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 deeply 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 rituximab containing chemom- 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, 2018]. The "BCR-high" gene expression signature was tested by RT-PCR [Bombe, Haematologica 2018], somatic mutations by high-throughput targeted resequencing [Ferrero, EHA 2017]. The optimal cutoff 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 were used for the MV, including cases with missing values.

4. RESULTS

**PFS**

- **MIPi**
  - **MIPi** (Intermediate vs low): **BM infiltration (yes vs. no)**
  - BM infiltration was a significant predictor for OS, as opposed to MIPi.
  - **BM infiltration (yes vs. no)**: 99.2% (89.9-100%)
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**OS**

- **OS**
  - **OS**
  - **OS**
  - **OS**
  - **OS**
  - **OS**

**MIPi** (Intermediate vs low) and multivariate. After a median follow-up of 51 months, several baseline biopredictors negatively impacted PFS in UV: BMinf, high FC-BMI/BP, MRD marker, IGH-UM, Ki-67≥30%, B-hist, TPS3 and KMT2D mut, "BCR-high" signature. No significant outcome discrimination could be made on the basis of stereotyped IGH or SOX11 staining. After BM BMinf, IGH-UM, B-hist, TPS3/KMT2D mut remained significant, as opposed to MIPi. Similar results were reported for OS by UV, indicating FC-BM/BP, Ki-67≥30%, B-hist, TPS3/KMT2D mut as significant predictors. Finally, after MV, Ki-67≥30%, Bhist and KMT2D mut remained significant for OS, as opposed to MIPi.

**BASELINE BIOPREDICTORS**

- **RT-PCR**
  - **RT-PCR**
  - **RT-PCR**
  - **RT-PCR**
  - **RT-PCR**

**MULTIVARIATE BIOPREDICTORS**

- **MULTIVARIATE BIOPREDICTORS**
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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, underlying the biological complexity of MCL. Notably, all these biomarkers are of relative simple and applicable determinants.

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