LETTER OPEN

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The integration of gene mutations and copy number variations refines the prognosis of mantle cell lymphoma: long-term results of the Fondazione Italiana Linfomi MCL0208 clinical trial

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TO THE EDITOR:

Despite recent efforts in characterizing the molecular profile of MCL, the upfront identification of high-risk MCL destined to early relapses still represents an unmet clinical need [1–5]. Within the rapidly evolving therapeutic scenario of MCL [6], the multicenter phase 3 FIL MCL0208 trial, which randomized untreated MCL patients to receive either lenalidomide maintenance or observation after autologous stem cell transplantation (ASCT), offers the opportunity to identify the prognostic role of gene mutations and copy number variations (CNVs) in MCL besides *TP53* abnormalities, thus improving precision medicine.

FIL-MCL0208 (NCT02354313) was a phase III, multicenter, open-label, randomized study, designed to determine the efficacy of lenalidomide as maintenance *versus* observation in young (18–65 years old), fit, advanced-stage, classic MCL patients, after high-dose chemo-immunotherapy followed by ASCT [7]. The clinical trial and the ancillary mutational study were approved by the Ethical Committees of all the enrolling centers.

Methods for sample preparation and analysis of the mutational status of nine genes (*ATM, TP53, CCND1, WHSC1, KMT2D, NOTCH1* exon *34, BIRC3, TRAF2* and *CXCR4)*, selected for being recurrently mutated in ≥5% of MCL (Supplementary Table S1), and the CNVs at a genome-wide level were previously reported [2]. The recurrent CNVs were identified by a dedicated bioinformatic pipeline, incorporating the Genomic Identification of Significant Targets in Cancer (GISTIC) and the Gene Expression and Dosage Integrator (GEDI) algorithms [8]. Minimal residual disease (MRD) analysis was performed as previously described [9, 10]. See also Supplementary appendix.

A total of 186 patients, with available gDNA extracted from sorted CD19+ tumor cells from bone marrow aspirates, were analyzed for gene mutations, and 165 patients for CNVs, out of the 300 enrolled in the FIL MCL0208 trial. Overall, 160 patients were analyzed for both gene mutations and CNVs.

The median current follow-up is 7.0 years. Characteristics of patients included in the molecular study were superimposable to those not included in the molecular analysis, except for a higher prevalence of bone marrow infiltration since DNA for biological studies was extracted from sorted CD19+ bone marrow cells (Table 1). However, no differences in PFS ($p = 0.72$) and OS ($p = 0.088$) have been observed between cases analyzed and not analyzed (Supplementary Fig. S1).

At the current follow-up, the 7-year PFS was 13.3% for *TP53*-mutated cases and 46.5% for wild-type cases ($p < 0.0001$), and the 7-year OS was 18.5% and 78.8%, respectively ($p < 0.0001$) (Supplementary Fig. S2A, B). Similarly, the 7-year PFS of 17p deleted cases was 9.3% compared to 48.4% for wild-type cases ($p < 0.0001$), and the 7-year OS was 35.5% and 79.4% ($p < 0.0001$), respectively (Supplementary Fig. S2C, D). Moreover, *KMT2D* mutations continued to associate with shorter PFS and OS, with a 7-year PFS of 28.5% compared to 45.7% for wild-type cases ($p = 0.006$) and with a 7-year OS of 53.4% compared to 76.5% for wild-type cases ($p = 0.011$) (Figure S2,E-F). By considering the different *TP53* alterations, patients with monoallelic *TP53* disruption (i.e., *TP53* mutation only or 17p del only) had identical poor PFS ($p = 0.786$, Supplementary Fig. S2G) but significantly better OS ($p = 0.030$, Supplementary Fig. S2H) compared to patients with biallelic *TP53* disruption (i.e., *TP53* mutation and 17p del). However, the outcome of patients with any *TP53* abnormality was still significantly lower than that of wild-type patients (Supplementary Fig. S3). These findings suggest that monoallelic *TP53* disruption can be partially rescued by second-line therapies (i.e., BTKi). Additionally, *KMT2D* mutations continued to confer an unfavorable prognosis in our cohort, though this finding still requires validation in other independent MCL series [2, 11].

