

Treatment-free remission in chronic myeloid leukemia patients treated front-line with nilotinib: 10-year follow-up of the GIMEMA CML 0307 study

Gabriele Gugliotta,¹ Fausto Castagnetti,¹ Massimo Breccia,² Luciano Levato,³ Tamara Intermesoli,⁴ Mariella D'Adda,⁵ Marzia Salvucci,⁶ Fabio Stagno,⁷ Giovanna Rege-Cambrin,⁸ Mario Tiribelli,⁹ Bruno Martino,¹⁰ Monica Bocchia,¹¹ Michele Cedrone,¹² Elena Trabacchi,¹³ Francesco Cavazzini,¹⁴ Ferdinando Porretto,¹⁵ Federica Sorà,¹⁶ Maria Pina Simula,¹⁷ Francesco Albano,¹⁸ Simona Soverini,¹ Robin Foà,² Fabrizio Pane,¹⁹ Michele Cavo,¹ Giuseppe Saglio,²⁰ Michele Baccarani²¹ and Gianantonio Rosti²² on behalf of the GIMEMA CML Working Party

¹Istituto di Ematologia Seragnoli, IRCCS Azienda Ospedaliero-Universitaria di Bologna, Bologna; ²Hematology, Department of Translational and Precision Medicine, Policlinico Umberto I, Sapienza University, Rome; ³Unità di Ematologia, Azienda Ospedaliera Pugliese-Ciaccio, Catanzaro; ⁴Unità di Ematologia, ASST Papa Giovanni XXIII, Bergamo; ⁵Unità di Ematologia, ASST Spedali Civili Brescia, Brescia; ⁶Unità di Ematologia, Ospedale S. Maria delle Croci, Ravenna; ⁷Hematology Section and BMT Unit, Rodolico Hospital, AOU Policlinico Rodolico - San Marco, Catania; ⁸Unità di Medicina Interna, Ospedale San Luigi Gonzaga, Università di Torino, Orbassano; ⁹Clinica Ematologica, Dipartimento di Area Medica, Azienda Sanitaria Universitaria Friuli Centrale, Udine; ¹⁰Unità di Ematologia, Grande Ospedale Metropolitano-G.O.M. Bianchi-Melacrino-Morelli, Reggio Calabria; ¹¹Hematology Unit, Azienda Ospedaliero-Universitaria Senese, Siena University, Siena; ¹²Unità di Ematologia, Ospedale San Giovanni Addolorata, Rome; ¹³Unità di Ematologia, Ospedale Guglielmo da Saliceto, Piacenza; ¹⁴Unità di Ematologia, Azienda Ospedaliero-Universitaria, Ferrara; ¹⁵Unità di Ematologia, Ospedale La Maddalena, Palermo; ¹⁶Unità di Ematologia, Fondazione Policlinico Universitario A Gemelli IRCSS, Università Cattolica, Roma; ¹⁷Ematologia e Centro Trapianti Midollo Osseo, Ospedale Oncologico Businco, Cagliari; ¹⁸Hematology and Stem Cell Transplantation Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), Aldo Moro University, Bari; ¹⁹Unità di Ematologia, Università Federico II, Naples; ²⁰Divisione Universitaria di Ematologia e Terapie Cellulari, A.O. Ordine Mauriziano, Turin; ²¹Istituto di Ematologia Seragnoli, Università di Bologna, Bologna and ²²IRCCS - Istituto Scientifico Romagnolo per lo Studio e la Cura dei Tumori (IRST), Meldola (FC), Italy.

Correspondence: G. Gugliotta
gabriele.gugliotta@unibo.it

Received: October 13, 2021.

Accepted: March 25, 2022.

Prepublished: April 7, 2022.

