Highlights in Ematologia
Treviso, 22-23 Novembre 2019

REGIONE VENETO
AZIENDA U.L.S.S. n. 2
della Marca Trevigiana

Real life:

l'approccio diagnostico terapeutico

al paziente ottuoagenario

nella Leucemia Mieloide Cronica

Fausto Castagnetti

Università di Bologna

Agenda

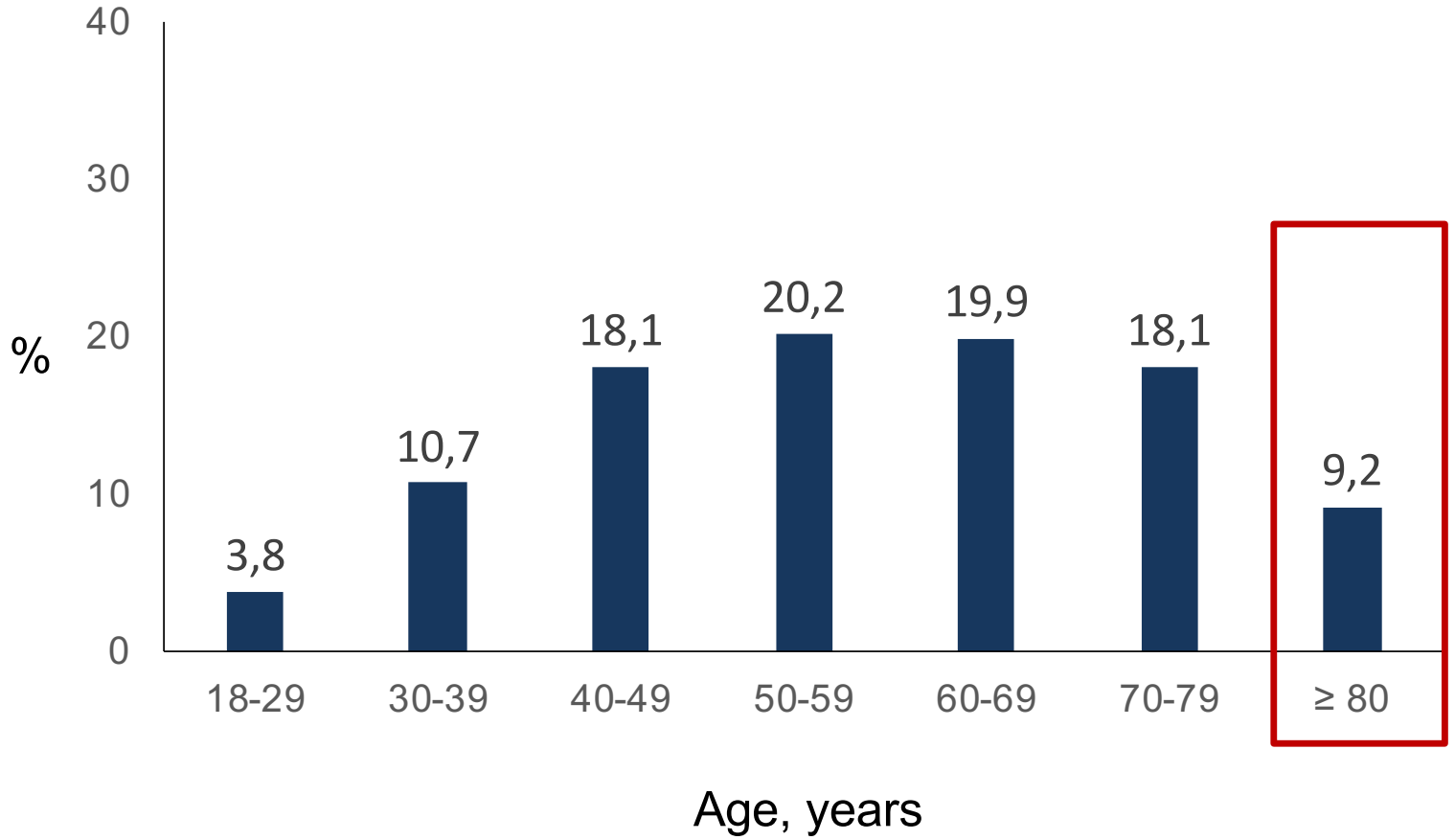
- Caratteristiche del paziente anziano affetto da LMC
- Efficacia dei TKIs nel paziente anziano
- Impatto clinico delle comorbidità
- Stratificazione del rischio di progressione nel paziente anziano
- Le raccomandazioni di trattamento