The clinical impact of lenalidomide maintenance was evaluated by grouping *TP53*-mutated and/or deleted and *KMT2D*-mutated cases ($N = 49$). Only 27/49 (55%) patients achieved at least a partial response and met criteria for randomization to lenalidomide vs placebo maintenance. Thirteen (48.1%) patients received lenalidomide and 14 (51.9%) placebo. In these high-risk patients, when adjusted in multivariate analysis for *TP53* disruption and *KMT2D* mutations, lenalidomide maintenance did not improve PFS (HR 0.92, 95% CI 0.54–1.56, $p = 0.800$) or OS (HR 1.10, 95% CI 0.50–2.40, $p = 0.800$).

CNVs were also evaluated in 165 patients enrolled in the MCL0208 trial. A total of 242 CNVs were identified in at least one patient and, consistent with the karyotype of MCL, the most frequent CNVs included gains affecting 3q27.1 (31% of patients), followed by deletion at 1p36.3-q21.1 (27%), 11q22.3 (26%), 13q33.1 (24%), 6q24.3 (20%) and 9p21.3 (*CDKN2A*) (19%) (Supplementary Fig. S4 and Supplementary Table S2). Besides *TP53* deletion, nine further CNVs, namely losses of *CDKN2A*, 14q32.2–q32.33, 22q13.31–q13.33, 22q11.21–q12.1, 14q24.3–q25.1, 1q42.12–q44, 6p21.33–p21.1, 9p13.3–p11.2 and copy neutral loss of heterozygosity 17q11.1–q21.1 significantly predicted PFS by univariate analysis after Bonferroni correction (Supplementary Tables S3, S4). Therefore, patients with at least

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Table 1. Clinical features of patients analyzed or not for copy number variations (CNV) and mutations.

Characteristic	CNV analysis			Mutation analysis		
	No, $N = 135$	Yes, $N = 165$	p-value	No, $N = 114$	Yes, $N = 186$	p-value
Age (years)			0.6			0.7
Median (Range)	57 (28, 66)	57 (32, 66)		58 (28, 66)	57 (32, 66)	
Gender			0.5			0.1
Female	27 (20%)	38 (23%)		19 (17%)	46 (25%)	
Male	108 (80%)	127 (77%)		95 (83%)	140 (75%)	
WBC x10^9/L			0.4			0.4
Median (Range)	7 (3, 196)	8 (1, 178)		8 (1, 196)	7 (3, 178)	
Ki67			0.2			0.2
Ki67 < 30%	76 (65%)	111 (72%)		64 (65%)	123 (72%)	
Ki67 ≥ 30%	41 (35%)	43 (28%)		35 (35%)	49 (28%)	
NA	18	11		15	14	
MIPIc			0.9			0.7
High risk	11 (9.4%)	13 (8.4%)		10 (10%)	14 (8.1%)	
Intermediate-High risk	13 (11%)	22 (14%)		11 (11%)	24 (14%)	
Intermediate-Low risk	35 (30%)	44 (29%)		32 (32%)	47 (27%)	
Low risk	58 (50%)	75 (49%)		46 (46%)	87 (51%)	
NA	18	11		15	14	
MIPI			0.5			0.5
High risk	20 (15%)	27 (16%)		21 (18%)	26 (14%)	
Intermediate risk	29 (21%)	44 (27%)		25 (22%)	48 (26%)	
Low risk	86 (64%)	94 (57%)		68 (60%)	112 (60%)	
Bone marrow infiltration by flow-cytometry (%)			<0.001			<0.001
Median (Range)	1 (0, 91)	11 (0, 93)		1 (0, 93)	10 (0, 87)	
NA	39	8		38	9	
Histology			>0.9			0.6
Blastoid	12 (8.9%)	14 (8.5%)		11 (9.6%)	15 (8.1%)	
Classic	123 (91%)	151 (92%)		103 (90%)	171 (92%)	
LDH > ULN	38 (28%)	61 (37%)	0.11	31 (27%)	68 (37%)	0.094
Bulky	39 (29%)	59 (36%)	0.2	32 (28%)	66 (35%)	0.2
ASCT	113 (84%)	136 (82%)	0.8	95 (83%)	154 (83%)	>0.9
Clinical response after ASCT			0.4			0.7
CR	100 (88%)	126 (93%)		87 (91%)	139 (91%)	
PR	9 (7.9%)	6 (4.4%)		5 (5.2%)	10 (6.5%)	
SD or PD	5 (4.4%)	3 (2.2%)		4 (4.2%)	4 (2.6%)	
NA	21	30		18	33	

n (%) Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test. *WBC* white blood cell count, *MIPIc* combined mantle cell lymphoma international prognostic index, *MIPI* mantle cell lymphoma international prognostic index, *LDH* Lactate dehydrogenase, *ULN* Upper Limit of Normal, *ASCT* autologous stem cell transplant.

one of the above-mentioned CNVs were grouped and named CNV9+.

