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COMPREHENSIVE ANALYSIS OF BASELINE OUTCOME BIOPREDICTORS IN YOUNGER PATIENTS WITH MANTLE CELL LYMPHOMA: THE ANCILLARY BIOLOGICAL STUDIES OF

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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 / Ferrero, S.; Zaccaria, G. M.; Barbero, D.; Evangelista, A.; Di Rocco, A.; Re, A.; Stefoni, V.; Cavallo, F.; Vitolo, U.; Balzarotti, M.; Rusconi, C.; da Silva, Gomes M.; Ghislieri, M.; Omedè, P.; Zamò, A.; Ciccone, G.; Gattei, V.; Gaidano, G.; Cortelazzo, S.; Ladetto, M.. - In: HEMASPHERE. - ISSN 2572-9241. - ELETTRONICO. - 3:(2019), pp. 569-570. (Intervento presentato al convegno European Hematology Association (EHA) tenutosi a Amsterdam nel 13/06/2019 - 16/06/2019) [10.1097/01.HS9.0000563272.02759.6b].

Availability:
This version is available at: 11583/2762893 since: 2019-10-22T20:05:40Z

Publisher:
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Published
DOI:10.1097/01.HS9.0000563272.02759.6b

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13 May 2024

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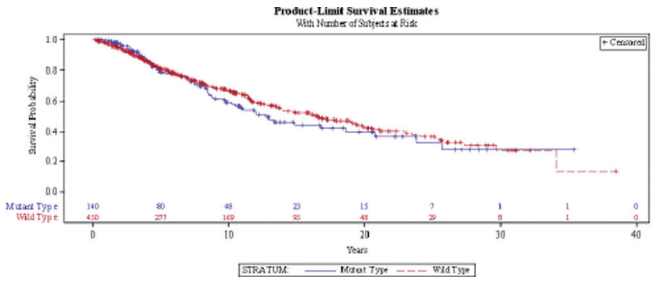
Background: Tazemetostat, a selective, oral inhibitor of the histone methyltransferase EZH2, has shown antitumor activity in patients with follicular lymphoma (FL). Gain-of-function (GOF) mutations in *EZH2* are found in 20–25% of tumors from FL patients, and mutant (MT) *EZH2* is widely considered an oncogenic driver of the disease. Some studies suggest GOF *EZH2* mutations may provide a prognostic benefit in the frontline setting (1L) in FL patients treated with immunochemotherapy regimens. However, the impact of mutant *EZH2* on clinical outcomes in the setting of relapsed/refractory (R/R) FL patients receiving systemic anticancer therapy beyond immunochemotherapy remains to be determined.
Aims: This multi-center study is intended to evaluate the impact of *EZH2* activating mutations on outcomes in patients with FL. Results of an interim analysis are presented.
Methods: Retrospective data on therapy types and clinical outcomes are being collected from 5 academic sites. Available data from 3 sites (Barts Cancer Institute, Institute Gustave Roussy, Semmelweis University) were analyzed to determine clinical outcome parameters and to compare those between patients with and without *EZH2* mutations. Best overall response rate (ORR), as judged by the treating physician at each site, were compared by *EZH2* status and stratified by line of therapy using the Cochran-Mantel-Haenszel chi-square test. Progression-free survival (PFS) and overall survival (OS) were calculated using the Kaplan-Meier method, and compared by the logrank test. Tumor tissues collected primarily at the time of diagnosis were analyzed for activating mutations of *EZH2* (Y646X, A682G, A692 V) using various approaches, including next generation sequencing, digital droplet PCR (BioRad) and the **cobas**® EZH2 Mutation Test (Roche Molecular Systems).
Results: Data from 590 patients with *EZH2* MT (n = 140) or wild-type (WT; n = 450) FL treated with systemic anticancer therapy between December 1972 and December 2017 at 3 academic centers were included for analyses. The frequency of *EZH2* activating mutations was 24%. In 1L, 43% of patients received immunochemotherapy. In second line (2L) and beyond, the majority of patients received chemotherapy (65–80%) and 14–20% received immunochemotherapy. Median follow-up from diagnosis was 10.5 years (95% CI, 9.7–11.5). No significant differences in ORR between MT and WT *EZH2* cohorts were found in either 1L or 2L or when third line and all subsequent lines of therapy were grouped together (3L+). In the combined dataset, ORR for MT and WT *EZH2* cases in 1L were 89% and 87%, respectively (P = 0.493) and 73% and 73%, respectively (P = 0.996) in 2L. The ORR for patients in 3L+ were 82% and 80% for MT and WT cohorts, respectively (P = 0.647). Analysis of PFS by line of therapy in the combined dataset suggested there were no statistically significant differences (P>0.05) between R/R FL patients with MT and WT *EZH2* for any line of therapy. In addition, OS was not statistically significantly different for patients with and without *EZH2* mutations (median OS 12.7 vs 16.6 years, respectively; P = 0.464; Figure).