Agenda

- Caratteristiche del paziente anziano affetto da LMC

Distribution by age of newly diagnosed CP CML patients

A population-based registry (Emilia-Romagna and Sicily, N = 337)

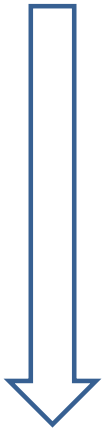


Castagnetti et al. Am. J. Hematol. 2017;92:82–87.

Incidence of CML over a population of 7,400,00 inhabitants ≥ 18 yrs

A population-based registry (Emilia-Romagna and Sicily, N = 337)

Age	Raw incidence / 100,000 / year		
	Females	Males	Overall
18-29	0.19	0.52	0.35
30-39	0.67	0.88	0.77
40-49	1.20	1.63	1.41
50-59	1.48	1.78	1.62
60-69	2.30	2.09	2.20
70-79	2.02	2.64	2.31
≥ 80	1.15	2.32	1.61
Overall	1.21	1.56	1.41



Castagnetti et al. Am. J. Hematol. 2017;92:82–87.

Prevalence of most common comorbidities

Any age

EUTOS Registry[1] (N = 2360)

Patients without comorbidities	44.5%
Patients with one comorbidity	28.7%
Patients with two comorbidities	15.3%
Patients with >2 comorbidities	11.5%

Hypertension	25.7%
Cardiovascular disorders	17.2%
Diabetes mellitus, all types	9.5%
Neurologic disorders	6.9%
Behavior disorders	2.3%
Chronic renal disease	2.6%
Chronic liver disease	2.2%
Others, or unspecified	31.7%

Very elderly (≥ 75 years)

Italian data[2] (N = 263)