CNV9+ cases showed higher median age compared to CNV9- patients (60 vs 56 years, $p = 0.002$) and were characterized by unfavorable baseline clinical features, including higher white blood cell count ($p = 0.013$), higher prevalence of Ki67 ≥ 30% ($p = 0.002$), higher MIPI score ($p < 0.001$), and higher blastoid histology prevalence ($p < 0.001$). Of note, no difference in the prevalence of *TP53* and *KMT2D* mutations emerged between CNV9+ and CNV9- patients. In addition, despite comparable rates of ASCT, CNV9+ patients had inferior CR rates compared to CNV9- patients ($p = 0.013$) (Supplementary Table S5), resulting in inferior PFS (7-year PFS 12.3% vs. 56.3%, $p < 0.001$) and OS (7-year OS 33.9% vs. 85.6%, $p < 0.001$, Supplementary Fig. S5). Besides *CDKN2A* loss [12], the biological mechanisms underlying the clinical aggressiveness of the identified CNVs, including the multitude of genes, remain unclear. Within the 22q11.1-q11.23 region, *BID*, a pro-apoptotic protein, emerges as a potential candidate gene, although this locus also encompasses the IG lambda light chain genes. The 1q42 region may implicate *ITPKB*, encoding a pro-apoptotic protein, while the 6p21.1 region harbors *NFKBIE*, a negative regulator of the NF-κB signaling pathway. The 9p13.3 region contains *PAX5*, whose loss has been associated with aggressive clinical behavior in MCL [13]. From the translational point of view, preclinical work has indicated *CDKN2A* loss as a potential biomarker of sensitivity to ATR inhibitors [14], suggesting that this class of agents could be explored in MCL.

