**COMPREHENSIVE ANALYSIS OF BASELINE OUTCOME BIOPREDICTORS IN YOUNGER PATIENTS WITH MANTLE CELL LYMPHOMA: THE ANCILLARY BIOLOGICAL STUDIES OF FONDAZIONE ITALIANA LINFOMI (FIL) MCL0208 CLINICAL TRIAL**

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## 1.INTRODUCTION

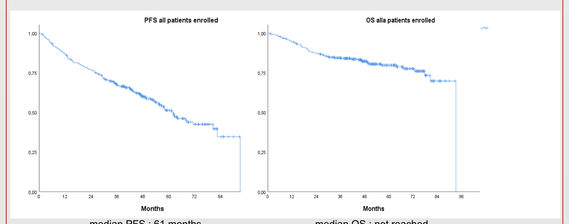
Despite the improvement in therapeutic schedules, a relevant fraction of mantle cell lymphoma (MCL) patients still experience primary treatment failure. This is due to a deep biological heterogeneity, not adequately dissected by the clinical predictors alone, as the MIPI

## 2.OBJECTIVE

The Fondazione Italiana Linfomi (FIL) MCL0208 trial is a prospective, randomized phase III trial comparing lenalidomide maintenance vs observation after an intensive citarabine containing chemo-immunotherapy followed by autologous transplantation in frontline MCL patients <66 years. Several biological ancillary studies were planned upfront, prospectively investigating the prognostic impact of putative biomarkers. Here we present a comprehensive analysis of the clinical impact of all the identified biopredictors.

## 3.METHODS

Trial details, as well as methods for immunohistochemistry, flow cytometry (FC), immunoglobulin heavy chain (IGH) gene sequencing and minimal residual disease (MRD) analysis have been presented.[Ferrero, ASH 2018] The "BCR-high" gene expression signature was tested by RT-PCR [Bomben, Haematologica 2018], somatic mutations by high-throughput targeted resequencing.[Ferrero, EHA 2017]. The optimal cut-off value for FC was determined by applying receiver operating curve (ROC) analysis. Survival analyses were performed by both univariate (UV) and multivariate (MV) Cox modeling via R (v.3.5.2): the variables showing a p<0.2 after UV were selected for the MV, including cases with missing values.




median PFS : 61 months

median OS : not reached

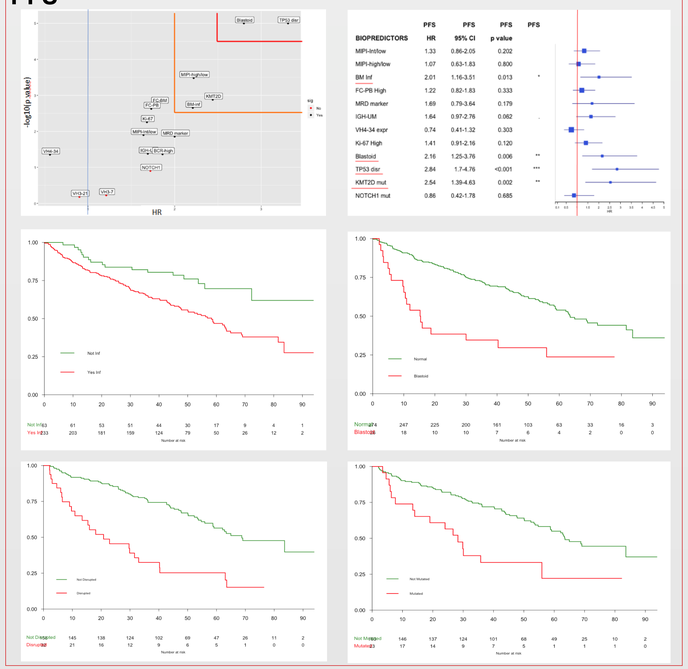
## 4.RESULTS

| PREDICTORS | RESULTS |
|---|---|
| **MIPI score** | 60% low risk<br>24% intermediate risk<br>16% high risk |
| **Baseline bone marrow infiltration** | 233/296 (79%) |
| **Baseline median FC value infiltration** | BM 7% (0.01-93)<br>PB 4% (0.02-92) |
| **Molecular marker for MRD** | 250/300 (83%) |
| **Available IGH sequence** | 211/250 (84%) |
| **IGH rearrangements** | IGHV3-21 (21%)<br>IGHV4-34 (16%)<br>IGHV3-7 (8%) |
| **Median IGH homology** | 99.2% (89.9-100) |
| **IGH unmutated (above 98% cut-off)** | 163/211(77%) |
| **Ki-67≥30%** | 84/271 (31%) |
| **SOX11+** | 167/183 (92%) |
| **Blastoid histology** | 26/300 (9%) |
| **TP53 disruption** | 32/190 (16%) |
| **KMT2D mutation** | 23/186 (12%) |
| **NOTCH1 mutations** | 14/186 (8%) |
| **"BCR-high" signature** | 40/83 (48%) |

