CLONAL HEMATOPOIESIS IN FOLLICULAR LYMPHOMA: ANALYSIS OF THE PHASE III FIL FOLL12 TRIAL

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Introduction

- Clonal hematopoiesis (CH) is an aging-related accumulation of somatic mutations in hematopoietic stem cells
- The impact of CH in newly diagnosed follicular lymphoma (FL) has not been evaluated yet

Aim

- To analyse the prevalence of CH in patients affected by FL in the prospective phase III FIL FOLL 12 trial
- Evaluate the potential prognostic impact of CH in terms of PFS and OS
- Assess the role of CH in terms of therapy-related toxicities in FL patients
- Monitor CH dynamics during chemoimmunotherapy (CIT)

Methods

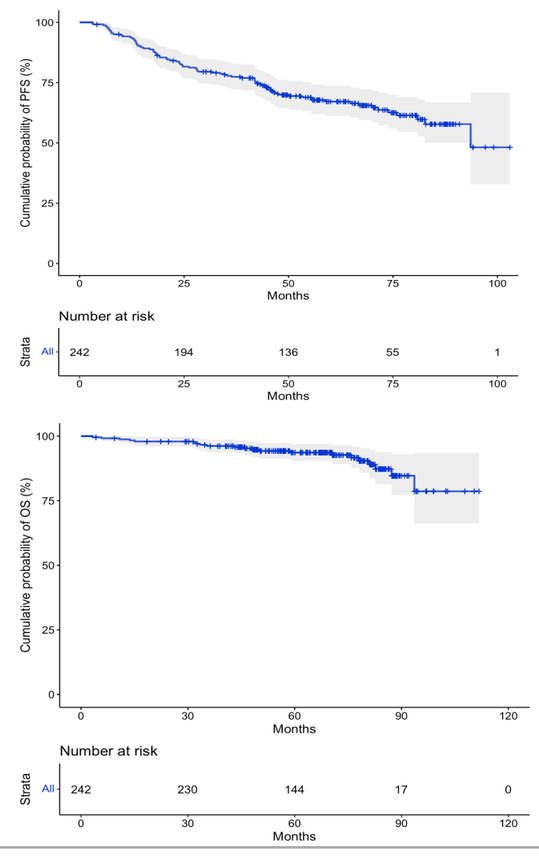
- Analysis of clinical characteristics and outcomes was conducted on 242 FL patients enrolled in the FIL FOLL12 trial, randomizing newly diagnosed FL to receive R-CHOP or R-Benda
- Baseline samples were available for all patients, and for 211 patients post-CIT
- CH was assessed through CAPP-seq on whole peripheral blood using a panel of 28 genes. A VAF of 1% was set for variant calling

