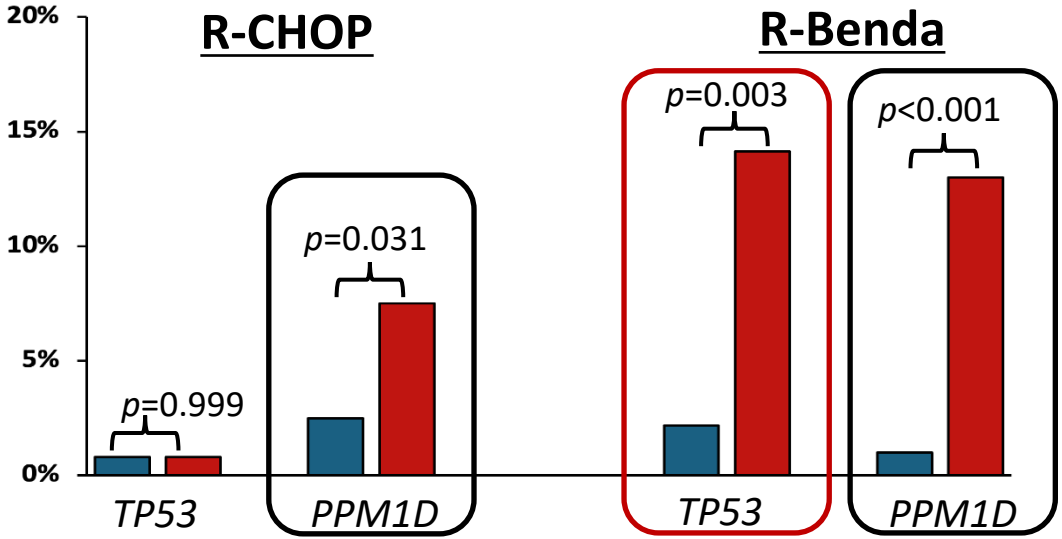


211 sequential patients
median time from CIT:
30 months (IQR 12-36)





R-CHOP and R-Benda differentially expand CH



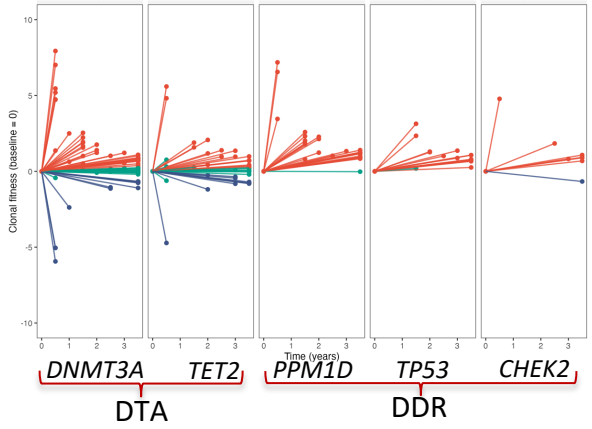
- Both R-CHOP and R-Benda drive *PPM1D* clonal expansion
- R-Benda selectively drives *TP53* clonal expansion
- All patients who acquired *TP53* mutations were MRD-negative at the time of sequential CH analysis

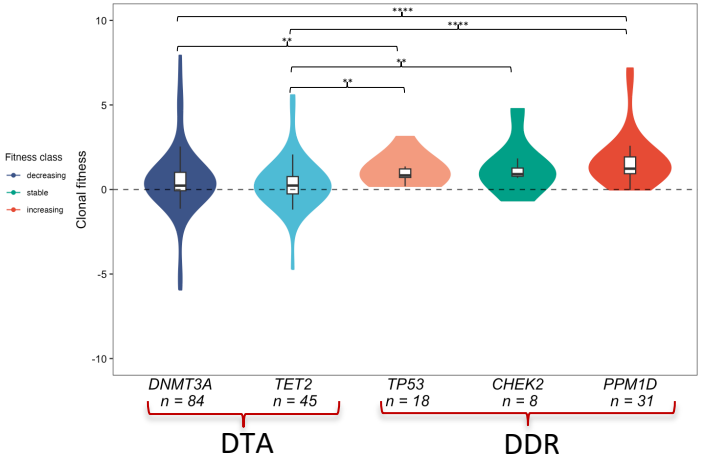
Clonal fitness landscape in sequential samples

Clonal finess estimation
Estimated clonal fitness (s, per year) using weighted regression on logit-transformed VAF over time.

$$v(t) = \frac{1}{2}\frac{1}{1 + Ae^{-st}}$$

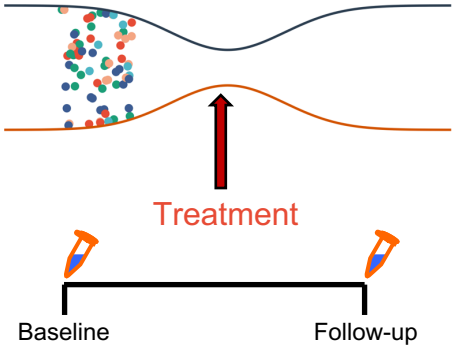
Classification
- ↑ **Increasing** s > +0.25 / yr
- ▬ **Stable** 95% CI of s includes 0
- ↓ **Decreasing** s < -0.25 / yr