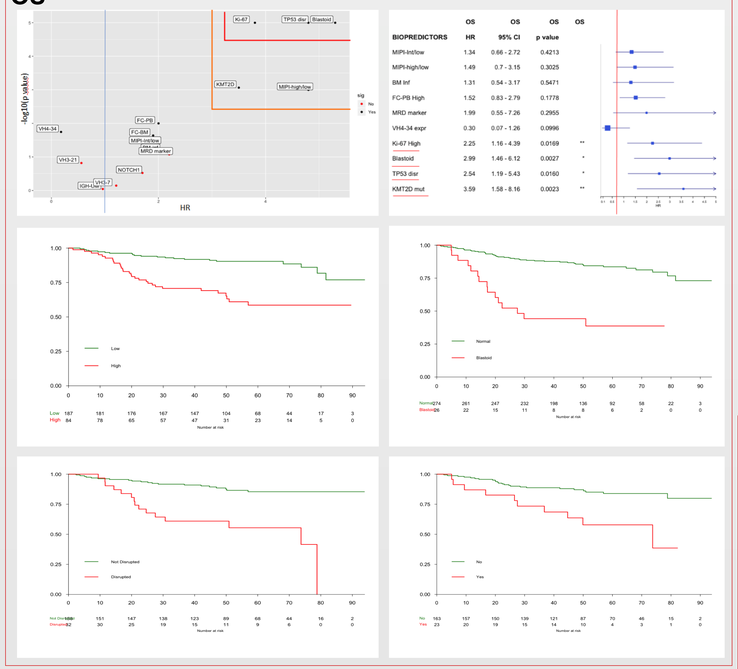
PFS impact in univariate and multivariate. After a median follow-up of 51 months, several baseline biopredictors negatively impacted PFS in UV: BMinf, high FC-BM/PB, MRD marker+, IGH-UM, Ki-67≥30%, B-hist, *TP53* and *KMT2D* mut, "BCR-high" signature. No significant outcome discrimination could be made on the basis of stereotyped IGH or SOX11 staining. After MV BMinf, IGH-UM, B-hist, *TP53/KMT2D* mut remained significant, as opposed to MIPI. Similar results were reported for OS by UV, indicating FC-BM/PB, Ki-67≥30%, B-hist, *TP53/KMT2D* mut as significant predictors. Finally, after MV, Ki-67≥30%, Bhist and *KMT2D* mut remained significant for OS, as opposed to MIPI.

