Towards a Better Understanding of Epidemiology, Survival and Treatment in Myeloproliferative Neoplasms: Results of the European LeukemiaNet Registry (ERNEST study)

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Background

With an estimated prevalence of 1 per 100 000 persons per year (as of May 2014, http://www.orpha.net), myelofibrosis is the rarest of Myeloproliferative Philadelphia negative Neoplasms (MPN): its descriptive and outcome-oriented epidemiology presents therefore a critical challenge, because of its fragmentation in many care centers, which are furthermore expected to be highly variable in their long-term and monitoring practices. The critical relevance of establishing a representative network of European major hematological centers has been identified as a priority goal to become a cultural and operational resource for promoting /implementing reliable and timely clinical-epidemiological studies.
Such network appears even more interesting as it could act as a permanent platform for integrated research programs, in a time which sees MF and more broadly MPN as areas which are rapidly evolving following the most recent genetic and molecular developments including the JAK-2 gene mutation and its emergent targeted (inhibitor) therapeutic agents.
We report here the results of the first phase of a program promoted by the European LeukemiaNet (ELN) collaboration and supported with an unrestricted educational grant by Novartis.

Country	Town	Responsible
Germany	Mannheim	*Andreas Reiter*
Germany	Leipzig	*Dietger Niederwieser*
Germany	Ulm	*Prof. Schlenk*
Germany	Aachen	*Prof. Koschmieder*
Germany	Jena	*Prof. Hochlaus*
Italy	Florence	*Alessandro Vannucchi*
Italy	Pavia	*Mario Cazzola*
Italy	Bergamo	*Alessandro Rambaldi*
Italy	Varese	*Francesco Passamonti*
Spain	Barcelona	*Francisco Cervantes*
Sweden	Gotheburg	*Björn Andreasson*
Sweden	Uddevalla	*Peter Johansson*
UK	London	*Claire Harrison*

Fig. 2

Study Chairman: **Tiziano Barbui**
Study Co-Chairperson: **Claire Harrison**

Coordinated by Fondazione Mario Negri Sud

Design and methods

The main steps of the research project were:
To verify the feasibility and the yield of a multicenter clinical network a the epidemiologically orphan area of a rare chronic disease.

Because of the care intensity and complexity of the clinical conditions, the data collection strategy had to adopt a very pragmatic approach: selection of core data expected to be available in the routine of a good clinical practice was assumed for the retrospective exploration of the clinical databases (in the digitalized or paper form available in each center) of participating centers.

A Biostatistics and Data Management Center (BDMC) was established to assure, through an intensive quality central scheme, the best possible compliance with the standard criteria of reliability and completeness of the data to be included in the central database.

The resulting profiles of the selected variables as presented in **Figure 1** could be seen as a first result of the survey, as they reflect the shared characteristics of the routinely available-good clinical care in the sample of 13 highly qualified hematological centers across 5 European countries (**Figure 2**).

The overall flow chart of the study, including inclusion criteria for registration and elegibility for analysis of the cohort is shown in **Figure 3**.

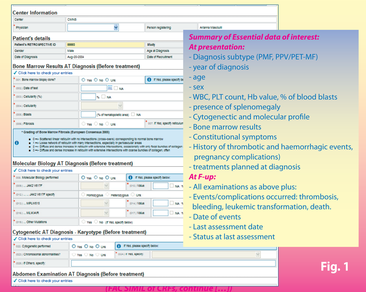


Fig. 1

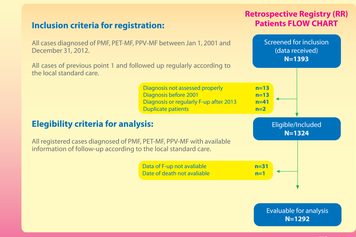


Fig. 3

Statistical aspects

Death from any cause was the main hard outcome endpoint evaluated to describe the natural history of the MF population.
Progression to leukemia has been explored as secondary endpoint.
Chi-square test and Mann-Whitney test were used to compare data at presentation by diagnosis for categorical and continuous variables respectively.
Standard time-to-event methods were used for data analysis, including log-rank test, Kaplan-Meier survival graphs.
Cox proportional hazard regression model was performed for multivariable analysis, adjusting for unbalanced and relevant prognostic covariates. Hazard ratios were calculated along with 95% confidence intervals (CI) and p-values < 0.05 were considered significant.