Results

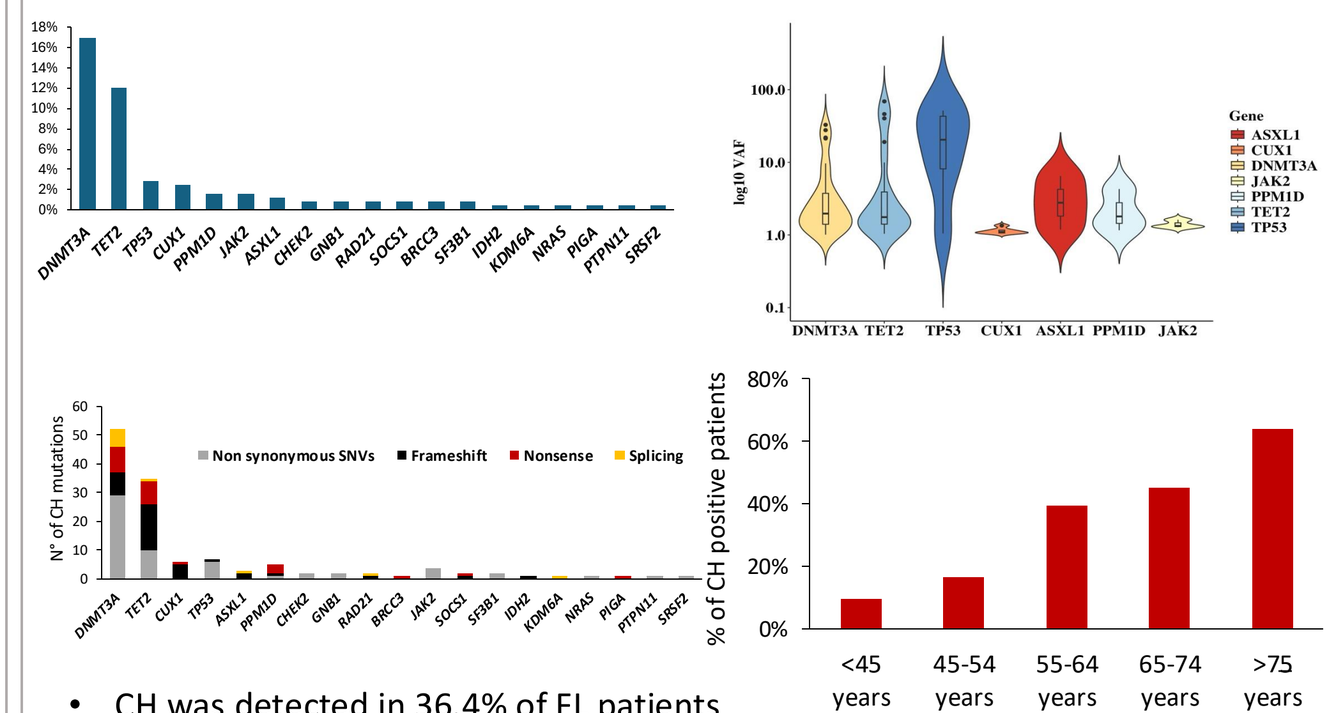
1. PATIENT CHARACTERISTICS

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)