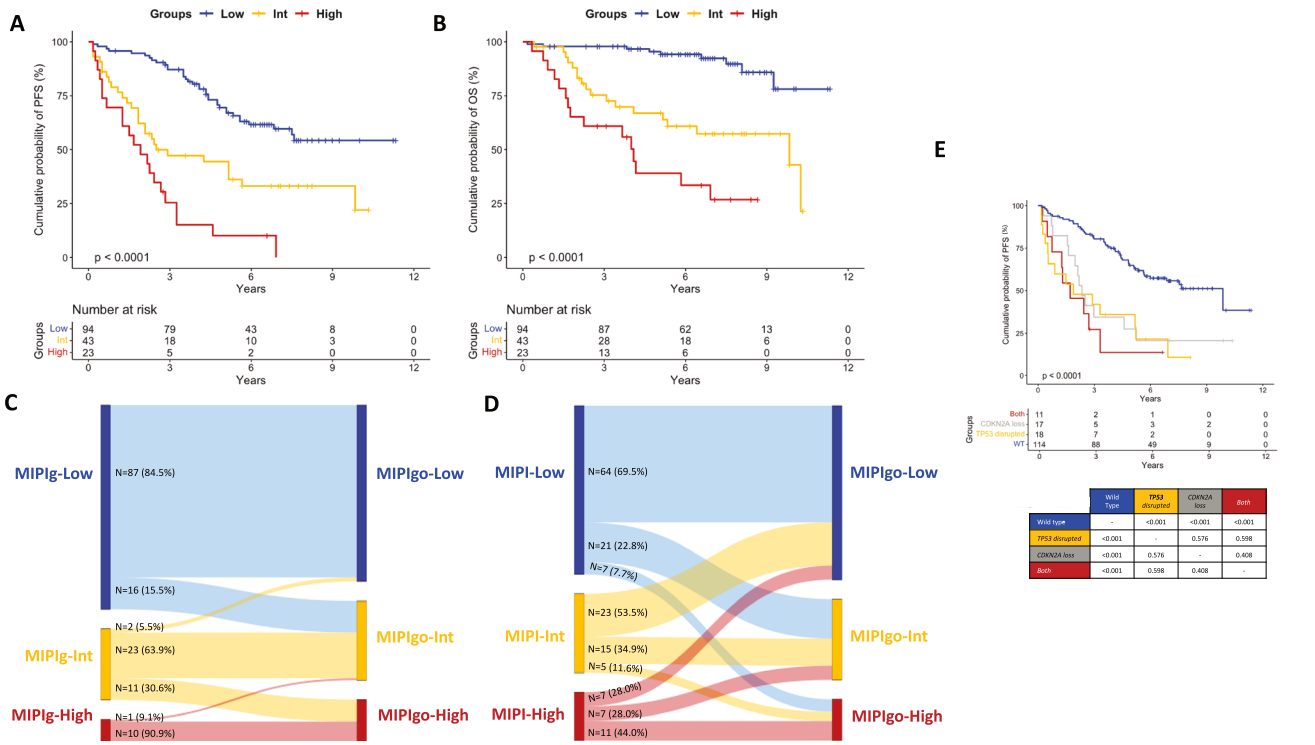

Fig. 1 The MIPIgo model and clinical impact of *TP53* disruption and *CDKN2A* loss. Kaplan–Meier estimates of PFS (**A**) and OS (**B**) of the novel "MIPIgo" model. Low-risk MIPIgo cases are represented by the blue line, intermediate-risk MIPIgo cases by the yellow line, and high-risk MIPIgo cases by the red line. **C** Sankey plot of MIPIg and MIPIgo. **D** Sankey plot of MIPI and MIPIgo. MIPI: mantle cell lymphoma international prognostic index. MIPI: combined mantle cell lymphoma international prognostic index. **E** Kaplan–Meier estimates of PFS of *TP53* disruption and *CDKN2A* deletion. Cases with *TP53* disruption are represented by the yellow line, cases with both *TP53* disruption and *CDKN2A* deletion are represented by the red line, cases with *CDKN2A* deletion are represented by the gray line, and cases without *TP53* disruption and *CDKN2A* deletion are represented by the blue line.

By using the same approach of MIPIg, a score was assigned to each predictor based on Cox regression analysis for PFS. *KMT2D* mutations (HR 2.03, 95% CI 1.08–3.84, $p = 0.29$), *TP53* disruptions (HR 2.28, 95% CI 1.24-4.18, $p = 0.008$), and CNV9+ (HR 2.42, 95% CI 1.42–4.10, $p = 0.001$) had superimposable HRs for PFS, thus scoring 1 point. Interestingly, the MIPI-c high-risk class lost its independent prognostic value (HR 1.41, 95% CI 0.66–3.01, $p = 0.400$), thus scoring 0 points (Supplementary Table S6). Consequently, a novel "genetics-only" (MIPIgo) model was developed, with patients grouped into three risk classes according to regression tree analysis: *i)* 0 points, low-risk (Low) group ($N = 94$); *ii)* 1 point, intermediate-risk (Int) group ($N = 43$); *iii)* ≥ 2 points, high risk (High) group ($N = 23$). The 7-year PFS for Low-, Int-, and High-risk groups was 59.6%, 33.1%, and 0%, respectively ($p < 0.0001$) (Fig. 1A). This model was also promising regarding OS (Fig. 1B). The novel genetic score improved the model discrimination ability (C-statistics of 0.685 for PFS and 0.770 for OS, Supplementary Table S7) compared to MIPIg, MIPIc, and MIPI. Overall, compared to MIPIg, the MIPIgo model upstaged 15.5% of Low-risk patients to Int-risk and 30.6% of Int-risk patients to High-risk (Fig. 1C), and, compared to MIPI, reclassifies 30.5% of Low-risk patients, 65.1% of Int-risk patients, and 56.0% of High-risk patients (Fig. 1D).