Results

Table 1. Characteristics of patients at diagnosis

	N evaluable	All Patients N =1292	PMF N (%) 791 (61.2)	PET-MF N (%) 242 (18.7)	PPV-MF N (%) 259 (20.1)
Gender, males	1292	770 (59.6)	506 (64.0)	124 (51.2)	140 (54.1)
Age, median (IQR)	1292	66.3 (56.2-73.4)	66.7 (56.1-73.4)	65.3 (53.6-73.6)	65.6 (57.0-73.4)
Years of diagnosis, n (%)	1292				
2001-04		289 (22.4)	182 (23.0)	57 (23.6)	50 (19.3)
2005-08		466 (36.1)	285 (36.0)	88 (36.4)	93 (35.9)
2009-12		537 (41.6)	324 (41.0)	97 (40.1)	116 (44.8)
IPSS, n (%)	1082	1082	664	210	208
0		176 (16.3)	102 (15.4)	39 (18.6)	35 (16.8)
1		344 (31.8)	209 (31.6)	79 (37.6)	56 (26.9)
2		354 (32.8)	213 (32.1)	55 (26.2)	86 (41.3)
≥3		208 (19.2)	140 (21.1)	37 (17.6)	31 (14.9)
Palpable spleen, n (%)	1222	1222	741	737	244
		972 (79.5)	577 (77.9)	179 (24.3)	216 (94.2)
Spleen value (cm from LCM), mean ±SD	777	777	446	144	167
		6.7 ± 5.8	6.3± 5.4*	5.6± 5.2*	8.9± -6.6
Chromosomal abnormalities	646	646	385	122	136
		229 (35.4)	135 (35.1)	33 (27.0)	61 (44.8)*

Abbreviations: IQR=Inter Quartile Range; SD=Standard Deviation; IPSS=International Prognostic Score System (Adverse point were assigned to age > 65 years (1 point), presence of constitutional symptoms (1 point), hemoglobin < 10 g/dl (1 point), leukocyte count >25 x 10^9/l (1 point) and blood blast > 1% (1 point): low-risk (0 points), intermediate -1-risk (1 point), intermediate -2-risk (2 points), high-risk (3 points or more)); (LCM=Left Costal Margin. *p<0.05)

Planned Treatments at diagnosis

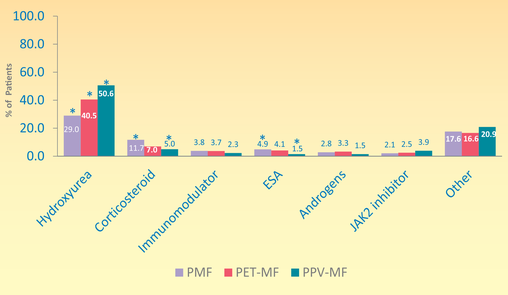
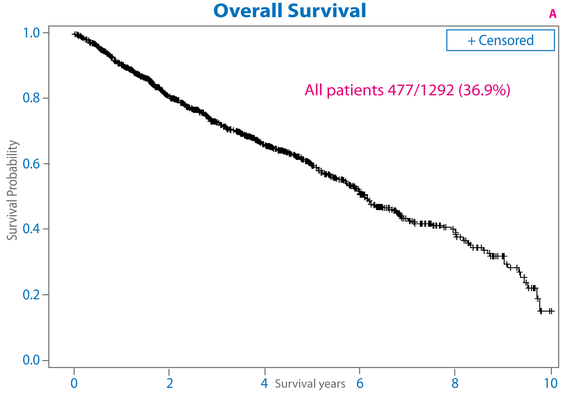


Figure 4. Therapies planned after diagnosis are shown according to diagnosis subtypes