<https://doi.org/10.3324/haematol.2021.280175>

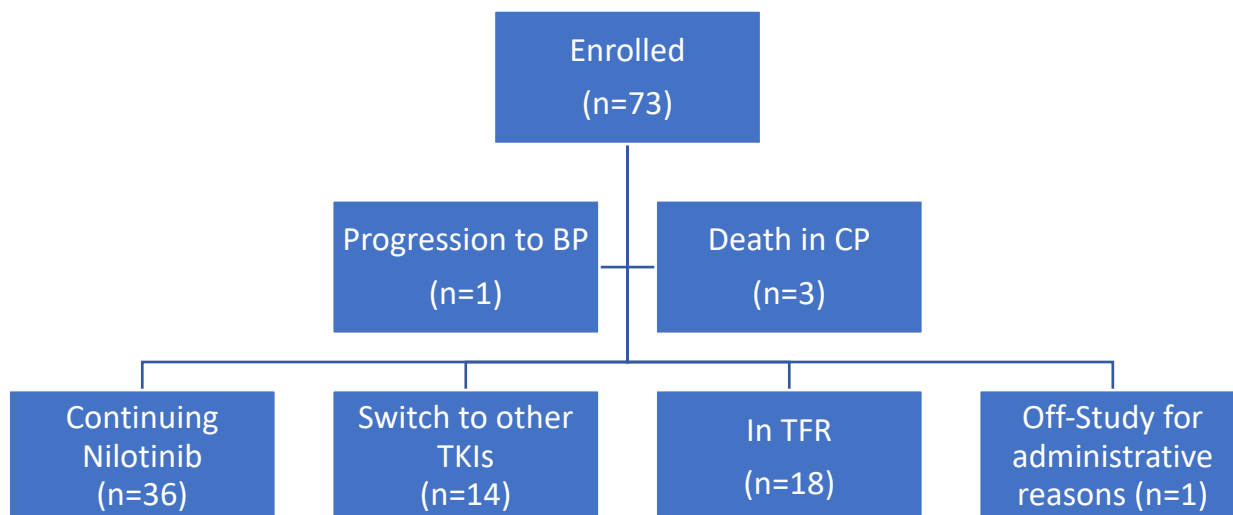
©2022 Ferrata Storti Foundation

Published under a CC BY-NC license



SUPPLEMENTARY MATERIAL

Figure S1. Patients disposition



BP: blast phase; CP: chronic phase; TKIs: tyrosine-kinase inhibitors; TFR: treatment-free remission

Table S1. Patients with BCR-ABL > 10% at 3 months

Patient	Age	Sex	Sokal	ELTS	Transcript type	NIL reduction / discontinuation for AE in the first 3 months	CCyR (1 st time)	MMR (1 st time)	MR4 (1 st time)	Progression to AP/BP	NIL duration (months)
1	65	M	High	High	e13a2	No	6 months	27 months	42 months	No	116
2	28	F	Low	Low	e13a2	Yes, for transaminase elevation G3	6 months	15 months	Not reached	No	76
3	25	M	Int	High	e13a2	Yes, for thrombocytopenia G3	6 months	Not reached	Not reached	No	60
4	56	F	Int	Low	e13a2	Yes, for hyperbilirubinemia G3	6 months	9 months	18 months	No	123

At 3 months BCR-ABL was > 10% in 4 patients, < 10% in 66 patients, and not evaluable in 3 patients.

ELTS: EUTOS long-term survival score; G3: grade 3, according to Common Terminology Criteria for Adverse Events; CCyR: complete cytogenetic response; MMR: major molecular response; MR4: deep molecular response; AP: accelerated phase; BP: blast phase.

Table S2. Response at milestones according to the ELN and GIMEMA recommendations

	At 3 months n (%)	At 6 months n (%)	At 12 months n (%)	At 24 months n (%)
ELN 2020				
• OPTIMAL	66 (90.4)	61 (83.6)	55 (75.3)	55 (75.3)
• WARNING	0	3 (4.1)	12 (16.4)	9 (12.3)
• FAILURE	3 (4.1)	1 (1.4)	2 (2.7)	0
• Not evaluable	4 (5.4)	8 (10.9)	4 (5.5)	9 (12.3)
GIMEMA				
• OPTIMAL	66 (90.4)	61 (83.6)	55 (75.3)	33 (45)
• WARNING	0	3 (4.1)	12 (16.4)	22 (30.1)
• FAILURE	3 (4.1)	1 (1.4)	2 (2.7)	9 (12.3)
• Not evaluable	4 (5.4)	8 (10.9)	4 (5.5)	9 (12.3)

Table S3. Ten-year TFR rates according to response at the ELN and GIMEMA milestones