Median follow-up: 72 months

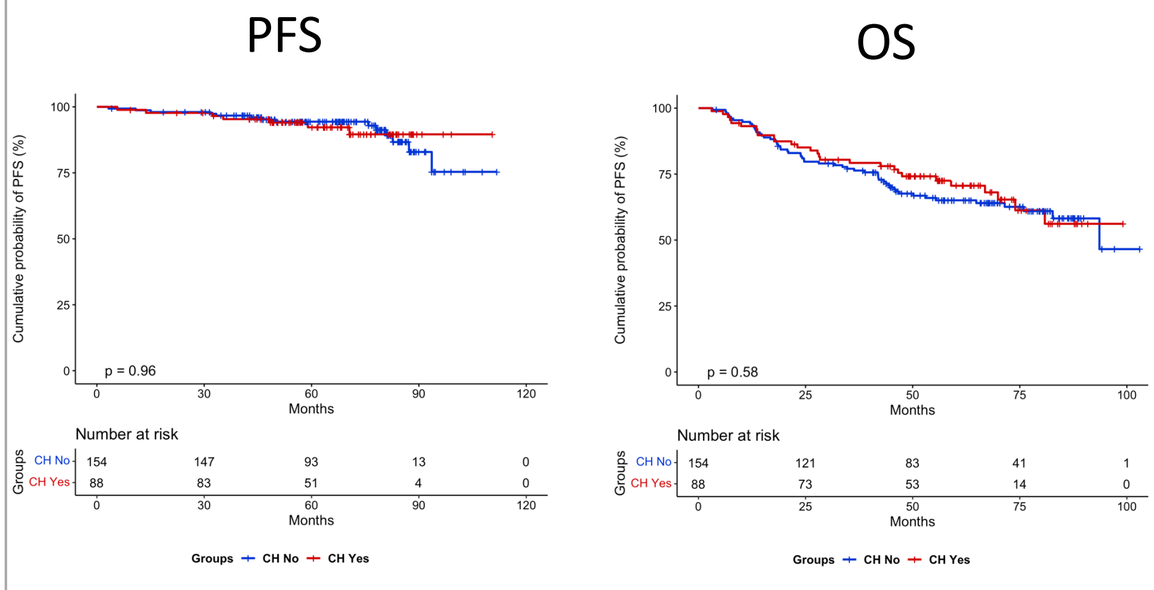


2. CH IN FOLLICULAR LYMPHOMA

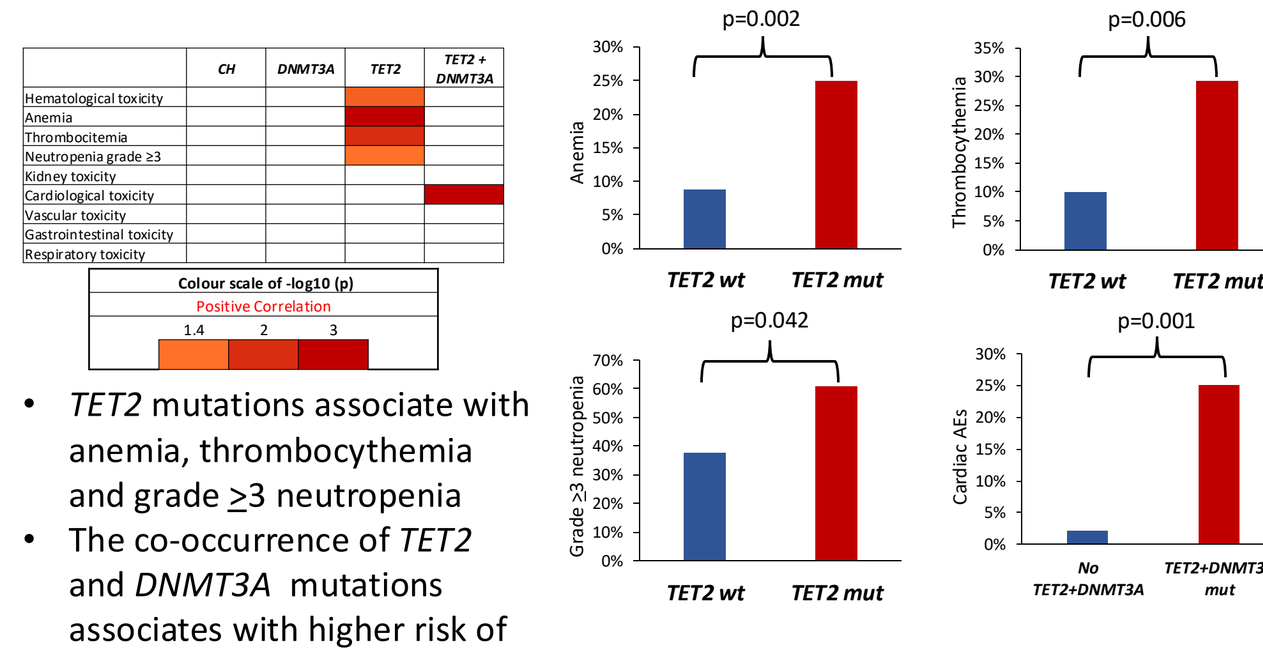


- CH was detected in 36.4% of FL patients
- The most frequent mutated genes were *DNMT3A* and *TET2*
- CH$^+$ patients had a significantly higher age compared to CH$^-$ cases