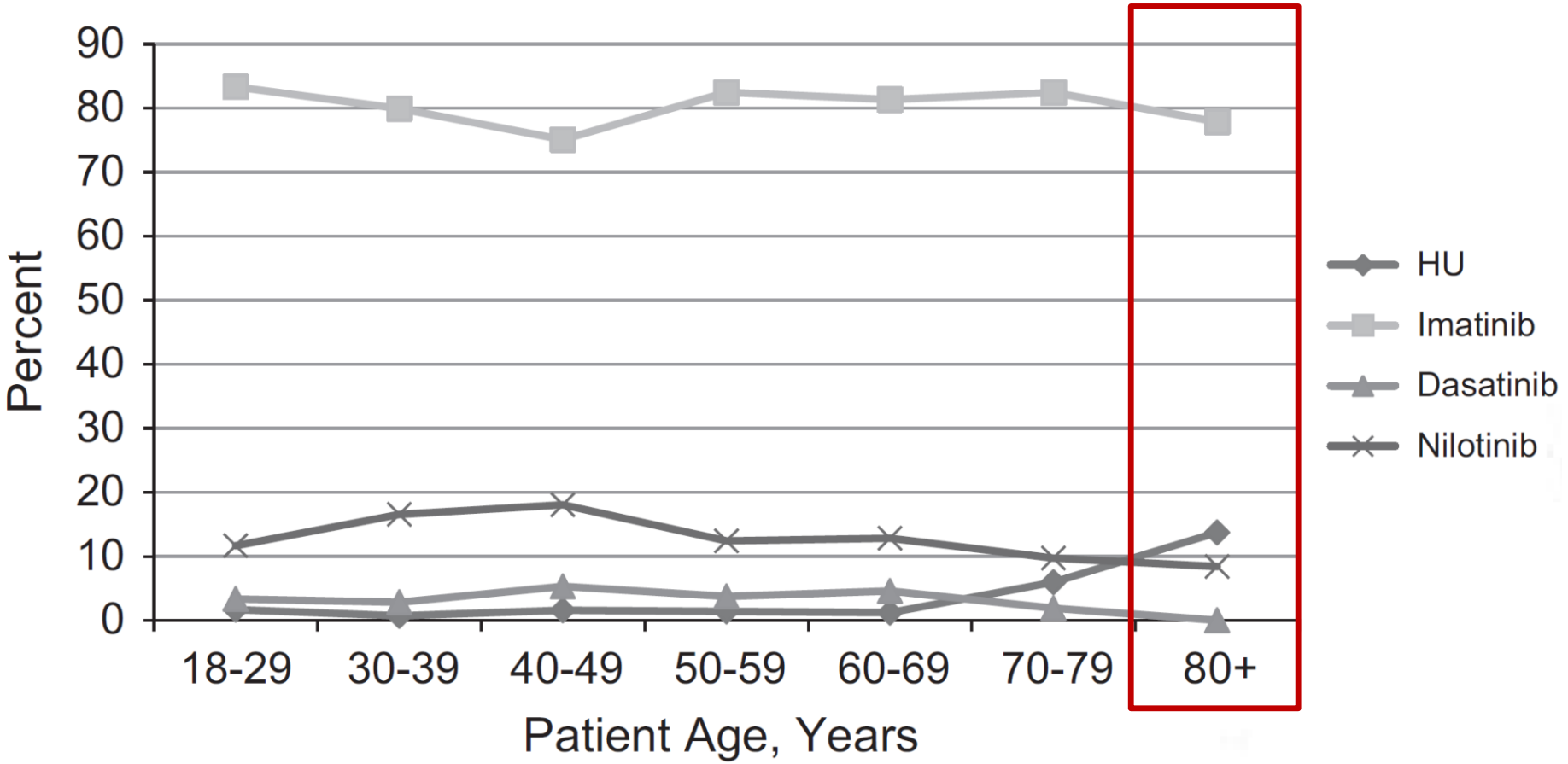
Comorbidities at diagnosis, *n* (%)	
0–1	63 (23.9)
2–3	147 (55.8)
≥4	53 (20.3)

Arterial hypertension	150 (61.9)
Arrythmias	41 (15.5)
Dyslipidemia	28 (10.6)
Cardiovascular disease	85 (32.3)
Diabetes	50 (19.7)
Previous neoplasm	59 (22.4)
Gastro intestinal disease	59 (22.4)
Kidney disease	26 (9.8)
Chronic bronchitis	25 (9.5)
Neurologic or psychiatric disorders	26 (9.8)
Thyroid dysfunction	22 (8.3)
Benign prostatic hyperplasia	22 (8.3)
Other	28 (10.6)