	At 3 months n (%)	At 6 months n (%)	At 12 months n (%)	At 24 months n (%)
ELN 2020				
• OPTIMAL	16/66 (24.2)	18/61 (29.5)	16/55 (21.3)	13/55 (23.6)
• WARNING	0/3	0/3	1/12 (8.3)	2/9 (22.2)
• FAILURE	0/3	0/1	0/2	0/0
• Not evaluable	2/4 (50)	0/8	1/4 (25)	3/9 (33.3)
GIMEMA				
• OPTIMAL	16/66 (24.2)	18/61 (29.5)	16/55 (21.3)	10/33 (30.3)
• WARNING	0/3	0/3	1/12 (8.3)	3/22 (13.6)
• FAILURE	0/3	0/1	0/2	2/9 (22.2)
• Not evaluable	2/4 (50)	0/8	1/4 (25)	3/9 (33.3)

Table S4. Patients with arterial obstructive events

Pt	AOE	Sex	Age at CML diagnosis (years)	CVRFs	Time to AOE (months)	Age at AOE (years)	Symptomatic	Treatment	NIL D/C for AOE	Follow-up after AOE (months)	Status	OS	Therapy at last contact
1	PAD [°]	F	84	S, DM	35	87	yes	Amputation	no [§]	33	dead [°]	68	-
2	PAD	F	67	HT, DM, C, BMI	38	69	yes	Vascular surgery	yes	84	alive	122	TFR
3	PAD	M	43	HT, DM, C, BMI	101	51	yes	Amputation	yes	24	alive	125	IM
4	PAD	M	59	S, DM, IHD	45	63	no	Medical	yes	77	alive	122	IM
5	PAD	M	77	HT	26	78	yes	Amputation	yes	96	alive	122	DAS
6	PAD	M	65	S	42	68	yes	Vascular surgery	yes	86	alive	128	IM
7	PAD	M	58	S	84	65	yes	Medical	yes	37	alive	121	DAS
8	Coronary - MI	F	50	HT	44	53	yes	Angioplasty+Stent	no ^{§§}	78	alive	122	IM
9	Coronary - MI	F	72	-	88	79	yes	Angioplasty+Stent	yes	34	alive	122	BOS
10	Coronary - MI ^{°°}	M	61	S, C, IHD, BMI	28	63	yes	Angioplasty+Stent	no [§]	97	alive	125	NIL
11	Coronary - MI	F	67	HT, C	24	69	yes	Angioplasty+Stent	no [§]	101	alive	125	NIL
12	Coronary - Angina	F	68	HT	64	73	yes	Angioplasty+Stent	TFR*	57	dead [^]	121	-
13	Carotid stenosis	M	68	HT	128	78	no	Vascular surgery	TFR*	1	alive	129	TFR
14	Carotid stenosis	M	43	-	75	49	no	Medical	no [§]	47	alive	122	TFR
15	Carotid stenosis	M	70	-	76	76	no	Medical	yes	43	alive	119	IM
16	Stroke	F	79	-	113	88	yes	Medical	no [§]	10	alive	123	NIL
17	Transient ischemic attack	M	65	HT	98	73	yes	Medical	yes	30	alive	128	TFR

[°] the patient had multiple AOE during the follow-up (peripheral arterial disease, stroke, and myocardial infarction); she died at 90 y from congestive heart failure

^{°°} the patient had multiple AOE during the follow-up (multiple coronary events)

[§] the patient continued NIL at a lower dose

^{§§} the patient continued NIL at a lower dose for 3 years before it was decided a precautionary switch to imatinib

* the patient was diagnosed with an AOE while in TFR

[^] the patient died at 78 y from dementia

AOE: arterial obstructive events; CVRFs: cardiovascular risk factors; D/C: discontinuation; OS: overall survival; PAD: peripheral arterial disease; MI: myocardial infarction; TIA: transient ischemic attack; S: smoking; DM: diabetes mellitus; HT: hypertension; C: hypercholesterolemia; BMI: body mass index >30; IHD: ischemic heart disease; TFR: treatment-free remission; IM: imatinib; DAS: dasatinib; BOS: bosutinib; NIL: nilotinib