Summary/Conclusion: These results reveal no difference in ORR or PFS by line of therapy in R/R FL patients with either MT or WT *EZH2*. Similarly, MT *EZH2* was not associated with significantly longer OS in this study. These findings suggest that MT *EZH2* does not act as a positive prognostic factor and that any clinical activity observed in patients with R/R FL treated with standard of care agents or tazemetostat is most likely due to the drugs' mechanism of action.

PS1248 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

S. Ferrero [1,2,*], G. M. Zaccaria [1], D. Barbero [1], A. Evangelista [3], A. Di Rocco [4], A. Re [5], V. Stefoni [6], F. Cavallo [1,2], U. Vitolo [7], M. Balzarotti [8], C. Rusconi [9], M. Gomes da Silva [10], M. Ghislieri [11], P. Omedè [2], A. Zamò [12], G. Ciccone [3], V. Gattei [13], G. Gaidano [14], S. Cortelazzo [15], M. Ladetto [16]

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Background: 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 (MCL International Prognostic Index).
Aims: The Fondazione Italiana Linfomi (FIL) MCL0208 trial (NCT02354313) 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.[Ladetto, ASH 2018] 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.
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.
Results: Among the 300 enrolled patients the MIPI scored 60% low, 24% intermediate and 16% high. Overall, 233/296 (79%) patients presented at baseline bone marrow (BM) infiltration (inf), for a median FC value of 7% (0.01–93) and 4% in peripheral blood, PB (0.02–92). 250/300 (83%) showed a molecular marker for MRD and 211 (84%) an available IGH sequence: IGHV3–21 (21%), IGHV4–34 (16%) and IGHV3–7 (8%) were the most frequent rearrangements. Median IGH homology was 99.2% (89.9–100), with 163 cases (77%) above the 98% cut-off (UM). 22 (10%) showed a stereotyped IGH. 84/271 patients (31%) showed Ki-67≥30%, 167/183 (92%) SOX11+, 27/300 (9%) blastoid histology (B-hist), 15/186 (8%) *TP53*, 23/186 (12%) *KMT2D* and 14/186 (8%) *NOTCH1* mutations (mut), 40/83 (48%) "BCR-high" signature. 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%, B-hist and *KMT2D* mut remained significant for OS, as opposed to MIPI (Table1).