| | PFS | | | | | | OS | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Univariate | | | Multivariate Cox n=300, events=139, C_index=0.71, CI_se=0.025 | | | Univariate | | | Multivariate Cox n=300, events=61, C_index=0.78, CI_se=0.031 | | |
| | HR | 95%_CI | p_value | HR | 95%_CI | p_value | HR | 95%_CI | p_value | HR | 95%_CI | p_value |
| **MIPI (Intermediate vs low)** | 1.64 | 1.11-2.43 | 0.01267 | 1.33 | 0.86-2.05 | 0.202 | 2 | 1.03 - 3.75 | 0.04 | 1.34 | 0.66 - 2.72 | 0.4213 |
| **MIPISt (high vs. low)** | 2.22 | 1.44-3.43 | 0.00033 | 1.07 | 0.63-1.83 | 0.800 | 4.8 | 2.66 - 8.7 | <0.001 | 1.49 | 0.7 - 3.15 | 0.3025 |
| **BM Infiltration (yes vs. no)** | 2.21 | 1.33-3.68 | 0.00222 | 2.01 | 1.16-3.51 | 0.013 * | 2.1 | 0.95 - 4.61 | 0.066 | 1.31 | 0.54 - 3.17 | 0.5471 |
| **FC-BM (high vs. low)** | 1.82 | 1.25-2.65 | 0.00172 | - | | | 1.9 | 1.1 - 3.46 | 0.023 | | | |
| **FC-PB (high vs. low)** | 1.73 | 1.21-2.45 | 0.00236 | 1.22 | 0.82-1.83 | 0.333 | 2 | 1.18 - 3.37 | 0.01 | 1.52 | 0.83 - 2.79 | 0.1778 |
| **MRD marker (yes vs. no)** | 2 | 1.15-3.48 | 0.01395 | 1.69 | 0.79-3.64 | 0.179 | 2.2 | 0.9 - 5.62 | 0.084 | 1.99 | 0.55 - 7.26 | 0.2955 |
| **IGH-UM** | 1.69 | 1.02-2.81 | 0.04176 | 1.64 | 0.97-2.76 | 0.062 • | 0.96 | 0.5 - 1.84 | 0.905 | | | |
| **VH3-21** | 0.9 | 0.57-1.4 | 0.66222 | - | | | 0.56 | 0.25 - 1.24 | 0.152 | | | |
| **VH3-7** | 1.21 | 0.59-2.5 | 0.5964 | - | | | 1.21 | 0.43 - 3.37 | 0.716 | | | |
| **VH4-34** | 0.56 | 0.32-0.99 | 0.04426 | 0.74 | 0.41-1.32 | 0.303 | 0.18 | 0.04 - 0.75 | 0.018 | 0.30 | 0.07 - 1.26 | 0.0996 . |
| **Ki-67 ≥ 30%** | 1.68 | 1.16-2.43 | 0.00555 | 1.41 | 0.91-2.16 | 0.120 | 3.8 | 2.19 - 6.68 | <0.00001 | 2.25 | 1.16 - 4.39 | 0.0169 ** |
| **Blastoid histology** | 2.8 | 1.72-4.55 | <0.00001 | 2.16 | 1.25-3.76 | 0.006 ** | 5.3 | 2.95 - 9.65 | <0.00001 | 2.99 | 1.46 - 6.12 | 0.0027 ** |
| **TP53 disruption** | 3.31 | 2.08-5.26 | <0.00001 | 2.84 | 1.7-4.76 | <0.001 *** | 4.8 | 2.45 - 9.45 | <0.00001 | 2.54 | 1.19 - 5.43 | 0.0160 * |
| **KMT2D mutation** | 2.44 | 1.42-4.22 | 0.00132 | 2.54 | 1.39-4.63 | 0.002 ** | 3.5 | 1.68 - 7.37 | 0.00086 | 3.59 | 1.58 - 8.16 | 0.0023 ** |
| **NOTCH1 mutation** | 1.72 | 0.86-3.42 | 0.12563 | 0.86 | 0.42-1.78 | 0.685 | 1.7 | 0.61 - 4.95 | 0.30 | | | |
| **BCR-high** | 1.86 | 1.02-3.4 | 0.04326 | - | | | - | - | - | | | |
| TOT | 16 | | | 12 | | | 15 | | | 10 | | |

**PFS**




**OS**




## 5. CONCLUSION

→First comprehensive analysis of the clinical impact of a composite panel of easily implementable biopredictors in a multicenter, prospective, clinical trial for MCL patients

→**Several known variables maintain their independent prognostic value**, underlining the biological complexity of MCL. Notably, all these biomarkers are of relative simple and applicable determination.

→Interestingly, the biological predictors emerged over clinical predictors, such as MIPI, **suggesting that biological features might be the key drivers of outcome in MCL.**

## 6.REFERENCES

**Ladetto ASH 2018.** Lenalidomide Maintenance after autologous stem cell transplantation prolong PFS in Young MCL patients: results of the randomized phase III MCL0208 trial from FIL (NCT02354313).

**Ferrero ASH 2018.** Comprehensive minimal residual disease (MRD) analysis of the Fondazione Italiana Linfomi (FIL) MCL0208 clinical trial for younger patients with mantle cell lymphoma: a kinetic model ensures the most accurate outcome prediction.

**Ferrero ICML 2017.** KMT2D and TP53 mutations predict poor PFS and OS in MCL receiving high dose therapy and ASCT: the FIL MCL0208 phase III trial.

**Bomben Haematologica 2018**. A B-cell receptor-related gene signature predicts survival in mantle cell lymphoma: results from the "Fondazione ItalianaLinfomi" MCL-0208 trial.

**Hoster Blood 2008.** A new prognostic index (MIPI) for patients with advanced-stage mantle cell lymphoma.

**Hoster JCO 2016.** Prognostic Value of Ki-67 Index, Cytology, and Growth Pattern in Mantle-Cell Lymphoma: Results From Randomized Trials of the European Mantle Cell Lymphoma Network.

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