3. CH DOES NOT INFLUENCE FL CLINICAL OUTCOMES

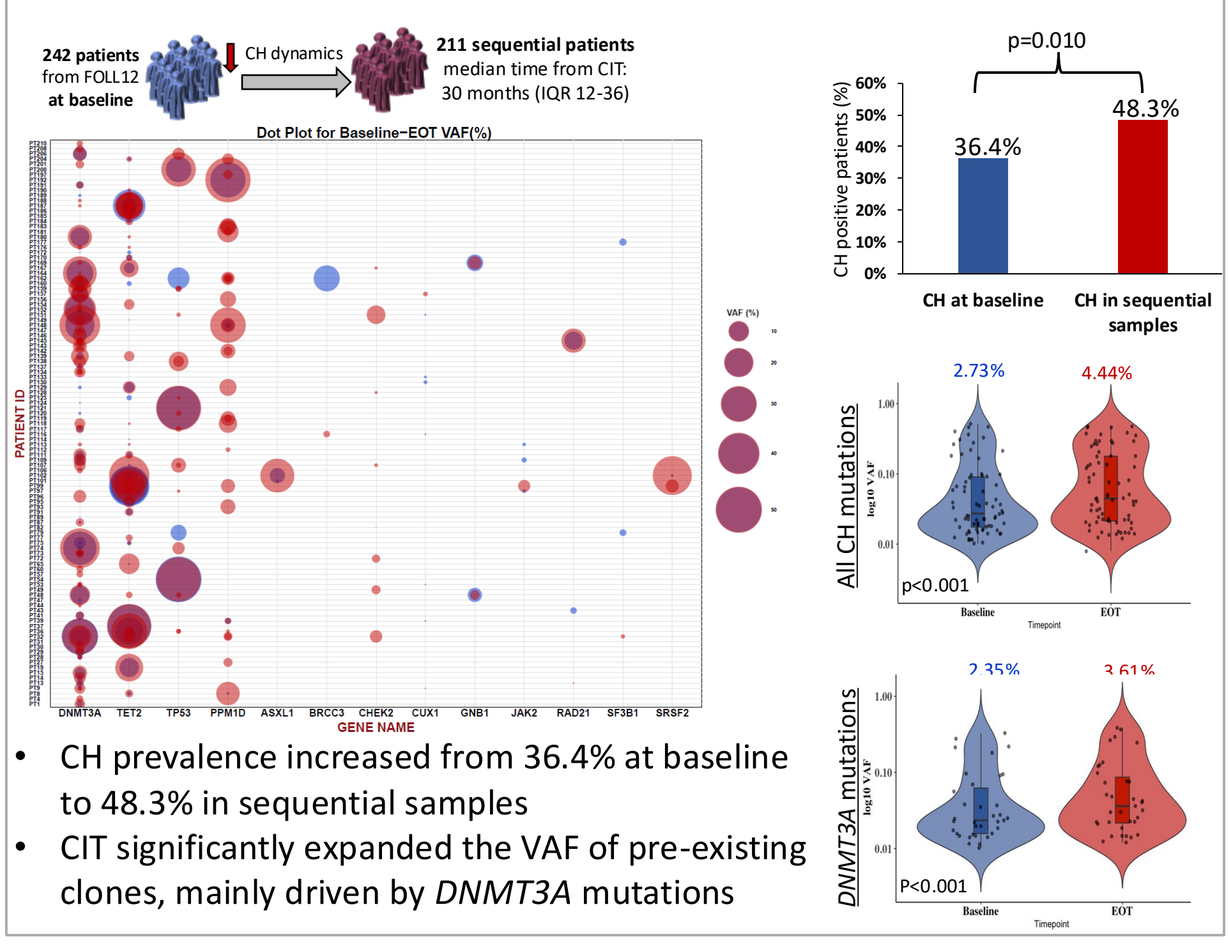


4. CH IS ASSOCIATED WITH THERAPY-RELATED TOXICITIES



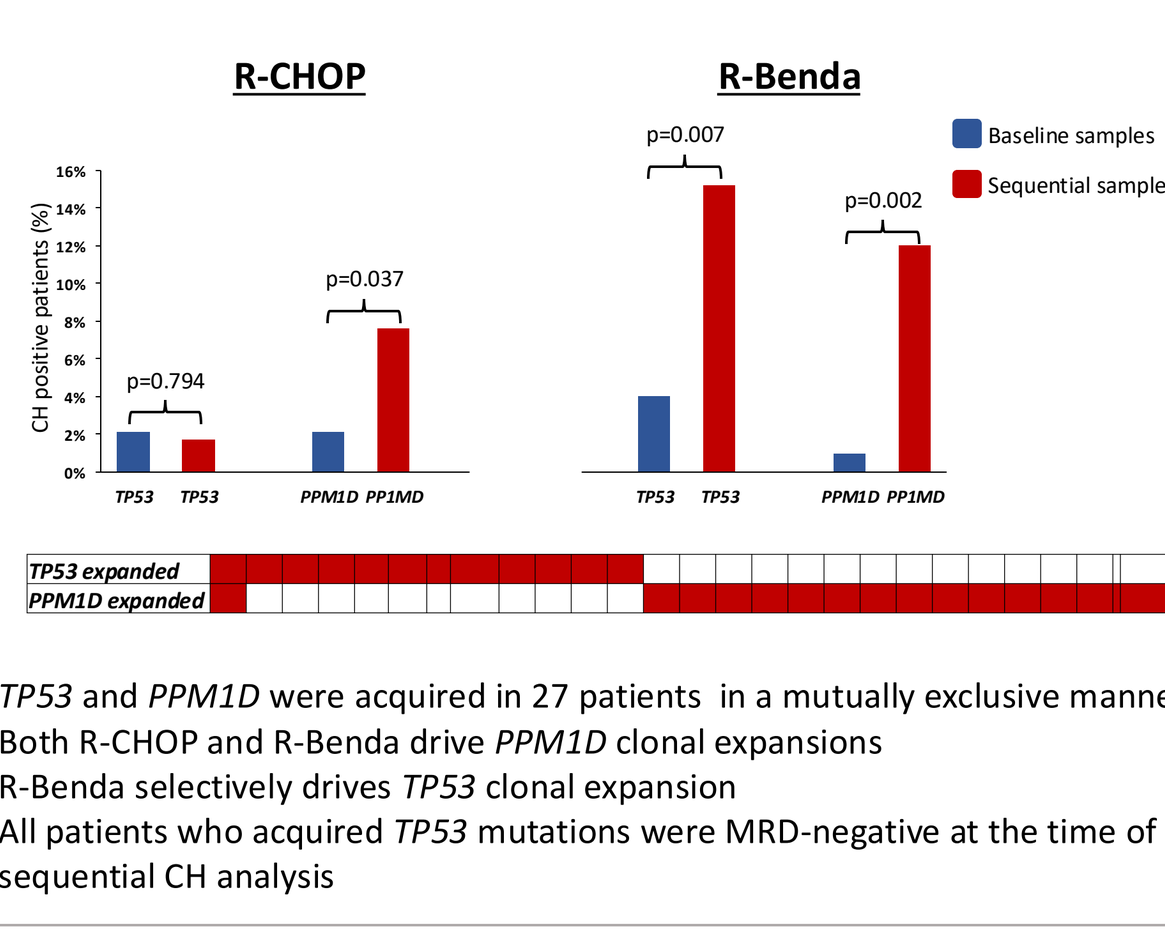
- *TET2* mutations associate with anemia, thrombocythemia and grade ≥3 neutropenia
- The co-occurrence of *TET2* and *DNMT3A* mutations associates with higher risk of cardiac AEs

5. CIT SIGNIFICANTLY EXPANDS CH PREVALENCE AND VAF



- CH prevalence increased from 36.4% at baseline to 48.3% in sequential samples
- CIT significantly expanded the VAF of pre-existing clones, mainly driven by *DNMT3A* mutations

6. R-CHOP AND BR DIFFERENTLY EXPAND CH CLONES



- *TP53* and *PPM1D* were acquired in 27 patients in a mutually exclusive manner
- Both R-CHOP and R-Benda drive *PPM1D* clonal expansions
- R-Benda selectively drives *TP53* clonal expansion
- All patients who acquired *TP53* mutations were MRD-negative at the time of sequential CH analysis

Discussion and conclusions

These data suggest that: *i*) CH does not associate with poor outcomes in FL patients; *ii*) TET2 mutations are linked to a higher risk of hematologic toxicities; *iii*) CIT promotes CH clonal expansion, particularly in DNA damage-response (DDR) genes such as *TP53* and *PPM1D*; *iv*) R-Benda, but not R-CHOP, selectively drives expansion of TP53-mutant CH clones. On these grounds, CH could serve as a biomarker to identify FL patients who may benefit from chemo-free approaches, reducing treatment-related toxicities and limiting CH expansion.

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