Nilotinib 300 mg twice daily: an academic single-arm study of newly diagnosed chronic phase chronic myeloid leukemia patients

Fausto Castagnetti,[1] Massimo Breccia,[2] Gabriele Gugliotta,[1] Bruno Martino,[3] Mariella D'Adda,[4] Fabio Stagno,[5] Angelo Michele Carella,[6] Paolo Avanzini,[7] Mario Tiribelli,[8] Elena Trabacchi,[9] Giuseppe Visani,[10] Marco Gobbi,[11] Marzia Salvucci,[12] Luciano Levato,[13] Gianni Binotto,[14] Silvana Franca Capalbo,[15] Maria Teresa Bochicchio,[1] Simona Soverini,[1] Michele Cavo,[1] Giovanni Martinelli,[1] Giuliana Alimena,[2] Fabrizio Pane,[16] Giuseppe Saglio,[17] Gianantonio Rosti,[1] and Michele Baccarani[18] on behalf of the GIMEMA CML Working Party

[1]Institute of Hematology "L. and A. Seràgnoli", Department of Experimental, Diagnostic and Specialty Medicine, "S. Orsola-Malpighi" University Hospital, University of Bologna; [2]Department of Cellular Biotechnologies and Hematology, "Sapienza" University of Rome; [3]Hematology Unit, Azienda Ospedaliera "Bianchi-Melacrino-Morelli", Reggio Calabria; [4]Hematology Unit, Azienda Ospedaliera "Spedali Civili", Brescia; [5]Chair of Hematology, University of Catania; [6]U.O. Ematologia I, IRCCS AOU S. Martino-IST, Genova; [7]Hematology Unit, Arcispedale Santa Maria Nuova, IRCCS, Reggio Emilia; [8]Division of Hematology and BMT, Department of Experimental and Clinical Medical Sciences, Azienda Ospedaliero-Universitaria di Udine; [9]Hematology and Bone Marrow Transplantation Unit, Department of Hematology and Oncology, "G. da Saliceto" Hospital, Piacenza; [10]Hematology and Stem Cell Transplantation Unit, Azienda Ospedaliera Ospedali Riuniti Marche Nord (AORMN), Pesaro; [11]Clinical Hematology Unit, IRCCS AOU S. Martino-IST, Genova; [12]Hematology Unit, "Santa Maria delle Croci" Hospital, Ravenna; [13]Hematology Unit, "Pugliese-Ciaccio" Hospital, Catanzaro; [14]Hematology and Clinical Immunology Unit, University of Padova, Padova; [15]Hematology Unit, Azienda Ospedaliero-Universitaria Ospedali Riuniti, Foggia; [16]Chair of Hematology, Department of Biochemistry and Medical Biotechnologies, "Federico II" University, Napoli; [17]Chair of Hematology, Department of Clinical and Biological Sciences, "S. Luigi Gonzaga" University Hospital, University of Torino, Orbassano (TO); [18]Department of Hematology and Oncology "L. and A. Seràgnoli", University of Bologna, Italy

 doi:10.3324/haematol.2016.144949

Received: February 23, 2016.

Accepted: July 28, 2016.

Pre-published: July 28, 2016.

Correspondence: fausto.castagnetti@unibo.it

SUPPLEMENTAL MATERIALS

Table 1s. Secondary endpoints of the study.

Toxicity and compliance to treatment
CCyR rate at 3, 6, 12, 18 and 24 months
Rate and degree of molecular response at 3, 6, 12, 18 and 24 months
Time to CCyR, MMR and deep MR
Outcome (OS, PFS, EFS)
Patient-reported QoL at baseline and at 3, 6, 12, 18 and 24 months

Legend:
CCyR: Complete Cytogenetic Response; MMR: Major molecular response; Deep MR: MR^4 and $MR^{4.5}$; OS: overall survival; PFS: progression-free survival; EFS: event-free survival; QoL: quality of life (the analysis of Qit will be reported in a separated report).

Table 2s. Patients with progression to accelerated or blastic phase.

	Baseline characteristics						Outcome					
N.	Age	Gender	CCA or variant Ph	Sokal score	Blasts (PB %)	Transcript type	Time to progression (mos)	Phenotype	BCR-ABL1 Mutations	Treatment	F-up (mos)	Status
1.	41	M	No	0.81	1	e13a2	1	Ly BC	T315I	CHT AlloSCT	30	Alive
2.	46	M	No	1.10	1	e14a2	4	AP	V280A	Dasatinib	31	Alive
3.	32	M	No	0.53	4	e14a2	6	AP	WT	AlloSCT	24	Alive
4.	43	M	No	0.59	0	e13a2	19	My BP	WT	Dasatinib	24	Alive

Legend:
M: male; CCA: clonal chromosomal abnormalities in Philadelphia-positive cells; PB %: percentage in peripheral blood; mos: months; Ly BC: lymphoid blast crisis; My BC: myeloid blast crisis; AP: accelerated phase; F-up: follow-up

Table 3s. Patient distribution according to fasting glucose, glycosylated hemoglobin, total cholesterol, LDL cholesterol, HDL cholesterol and triglycerides by time. The levels recommended by the American Diabetologist Association (ADA) and American Association of Clinical Endocrinologist (AACE) were selected.