1. Hoffmann et al. Leukemia (2015) 29, 1336–1343
2. Crugnola M et al. Annals of Hematology. 2019; 98:2329–38

Patients treated with IM, NIL, DAS and HU by age

EUTOS Registry **N = 2212**



Hoffmann et al. Leukemia. 2017;31(3):593-601

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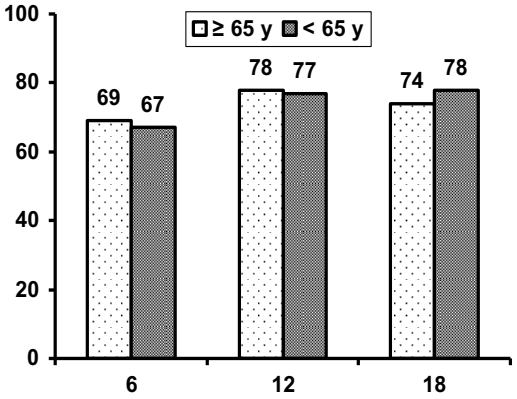
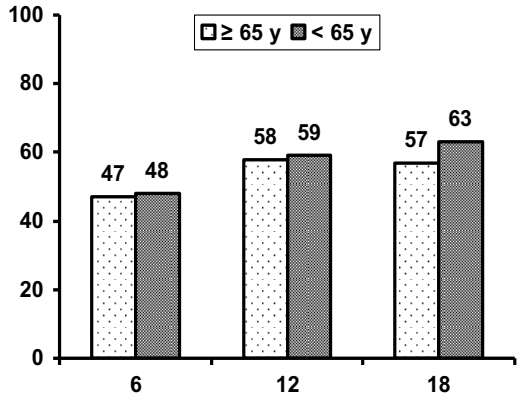
AGE DOES NOT INFLUENCE RESPONSE AND DISEASE TRANSFORMATION IN CML PATIENTS TREATED WITH IMATINIB IN EARLY CHRONIC PHASE

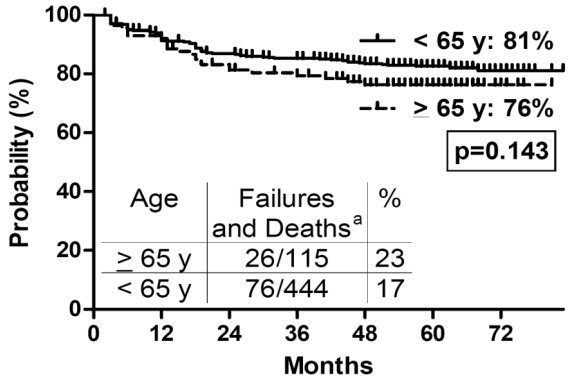
CCyR Rate at Each Time Point



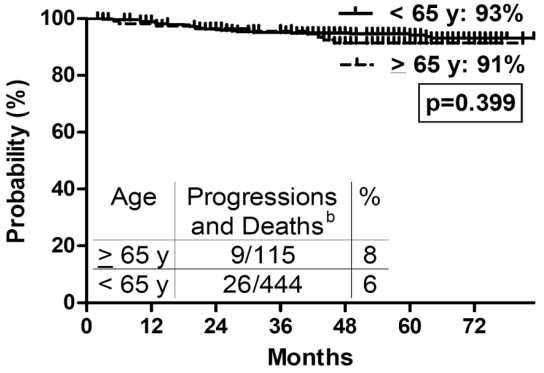
MMR Rate at Each Time Point



Failure-Free Survival



Progression-Free Survival



Gugliotta et al. Blood 2011.

GIMEMA CML WP

Very elderly (> 75 years old) CML patients treated with IM

Cytogenetic and molecular response N = 263

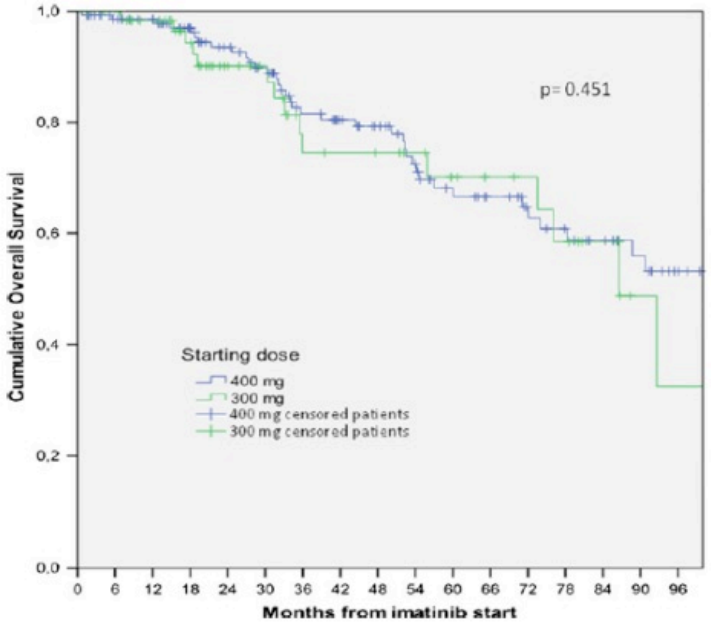
	Age < 80 years	Age ≥ 80 years	*p*
Complete haematologic response, *n* (%)	154 (92.2)	90 (93.7)	0.439
Complete cytogenetic response, *n* (%)	123 (73.6)	61 (63.5)	0.088
Major molecular response, *n* (%)	97 (58.0)	51 (53.1)	0.435
Deep molecular response, *n* (%)	40 (23.9)	23 (24.0)	0.852