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	Progression Free Survival						Overall Survival					
				N = 300, events = 167						N = 300, events = 60		
	Univariate Cox			Multivariate Cox			Univariate Cox			Multivariate Cox		
	HR	95%_CI	p_value	HR	95%_CI	p_value	HR	95%_CI	p_value	HR	95%_CI	p_value
MIPI (intermediate vs. low)	1.71	(1.15 - 2.53)	<0.01	1.25	(0.81 - 1.94)		1.87	(0.97 - 3.6)	0.06	1.15	(0.55 - 2.37)	
MIPI (high vs. low)	2.28	(1.47 - 3.53)	<0.001	1.24	(0.73 - 2.09)		4.79	(2.65 - 8.27)	<0.001	1.52	(0.74 - 3.15)	
BM infiltration (yes vs. no)	2.35	(1.39 - 3.96)	<0.01	2.15	(1.21 - 3.79)	<0.01	2.07	(0.94 - 4.56)	0.07	1.34	(0.56 - 3.17)	
FC-BM (high vs. low)	1.86	(1.28 - 2.72)	<0.01	-			2.04	(1.14 - 3.66)	0.02	-		
FC-PB (high vs. low)	1.75	(1.23 - 2.49)	<0.01	1.22	(0.81 - 1.82)		2.07	(1.22 - 3.52)	<0.01	1.58	(0.85 - 2.95)	
MRD marker (yes vs. no)	2.13	(1.2 - 3.78)	<0.01	1.83	(0.84 - 4.01)		2.23	(0.89 - 5.57)	0.09	2.12	(0.79 -5.67)	0.13
IGH-UM	1.66	(1 - 2.77)	<0.05	1.67	(1 - 2.81)	0.05	0.92	(0.48 - 1.76)		-		
Ki-67 ≥ 30%	1.67	(1.15 - 2.41)	<0.01	1.43	(0.93 - 2.18)	0.10	3.99	(2.27 - 7.04)	<0.001	2.50	(1.29 -4.86)	<0.01
Blastoid histology	2.82	(1.73 - 4.6)	<0.001	2.50	(1.45 - 4.32)	0.001	5.32	(2.94 - 9.61)	<0.001	3.40	(1.74 - 7.04)	0.001
TP53 mutation	2.83	(1.57 - 5.1)	<0.001	2.43	(1.28 - 4.63)	<0.01	5.21	(2.41 - 11.25)	<0.001	2.18	(0.91 - 5.21)	0.08
KMT2D mutation	2.41	(1.39 - 4.15)	<0.01	2.29	(1.26 - 4.16)	<0.01	3.59	(1.71 - 7.55)	<0.001	3.53	(1.53 - 8.16)	<0.01
NOTCH1 mutation	1.71	(0.86 - 3.41)	0.13	0.85	(0.4 - 1.82)		1.78	(0.63 - 5.07)				
BCR-high	1.84	(1.01-3.36)	0.05	-			-					

Summary/Conclusion: This is the 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 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 outperformed the predictive value of clinical predictors, such as MIPI, suggesting that biological features are the key drivers of outcome in MCL.

PS1249 EXTRANODAL AND SPLEEN DISEASE DETECTED BY FDG-PET/CT IS ASSOCIATED WITH EARLY CLINICAL FAILURE IN UNTREATED FOLLICULAR LYMPHOMA

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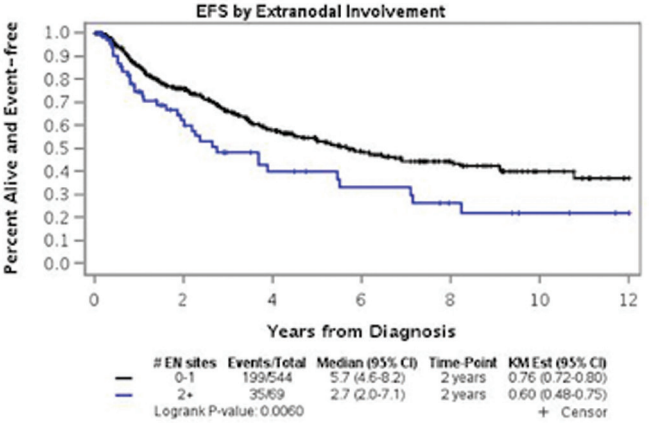
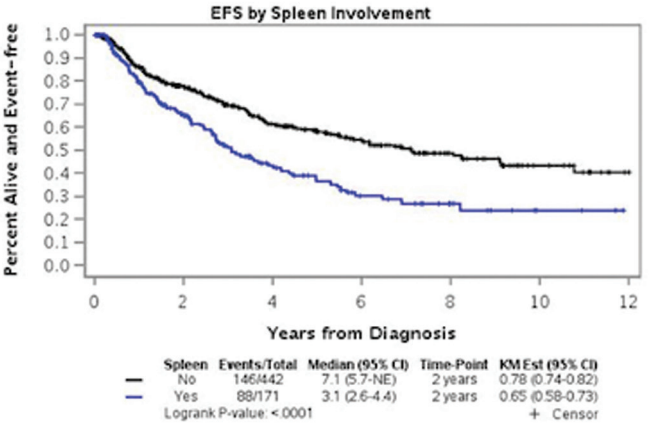
Background: Predicting early clinical failure in patients with untreated follicular lymphoma (FL) is important but difficult. Lymphoma involvement of extranodal (EN) sites is better detected by FDG-PET/CT than CT alone, but PET parameters are not part of the usual predictive indices.
Aims: We aimed to determine the incidence and patterns of EN and spleen disease, and learn if they were useful in predicting early clinical failure.