To balance the prognostic accuracy of the MIPIgo model with its applicability in clinical practice, we focused on *TP53* disruption, *KMT2D* mutation, and *CDKN2A* loss, the most prognostically significant and frequent CNV9 in our cohort. By multivariate analysis, *TP53* disruption (HR 3.07, 95% CI 1.75–5.39, $p < 0.001$), *KMT2D* mutations (HR 2.29, 95% CI 1.18–4.45, $p = 0.01$), and *CDKN2A* loss (HR 1.79, 95% CI 1.02–3.14, $p = 0.04$) independently predicted shorter PFS (Supplementary Fig. S6). By considering only *TP53* disruption and *CDKN2A* loss, patients with *TP53* disruption only ($N = 18$), patients with *CDKN2A* loss only ($N = 17$), or both ($N = 11$), had superimposable poor PFS (Fig. 1E). If validated in independent cohorts of young and elderly MCL cases, the independent prognostic role of *TP53* disruption, *KMT2D* mutations, and *CDKN2A* loss could support the development of simplified molecular prognostic approaches for untreated MCL. Finally, *TP53* disruption (Supplementary Fig. S7A), *KMT2D* mutations (Supplementary Fig. S7B), and *CDKN2A* loss (Supplementary Fig. S7C) were associated with a non-significant trend towards lower MRD negativity rates at 6 and 12 months after ASCT.

A homogenous approach to establishing the MCL genetic risk is lacking. Preliminary data from the TRIANGLE trial, including BTKis in first-line treatment [15], suggest that ibrutinib combinations might mitigate the poor prognostic impact of *TP53* mutations. Still, no data are available for *KMT2D* mutations and *CDKN2A* loss. Overall, the MIPIgo model developed in this study, along with its simplified version incorporating only *TP53* disruption, *KMT2D* mutations, and *CDKN2A* loss, if validated in independent cohorts, may help investigate novel molecular-guided therapeutic approaches, including BTKi, CAR-T cells, or bispecific antibodies. Therefore, to capture high-risk MCL patients, testing for *TP53* aberrations (mutations and deletions), *KMT2D* mutations, and *CDKN2A* loss should be included in routine staging work-up at diagnosis.

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DATA AVAILABILITY

The datasets generated and/or analyzed during the current study are available from the corresponding author upon reasonable request.

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AUTHOR CONTRIBUTIONS

RM and SR were equally responsible for conducting the research, assembling and analyzing data, interpreting results, and writing the manuscript. LC and AR contributed to molecular analysis and manuscript writing. EG contributed to results interpretation. AE contributed to statistical analysis. DT, MA, A. Bruscaggin, GMZ, AMC, ADR, MM, FC, MC, ML, CS, PMS, CV, A. Billio, IC, CC, EP, SG, CP, FM, AM, DR, GG, ML, FB, and SF provided biological samples for the study, contributed to results interpretation, and reviewed the manuscript. DR and GG supervised data analysis and provided feedback on the report. ML contributed to the design of the study, supervised the conduction of the research, contributed to results interpretation, and manuscript writing. FB and SF designed the study and were equally responsible for supervising the conduction of the research, results interpretation, and manuscript revision. All authors approved the final version of the manuscript.

COMPETING INTERESTS

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research funding from Gilead, Beigene and Morphosys. ML has relationship in terms of consultancy, participation to advisory boards, invitation to scientific meetings, institutional research support and contracts with: AbbVie, Acerta, Amgen, ADC Therapeutics, BeiGene, Celgene/BMS, Eusapharma, GSKI, Gentili, Gilead/Kite, Novartis, Incyte J&J, Jazz, Lilly, Regeneron, Roche, Sandoz; he has non-financial interests as PI or strategic investigator in studies supported by: Celgene, J&J, BeiGene, ADC Therapeutics. GG has been consulting in Advisory Boards for Abbvie, AstraZeneca, Beigene, Incyte, Johnson & Johnson, and Lilly, and received speaker's honoraria from Abbvie, AstraZeneca, Beigene, Hikma, Incyte, Johnson & Johnson, and Lilly. The remaining authors have no conflicts of interest to declare.

ETHICAL APPROVAL

All study methods were performed in accordance with relevant guidelines and regulations. The clinical trial and the ancillary mutational study were approved by the Ethical Committees of all the enrolling centers. Written informed consent was obtained from all subjects.

ADDITIONAL INFORMATION

Supplementary information The online version contains supplementary material available at https://doi.org/10.1038/s41375-025-02795-0.

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