Crugnola M et al. Annals of Hematology. 2019; 98:2329–38

Very elderly (> 75 years old) CML patients treated with IM

Dose reductions

	Age < 80 years	Age ≥ 80 years	*p*
Permanent dose reduction, *n* (%)	76/167 (45.5%)	46/96 (48%)	0.706
Temporary imatinib discontinuation, *n* (%)	48/167 (28.7%)	27/96 (28.1%)	0.915
Permanent imatinib interruption, *n* (%)	20/167 (12%)	10/96 (10.4%)	0.702

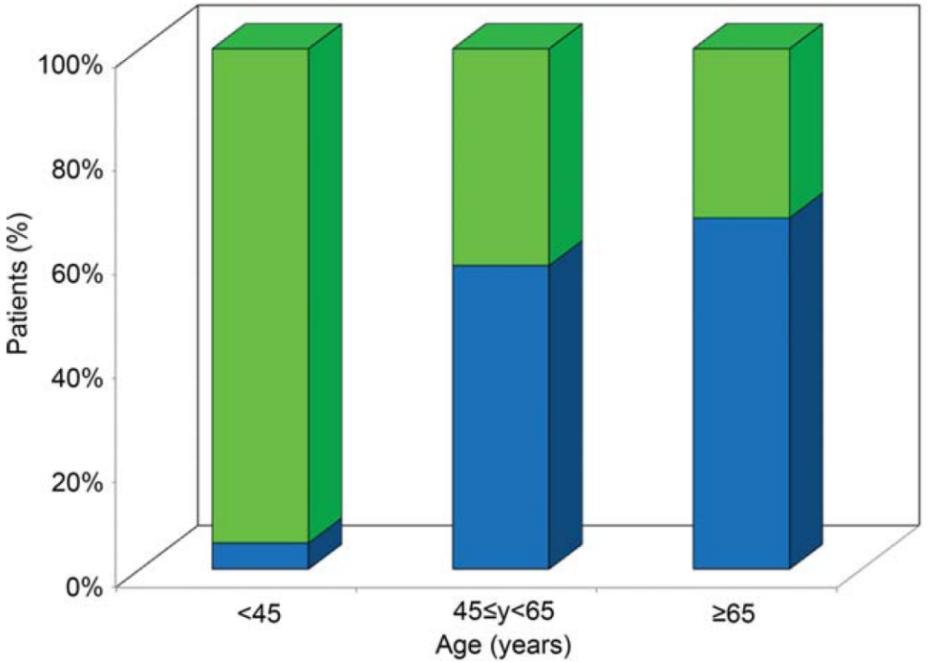


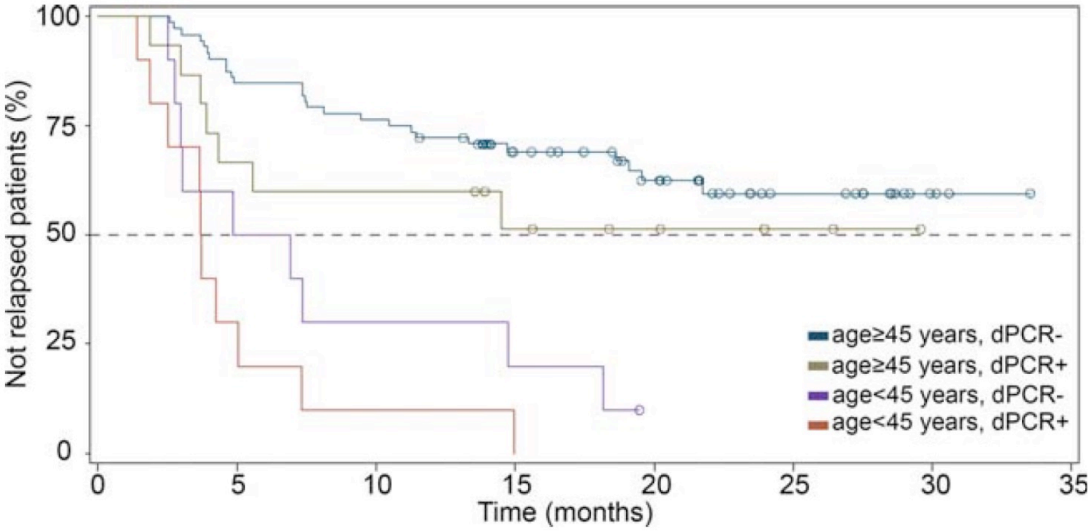
