XIX CONGRESSO NAZIONALE SIES2026
Firenze | 4-6 marzo 2026 Palazzo degli Affari

Lymphomas

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

N. Maher[1|2], R. Moia[2], M. Almasri[2], E. Genuardi[3], M. Drandi[3], C. Cosentino[2], R. Soscia[4], Gm. Assanto[4], A. Tucci[5], C. Boccomini[6], P. Corradini[7], J. Olivieri[8], L. Arcaini9|[10], F. Ballerini[11], F. Cavallo[12], B. Puccini[13], C. Patti[14], C. Stelitano[15], A. Pulsoni[16], A. Santoro[17], A. Pinto[18], V.R. Zilioli[19], L. Marcheselli[20], S. Ciavarella[21], R. Bomben[22], S. Galimberti[23], I. Del Giudice[4], M. Ladetto[1], G. Gaidano[2], S. Luminari[24], S. Ferrero[3]

[1]SCDU Ematologia, Department of Translational Medicine, AOU SS Antonio e Biagio E Cesare Arrigo, Università del Piemonte Orientale; [2]Division of Hematology, Department of Translational Medicine, AOU Maggiore della Carità di Novara, Università del Piemonte Orientale; [3]Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Torino; [4]Hematology, Department of Translational and Precision Medicine, 'Sapienza' University of Rome – AOU Policlinico Umberto I; [5]Division of Hematology, ASST Spedali Civili; [6]Hematology Division, A. O. U. Città della Salute e della Scienza di Torino; [7]Division of Hematology, Fondazione IRCCS Istituto Nazionale dei Tumori; [8]Hematology and SCT Unit, Azienda Sanitaria Universitaria Integrata Santa Maria della Misericordia; [9]Division of Hematology, Fondazione IRCCS Policlinico San Matteo, University of Pavia; [10]Department of Molecular Medicine, University of Pavia; [11]IRCCS Ospedale Policlinico San Martino; [12]Division of Hematology, University Hospital A. O. U. "Città della Salute e della Scienza"; Division of Hematology, Department of Molecular Biotechnologies and Health Sciences, University of Turin; [13]Hematology Unit, Careggi University Hospital; [14]Oncohematology Azienda Ospedali Riuniti Villa Sofia-V. Cervello Palermo; [15]Grande Ospedale Metropolitano, Bianchi Melacrino Morelli, Ematologia Reggio Calabria; [16] Department of Hematology, SM Goretti Hospital, University Polo Pontino; [17] IRCCS Humanitas Research Hospital, Transplantation Unit Department of Oncology and Haematology; [18] Hematology-Oncology and Stem Cell Transplantation Unit, Istituto Nazionale Tumori-IRCCS-Fondazione 'G. Pascale'; [19] Division of Hematology, ASST Grande Ospedale Metropolitano Niguarda; [20] Uffici Studi Fondazione Italiana Linfomi; [21]Hematology and Cell Therapy Unit, IRCCS Istituto Tumori 'Giovanni Paolo II'; [22]Centro di Riferimento Oncologico di Aviano; [23] Hematology Division, Pisa University Hospital, Department of Clinical and Experimental Medicine, University of Pisa; [24] Ematologia, Azienda Unità Sanitaria Locale – IRCCS Reggio Emilia.

Background: Clonal Hematopoiesis (CH) is an age-related phenomenon, characterized by somatic mutations in hematopoietic stem cells involved in myeloid malignancies in individuals without myeloid neoplasms. The clinical interplay between CH and follicular lymphoma (FL), has not been fully elucidated yet.

Methods: The study analyzed 242 FL patients treated with RCHOP or BR in the phase III FIL FOLL12 trial. Genomic DNA from baseline (N=242) and sequential samples (N=211) were available from whole peripheral blood and assessed for CH using CAPP-Seq-based NGS. The gene panel included 28 CH-related genes and a 1% VAF was set for variant calling. Clonal fitness (s, per year) was estimated from weighted regression on logit-transformed VAF. Clones were classified as increasing (s > 0.25/yr), decreasing (s < –0.25/yr), or stable when the 95% CI included zero.

Results: At baseline, CH mutations were identified in 88 cases (36.4%) with *DNMT3A* (16.9%) and *TET2* (12.0%) being the most common affected genes. CH^+ patients had a significantly higher median age of 66 years compared to 57 for CH^- patients (P<0.001). CH^+ patients showed superimposable PFS and OS compared to CH^- patients with a 72-month PFS of 65.4% compared to 62.6% (P=0.579) and a 72-month OS of 91.3% compared to 93.9% in CH^- patients (P=0.532), respectively. CH was associated with increased hematologic toxicities, with *TET2* mutations predicting higher rates of anemia (25.0% vs. 8.7%; P=0.002), thrombocytopenia (29.2% vs. 10.0%; P=0.002), and grade ≥3 neutropenia (72.2% vs. 35.7%; P=0.042). The dynamics of CH were assessed in 211 paired samples collected after chemo-immunotherapy (CIT; median follow-up 30 months, IQR 12–36). CH prevalence increased from 36.4% to 48.3% (P=0.01), consistent with therapy-driven clonal selection. Canonical CH mutations (*DNMT3A*/*TET2*) remained largely stable over time (median s~+0.23/yr), whereas DNA damage response (DDR) gene mutations (*PPM1D*, *CHEK2*, *TP53*) exhibited markedly elevated clonal fitness (*PPM1D*~+1.23/yr; *CHEK2*~+0.90/yr; *TP53*~+0.79/yr), supporting strong positive selection under CIT. Both regimens promoted *PPM1D*/*CHEK2* expansion, while *TP53* growth was exclusive to BR (4.0% vs. 15.2%, P=0.007; RCHOP: 2.1% vs. 1.7%, P=0.794). Importantly, CIT-driven enrichment of high-fitness DDR clones was associated with a three-fold increase in secondary malignancy risk (OR=3.056; P=0.008), indicating a major contribution to long-term toxicity.

Conclusions: CH does not associate with poor outcomes in FL patients when treated in 1st line with standard of care RCHOP or BR regimens. However, *TET2* mutations associate with a higher frequency of hematological toxicity in FL treated with CIT. CIT promotes the expansion of DDR-mutated CH clones, with *TP53* growth occurring exclusively after BR. High-fitness DDR clones predict a three-fold increase in secondary malignancy risk, supporting CH profiling as a biomarker to guide chemo-free approaches and limit treatment-related toxicity.