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

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

Simone Ferrero* 1, 2, Gian Maria Zaccaria1, Daniela Barbero1, Andrea Evangelista3, Alice Di Rocco4, Alessandro Re5, Vittorio Stefoni6, Federica Cavallo1, 2, Umberto Vitolo7, Monica Balzarotti8, Chiara Rusconi9, Maria Gomes da Silva10, Marco Ghislieri11, Paola Omedè2, Alberto Zamò12, Giovannino Ciccone3, Valter Gattei13, Gianluca Gaidano14, Sergio Cortelazzo15, Marco Ladetto16

1Molecular Biotechnologies and Health Sciences - Hematology Division, Università di Torino, 2SC Ematologia I, AOU Città della Salute e della Scienza di Torino, 3Unit of Clinical Epidemiology, CPO, Città della Salute e della Scienza, Hospital of Turin, Torino, 4Department of Cellular Biotechnologies and Hematology, Sapienza University, Roma, 5Division of Hematology, Spedali Civili, Brescia, 6Institute of Hematology "L. e A. Seràgnoli", University of Bologna, Bologna, 7SC Ematologia II, AOU Città della Salute e della Scienza di Torino, Torino, 8Division of Hematology, Humanitas Cancer Center, 9Division of Haematology, Department of Haematology and Oncology, Niguarda Cancer Center, ASST Grande Ospedale Metropolitano Niguarda, Milano, Italy, 10Departamento de Hematologia, Instituto Português de Oncologia, Lisboa, Portugal, 11Department of Electronics and Telecommunications of Politecnico of Torino, 12Department of Oncology, Pathology, University of Turin, Torino, 13Clinical and Experimental Onco-Hematology Unit, IRCCS CRO Aviano-National Cancer Institute, Aviano, 14Division of Hematology, Department of Translational Medicine, Novara, 15 Humanitas/Gavazzeni Cancer Center, Bergamo, 16Hematology Division, A.O. SS Antonio e Biagio and Cesare Arrigo, Alessandria, Italy

1.INTRODUCTION

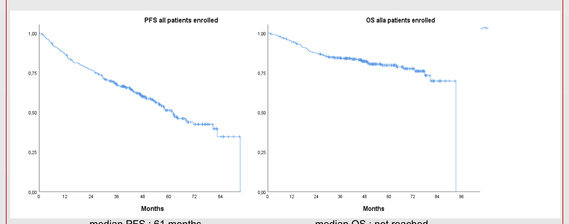
Despite the improvement in therapeutic schedules, a relevant fraction of mantle cell lymphoma (MCL) patients still experience primary treatment failure. This is due to a deep biological heterogeneity, not adequately dissected by the clinical predictors alone, as the MIPI

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

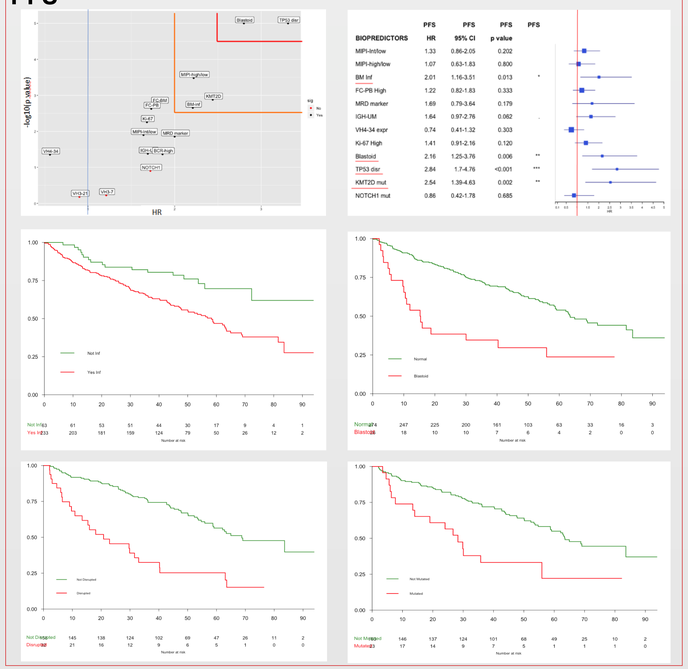
4.RESULTS

PREDICTORS	RESULTS
MIPI score	60% low risk 24% intermediate risk 16% high risk
Baseline bone marrow infiltration	233/296 (79%)
Baseline median FC value infiltration	BM 7% (0.01-93) PB 4% (0.02-92)
Molecular marker for MRD	250/300 (83%)
Available IGH sequence	211/250 (84%)
IGH rearrangements	IGHV3-21 (21%) IGHV4-34 (16%) 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%)

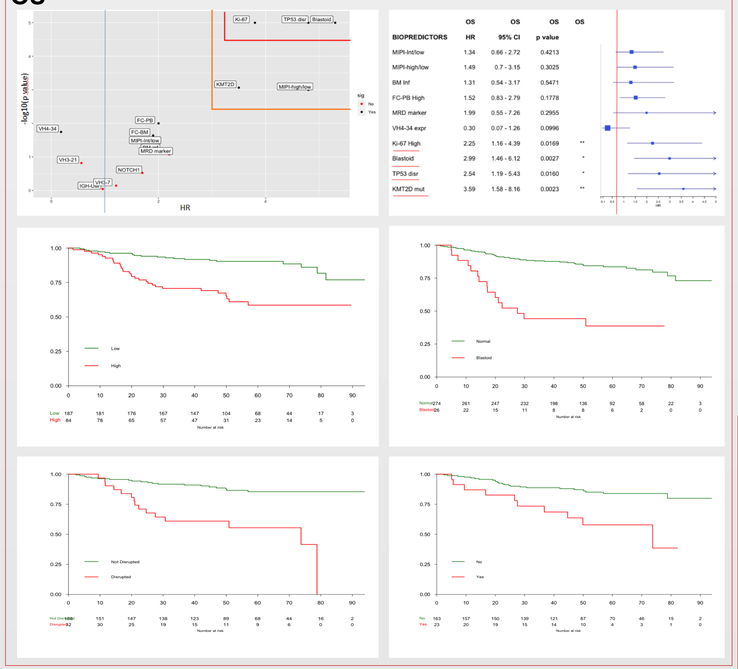
PFS impact in univariate and multivariate. After a median follow-up of 51 months, several baseline biopredictors negatively impacted PFS in UV: BMinf, high FC-BM/PB, MRD marker+, IGH-UM, Ki-67≥30%, B-hist, *TP53* and *KMT2D* mut, "BCR-high" signature. No significant outcome discrimination could be made 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.

7.ACKNOWLEDGEMENTS prof. Boccadolo M., lab team of Molecular Biotechnologies and Flow Cytometry of Health Sciences University of Torino

8.CONTACT INFORMATION simone.ferrero@unito.it; gianmaria.zaccaria@unito.it