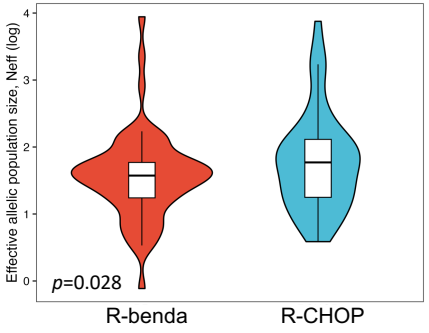


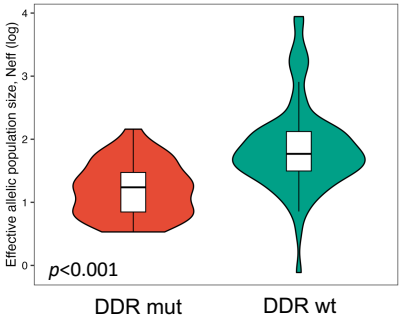


Bottleneck effect

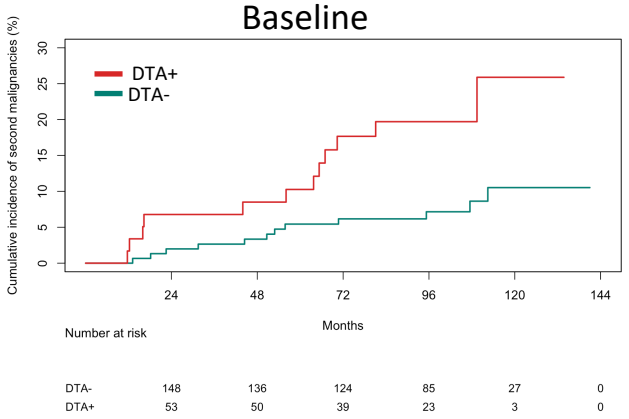
$$N_{\text{eff}} = \frac{k}{2\sum_i^s KL(f_2|f_1)}$$

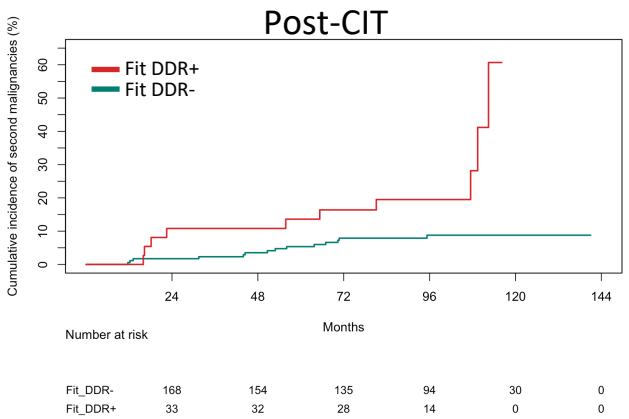


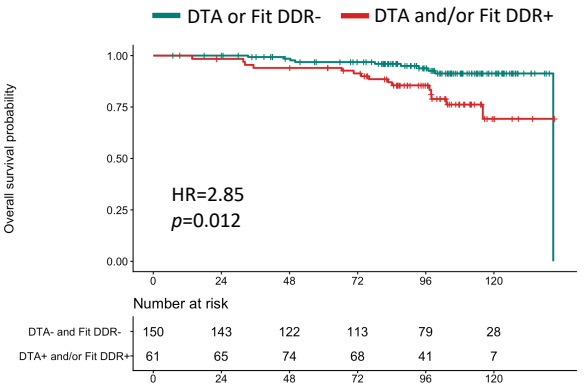




The impact of DDR mutations on the development of second primary malignancies (SPM)







Variable		N	Hazard Ratio	p-value
Fit_DDR	No	174	Reference	
	Yes	37	2.63 (1.07, 6.50)	0.0354
DTA	No	152	Reference	
	Yes	59	2.32 (1.01, 5.32)	0.0461
Age	<65	128	Reference	
	≥65	83	1.85 (0.77, 4.48)	0.1711
Treatment	R-CHOP	119	Reference	
	R-benda	92	0.97 (0.42, 2.24)	0.9477

- Baseline DTA and post-treatment fit DDR mutations independently associate with increased risk of SPM
- Patients with DTA or post-treatment fit DDR mutations have inferior OS in FL

Conclusions

- CH is common in newly diagnosed FL
- CH *TET2* mutations associate with a higher risk of hematological toxicities
- R-Benda, compared to R-CHOP, imposes a higher bottleneck on CH clonal expansion of DDR genes
- Patients harboring baseline DTA or post-treatment fit DDR mutations have an increased risk of second primary malignancies
- CH may serve as a potential biomarker to prioritize FL patients to chemo-free approaches, sparing unnecessary CIT-related adverse events

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