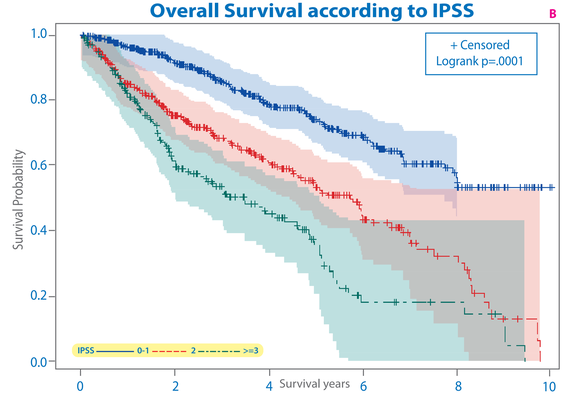


Figure 5. Survival in the whole cohort of 1292 patients median survival 6.2 years) is shown in Panel A.
Survival by IPSS is shown in Panel B. (Adverse point were assigned to age > 65 years (1 point), presence of constitutional symptoms (1 point), hemoglobin < 10 g/dl (1 point), leukocyte count >25 x 10^9/l (1 point) and blood blast > 1% (1 point): low-risk (0 points), intermediate -1-risk (1 point), intermediate -2-risk (2 points), high-risk (3 points)).
(patients with IPSS 0 and 1 were grouped because of scarce number of cases in the lowest Risk Class [IPSS=0])

Table 2. Deaths during clinical course

	All Patients N =1292	PMF N (%) 791 (61.2)	PET-MF N (%) 242 (18.7)	PPV-MF N (%) 259 (20.1)
Median follow-up years (IQR)	2.8 (1.4 – 5.2)	2.9 (1.5-5.4)	2.7 (1.3-5.1)	2.6 (1.2-4.5)
Deaths, n (%)	477 (36.9)	318 (40.2)	81 (33.5)	78 (30.1)
Cause of deaths				
Acute Leukemia	68 (14.3)	37 (11.6)	17 (21.0)	14 (18.0)
Non-Leukemic progressive disease	61 (12.8)	40 (12.6)	11 (13.6)	10 (12.8)
Infection	44 (9.2)	34 (10.7)	4 (4.9)	6 (7.7)
Cardiovascular complications (thrombotic/haemorrhagic events)	37 (7.8)	25 (7.8)	4 (4.9)	8 (10.2)
Secondary Malignancy	20 (4.1)	12 (3.8)	2 (2.5)	6 (7.7)
Transplant related mortality	14 (2.9)	9 (2.8)	4 (4.9)	1 (1.3)
Other causes with incidences of 2 or less	10 (2.1)	6 (1.9)	1 (1.2)	3 (3.8)
Renal failure	6 (1.3)	4 (1.3)	2 (2.5)	0
Multiple organ failiure	6 (1.3)	4 (1.3)	1 (1.2)	1 (1.3)
Unknown	211 (44.2)	147 (46.2)	35(43.2)	29 (37.2)
Leukemic transformation, n (%)	124 (9.6)	84 (10.6)	21 (8.7)	19 (7.3)

Table 3. Multivariable Cox Model Analysis on overall survival

	N Evaluable	Events/Pts (%)	Hazard ratio (95% CI)	P-value
Total Death		477/1292 (36.9)		
Sex	1292			-
Female		156/522 (29.9)	1.00	
Male		321/770 (41.7)	1.41 (1.16-1.72)	0.0005
Diagnosis	1292			
PMF		318/791 (40.2)	1.00	
PET-MF		81/242 (33.5)	1.17 (0-91-1.50)	0.23
PPV-MF		78/259 (30.1)	0.95 (0.74-1.22)	0.67
IPSS score	1082			
0-1		118/520 (22.7)	1.00	
2		150/354 (42.4)	2.37 (1.86-3.02)	<0.0001
≥3		115/208 (55.3)	3.56 (2.75-4.62)	<0.0001

Cox proportional hazards model adjusted for gender, diagnosis subtype and IPSS score. The event of interest is death during follow-up for any cause.
(patients with IPSS 0 and 1 were grouped because of scarce number of cases in the lowest Risk Class [IPSS=0])

Table 4. Multivariable Cox Model Analysis on Leukemic Transformation

	N Evaluable	Events/Pts (%)	Hazard ratio (95% CI)	P-value
Leukemic Transformation		124/1292 (9.6)		
Sex	1292			-
Female		54/522 (10.3)	1.00	
Male		70/770 (9.1)	0.93 (0.64-1.35)	0.70
Diagnosis	1292			
PMF		84/791 (10.6)	1.00	
PET-MF		21/242 (8.7)	1.10 (0.67-1.79)	0.72
PPV-MF		19/259 (7.3)	0.89 (0.53-1.47)	0.65
IPSS score	1082			
0-1		27/520 (5.2)	1.00	
2		31/354 (8.8)	2.05 (1.20-3.49)	0.008
≥3		36/208 (17.3)	4.74 (2.83-7.95)	<0.0001