	Fasting glucose, mg/dL			HbA1c, %		
	126-150	151-200	≥ 200	6.5-6.9	7.0-7.9	≥ 8.0
Baseline	4%	1%	0	5%	4%	2%
1 month	3%	5%	2%	7%	4%	1%
2 months	6%	3%	1%	4%	4%	0
3 months	5%	6%	1%	3%	6%	1%
6 months	2%	6%	1%	3%	3%	3%
12 months	7%	3%	2%	4%	1%	2%
18 months	5%	4%	2%	5%	2%	2%
24 months	7%	3%	2%	3%	3%	3%
	Total cholesterol, mg/dL			Triglycerides, mg/dL		
	< 200	200-239	≥ 240	150-199	200-499	≥ 500
Baseline	75%	21%	4%	27%	22%	0
1 month	66%	27%	7%	9%	4%	0
2 months	57%	32%	11%	13%	2%	0
3 months	47%	36%	16%	14%	6%	0
6 months	38%	39%	24%	14%	6%	0
12 months	37%	36%	27%	19%	5%	0
18 months	37%	29%	33%	13%	6%	0
24 months	36%	34%	29%	11%	9%	0
	LDL cholesterol, mg/dL			HDL cholesterol, mg/dL		
				< 40 (M) < 50 (F)	40-59 (M) 50-59 (F)	
	130-159	160-189	> 190			> 60
Baseline	17%	5%	1%	70%	19%	11%
1 month	28%	8%	1%	26%	42%	32%
2 months	19%	9%	2%	22%	40%	38%
3 months	31%	14%	3%	18%	42%	40%
6 months	30%	19%	5%	20%	46%	34%
12 months	26%	20%	4%	19%	40%	41%
18 months	22%	20%	9%	15%	37%	48%
24 months	33%	17%	3%	10%	42%	48%

Legend:
HbA1c: glycosylated hemoglobin; M: males; F: females

Table 4s. Molecular responses in the ENESTnd study, in the ENEST1st study and in this GIMEMA CML WP study, with nilotinib 300 mg TD.

Molecular response	$MR^{3.0}$			$MR^{4.0}$			$MR^{4.5}$		
Study	ENnd	EN1st	GIM	ENnd	En1ST	GIM	ENnd	EN1st	GIM
6 months									
- Response AT	33%	NR	53%	NR	NR	12%	NR	NR	2%
- Response BY	34%	53%	50%	9%	20%	12%	4%	15%	2%
12 months									
- Response AT	44%	56%	57%	NR	31%	28%	NR	15%	7%
- Response BY	46%	69%	67%	15%	37%	28%	12%	21%	10%
18 months									
- Response AT	NR	66%	63%	NR	38%	31%	NR	21%	11%
- Response BY	63%	77%	75%	32%	49%	38%	19%	32%	17%
24 months									
- Response AT	NR	61%	65%	NR	40%	46%	NR	22%	17%
- Response BY	71%	80%	78%	39%	55%	51%	25%	39%	24%

Legend:
Response AT timepoints is the percentage of patients who were in that response at that time, calculated by dividing the number of patients with that response at that time by the the number of all patients; Response BY timepoints is the cumulative probability of achieving that response within each time interval, calculated by the Kaplan-Meier method; ENnd: ENESTnd study; EN1st: ENEST1st study; GIM: GIMEMA CML WP study; NR: not reported.
Notes:
Data from different studies, to be interpreted with caution; the enrollment criteria and the guidelines for dose adaptation and treatment discontinuation were not identical. The minimum follow-up, 2 years, is equal in all three studies. The number of patients was 282 in the ENESTnd study [2-4], 1089 in ENEST1st study [10], and 130 in the GIMEMA study. The median age was 47, 53 and 50 years. High risk patients (Sokal) were 28%, 18%, and 21%, respectively. The patients who were still on nilotinib at 2 years were 74%, 81%, and 80%, respectively.

Figure 1s. Arterial event-free survival by cardiovascular risk.

The estimated 30-month arterial event-free survival was 96% (95% CI, 87-99%) in patients with low and intermediate cardiovascular risk and 77% (95% CI, 60-88%) in patients with high and very high cardiovascular risk according to the European Guidelines on cardiovascular disease prevention in clinical practice, version 2012 ($p < 0.001$).