Table 1: Extranodal and spleen involvement by PET/CT as predictors of event-free survival

Variable	[0,2-3]Multivariate analysis for EFS	
	HR	P value
Bone involvement (n = 204)	1.20 (0.90–1.60)	0.21
# of EN sites (≥2 vs. 0–1) (n = 69)	1.43 (0.99–2.07)	0.06
Multifocal on diffuse pattern of bone involvement (n = 41)	1.71 (1.10–2.65)	0.02
Spleen involvement (n = 171)	1.49 (1.11–2.00)	<0.01
Soft tissue involvement (n = 43)	1.67 (1.06–2.62)	0.02

Methods: PET/CT images from 613 cases of newly diagnosed FL between 2003 – 2016 were retrospectively reviewed for EN and spleen involvement. The location, number, and pattern of EN sites, as well as splenic involvement, were recorded. Associations with outcomes were assessed using event-free survival (EFS), overall survival (OS), and early clinical failure at 24 months (EFS24).
Results: 49% (301/613) of patients had PET/CT-detected EN involvement, and 28% (171/613) had spleen involvement. Presence of ≥2 EN sites, spleen, bone or soft tissue involvement all predicted failure to achieve EFS24. These factors, as well as pattern of bone involvement by imaging, were predictors of EFS on univariate analysis; presence of ≥2 EN sites and bone involvement pattern were also predictive of OS. In a multivariate analysis with FLIPI-2 factors, spleen involvement, pattern of bone involvement, and soft tissue involvement independently predicted a lower EFS (Table 1). When the multivariate analysis was performed using PRIMA-PI factors (marrow and B2 M), the presence of ≥2 EN sites was an adverse independent prognostic factor for OS (HR 2.28; 95% CI 1.01–5.18; p = 0.05).





Summary/Conclusion: Baseline PET/CT identifies EN and spleen sites of disease that can predict early clinical failure in FL. These results, when combined with other factors, may better identify high-risk patients and guide appropriate therapy.

PS1250 PRIMARY THERAPY AND SURVIVAL OF FOLLICULAR LYMPHOMA IN THE NETHERLANDS: A POPULATION-BASED ANALYSIS AMONG 12,008 PATIENTS DIAGNOSED FROM 1989 TO 2016

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Background: Follicular lymphoma (FL) is a heterogenous malignancy, reflected, in part, by the highly variable clinical course. Major advances over the past decades in diagnosis, classification, and management—especially the introduction of rituximab—have significantly contributed to improved survival among patients with FL. At present, however, population-based studies that comprehensively assessed the contribution of these advances on survival according to disease stage are scarce.
Aims: The aim of this nationwide population-based study was to assess trends in primary therapy and survival among patients with FL in the Netherlands during a 28-year period.
Methods: We selected all adult (≥18 years) FL patients diagnosed between 1989–2016 from the nationwide Netherlands Cancer Registry (NCR), with survival follow-up till January 1, 2018. Data on primary therapy—i.e. no anti-neoplastic therapy, treatment with a chemotherapeutic backbone