Cox proportional hazards model adjusted for gender, diagnosis subtype and IPSS score. The event of interest is progression of disease to Acute Myeloid Leukemia during follow-up.
(patients with IPSS 0 and 1 were grouped because of scarce number of cases in the lowest Risk Class [IPSS=0])

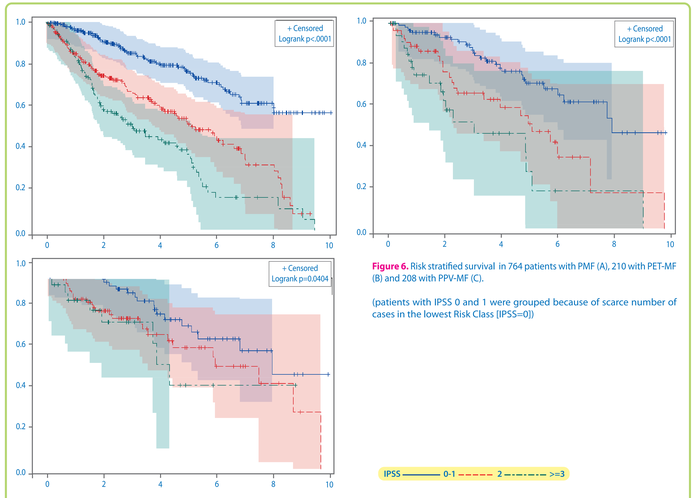


Figure 6. Risk stratified survival in 764 patients with PMF (A), 210 with PET-MF (B) and 208 with PPV-MF (C).

(patients with IPSS 0 and 1 were grouped because of scarce number of cases in the lowest Risk Class [IPSS=0])

Table 5. Multivariable Cox Model Analysis on overall survival by diagnosis subgroups

	PMF			PET-MF			PPV-MF		
	Events/Pts (%)	Hazard ratio (95% CI)	P-value	Events/Pts (%)	Hazard ratio (95% CI)	P-value	Events/Pts (%)	Hazard ratio (95% CI)	P-value
Total Death	318/791 (40.2)			81/242 (33.5)			78/259 (30.1)		
Sex			-						
Female	88/285 (30.9)	1.00		39/118 (33.1)	1.00		29/119 (24.4)	1.00	
Male	230/506 (45.5)	1.43 (1.12-1.83)	0.004	42/124 (33.9)	1.54 (0.98-2.41)	0.06	49/140 (35.0)	1.41 (0.89-2.25)	0.14
IPSS score									
0-1	69/311 (22.2)	1.00		29/118 (23.7)	1.00		21/91 (23.1)	1.00	
2	96/213 (45.1)	2.48 (1.82-3.38)	<.0001	24/55 (43.6)	2.93 (1.68-5.10)	0.0001	30/86 (34.9)	1.59 (0.90-2.80)	0.11
≥3	86/140 (61.4)	3.67 (2.67-5.05)	<0.0001	18/37 (48.7)	5.37 (2.89-9.98)	<0.0001	11/31 (35.5)	2.03 (0.97-4.23)	0.06

Cox proportional hazards model adjusted for gender and IPSS score for each diagnosis subtype is reported. The event of interest is death during follow-up for any cause.
(patients with IPSS 0 and 1 were grouped because of scarce number of cases in the lowest Risk Class [IPSS=0])

Conclusions

The intensive quality control needed to assure reliability, representativeness and comparability of the data across international centers with expertise in this field confirms both the interest, but also the challenge of a cooperative epidemiological effort capable of representing a knowledge producing shared resource in the area of MF and other rare diseases.

The prognostic significance of IPSS has been confirmed both for death and leukemic transformation, but a different pattern of predictivity for overall survival emerged when the analysis was stratified according to the diagnosis subtypes. The determinants included in IPSS strongly affect the survival of patients with PET-MF as well as PMF while new prognostic factors deserve to be exploited for PPV-MF.

Based also on the methodological and operational challenges resulting from the first phase of the study, a prospective observational cohort has been activated starting on September 2013, thus allowing a more in depth analysis and assessment of the above findings.

Graphic by Barbara Ferri