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

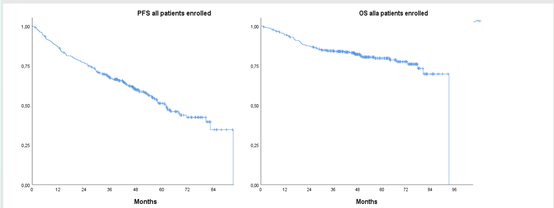
Despite the improvement in therapeutic schedules, a relevant fraction of mantle cell lymphoma (MCL) patients still experience primary treatment failure. This is due to a deep biological heterogeneity, not adequately dissected by the clinical predictors alone, as the MIPI

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

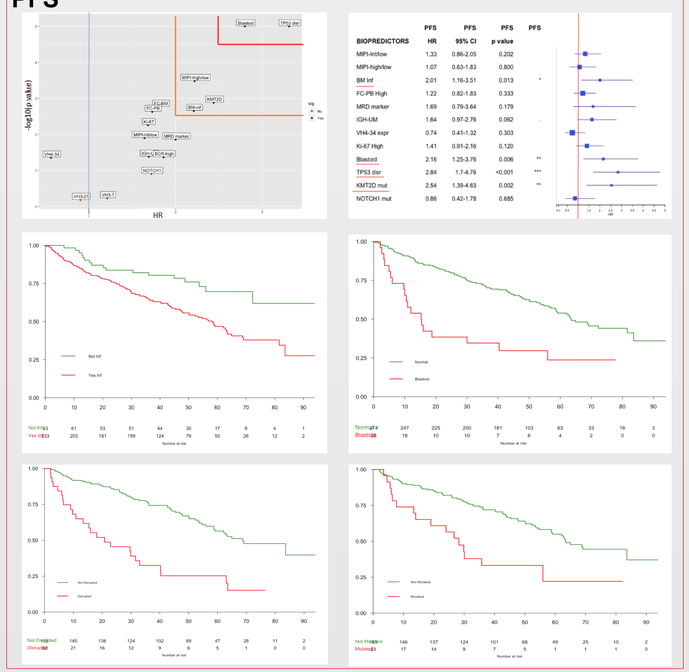
4.RESULTS

PREDICTORS	RESULTS
MIPI score	60% low risk 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%)

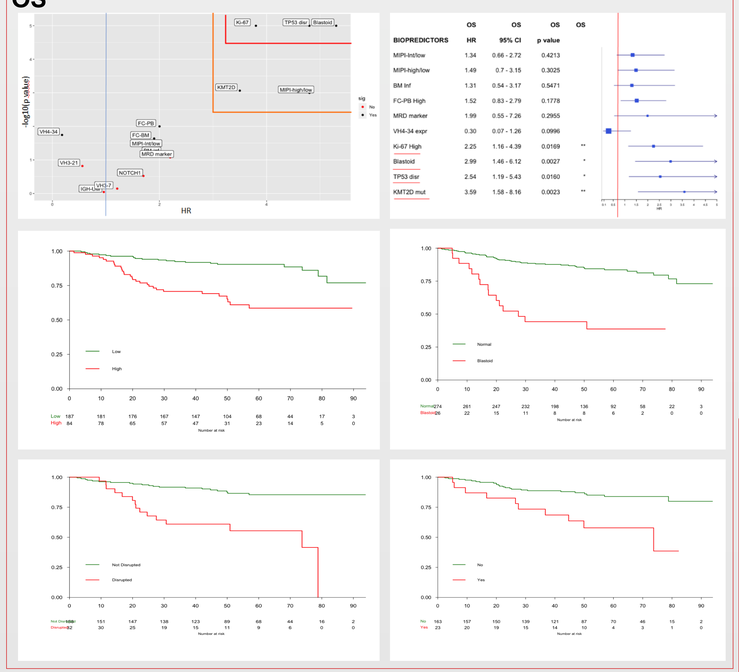
PFS impact in univariate and multivariate. After a median follow-up of 51 months, several baseline biopredictors negatively impacted PFS in UV: BMinf, high FC-BM/PB, MRD marker+, IGH-UM, Ki-67≥30%, B-hist, *TP53* and *KMT2D* mut, "BCR-high" signature. No significant outcome discrimination could be made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

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