## Abstract: P1149

# Title: EZH2 ABERRATIONS IN ADVANCED FOLLICULAR LYMPHOMA: FIRST TRANSLATIONAL RESULTS OF FOLL-EZ, AN ANCILLARY STUDY FROM THE FONDAZIONE ITALIANA LINFOMI (FIL) FOLL12 TRIAL

**Abstract Type: Poster Presentation**

**Topic: Indolent and mantle-cell non-Hodgkin lymphoma - Clinical**

**Background:**

Gain-of-function mutations in the Enhancer of Zeste Homolog 2 (*EZH2*) gene are prevalent in follicular lymphoma (FL) and encode for a histone methyltransferase, which can also be over-expressed by copy number variations (CNV). The clinical impact of *EZH2* aberrations in FL is debated, with some studies suggesting a favorable outcome, especially when patients received R-CHOP/CVP

**Aims:**

In the "FOLL-EZ" study we explored the role of *EZH2* in modifying the first line treatment effect in the prospective trial "FOLL12" of the Fondazione Italiana Linfomi (FIL, EudraCT 2012-003170-60), enrolling FL patients treated either with R-CHOP or bendamustine-rituximab (BR), according to physician's choice.

**Methods:**

Leftover DNA samples from bone marrow (BM) aspirates at baseline, centralized at the FIL MRD Network labs, were tested by a multiplex droplet digital PCR (ddPCR) for the detection of *EZH2* mutations and by a ddPCR CNV assay for the *EZH2* region (chr 7q36.1).

**Results:**

Overall, 409 samples were tested for mutations and 359 for CNV. An *EZH2* mutation was found in 137 cases (33%), being more frequent in patients with a documented histological infiltration at the BM biopsy (BM+ n=124/309, 40%) than in BM- (n=13/100, 13%). 68 cases were mutated in Y646 (50%), 41 in A682G (30%) and 73 in A692V (53%), with a median variant allele frequency (VAF) of 0.13% (0.01-32%): 102 cases (74%) showed one single mutation, 30 cases two and 6 cases all the 3 mutations. Interestingly, *EZH2* mutated patients showed less favorable clinical features than the WT: higher B2M (>ULN 72% vs 53%, p<0.001), lower Hb (Hb<12, 26% vs 15%, p=0.015), more frequent BM+ (91% vs 68%, p<0.001), higher FLIPI-2 (61% HR vs 40%, p<0.001), higher metabolic tumor volume (MTV>200 ml: 71% vs 57%, p=0.011) and maximum tumor dissemination (Dmax>400 mm: 34% vs 21%, p=0.013). Nonetheless, this did not translate into worse outcome (5-year PFS 60% vs 64%, p=0.519). Overall, no difference in PFS was observed between R-CHOP (n=239) and BR-treated (n=170) patients (5-y PFS 60% vs 67%, p=0.652); *EZH2* mutations had no statistically significant impact in modifying the treatment effect of either schedule, despite a trend towards better performance of BR vs R-CHOP in *EZH2* mutated cases: PFS HR of R-CHOP vs BR was 1.77 (95CI 0.96-3.29, p=0.067) for mutated and 0.89 (95CI 0.60-1.32, p=0.564) for WT patients, Figure 1A. In a subgroup analysis, the 30 *EZH2* mutated patients who received R-CHOP not followed by R maintenance had the worst outcome (5-y PFS 24%, p=0.007). Regarding *EZH2* CNV, a gain was found in 50 cases (14%) and a loss in 9 (3%): among the 337 patients analysed for both mutations and CNV, 13 carried both *EZH2* mutation and gain (4%), 106 had mutations only (31%) and 31 had gain only (9%). The 50 patients with CN gain had less BM involvement (62% vs 79%, p=0.018) but no differences in other baseline clinical features nor in outcome; interestingly, among R-CHOP treated patients (n=199) those with *EZH2* gain only (n=20) showed a trend towards better outcome (5-y PFS: 75% vs 59%, p=0.053, Figure 1B).

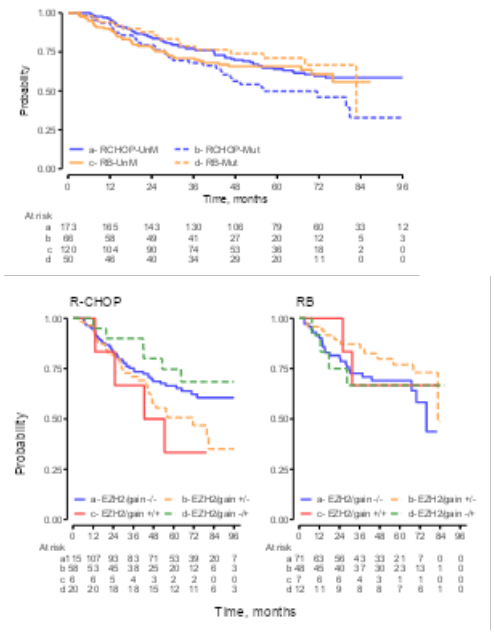
**Summary/Conclusion:**

*EZH2* aberrations were tested by ddPCR in 409 BM samples from the largest, prospective series of FL, so far:

unexpectedly, we found high prevalence of A692V mutation and described trends towards discordant impact of *EZH2* mutations vs gains in modifying the effect of first line therapy, so further investigation is needed before using this biomarker for treatment choice modulation in FL. To better address this issue, testing of diagnostic lymph node samples is ongoing.

**Figure 1. PFS stratified by first line treatment received (R-CHOP/BR) and*EZH2* mutational status (A) or *EZH2* mutational status and copy number gain (B).**

**A B**




**Keywords:** EZH2, Prediction, Clinical trial, Follicular lymphoma