30% of patients have been treated with 300 mg daily (instead of 400 mg daily) as initial dose

Crugnola M et al. Annals of Hematology. 2019; 98:2329–38
Latagliata et al. Drugs Aging. 2013; 30:629–637

ISAV study

Higher TFR rates in elderly patients





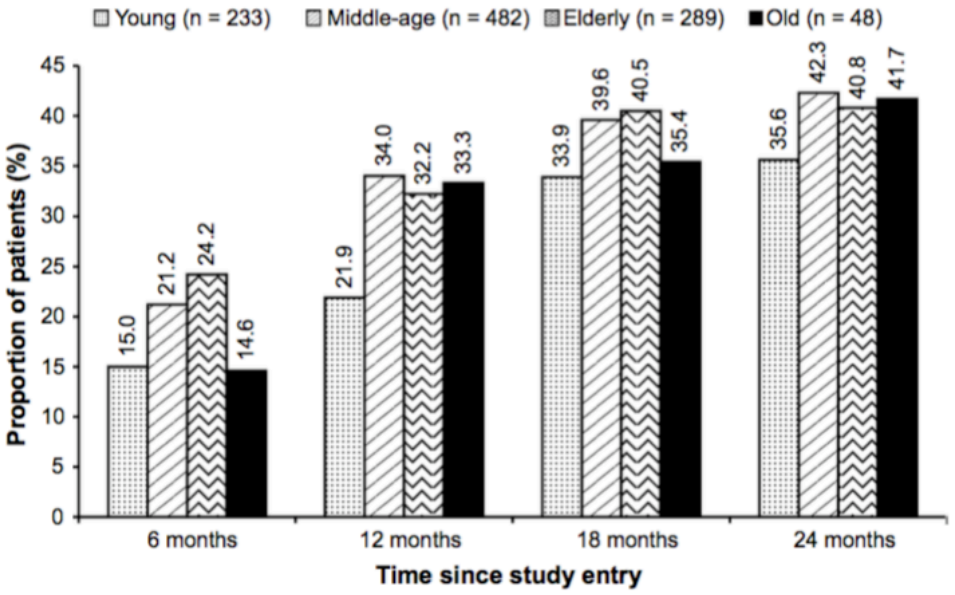
		Total Patients (N=108)	Not Relapsed (N=56)		Relapsed (N=52)		p-value
		N	N	%	N	%	
Age (years)	< 45	20	1	5	19	95	<0.0001
	45 ≤ 65	48	28	58	20	42	
	≥65	40	27	68	13	32	

Mori et al. Am. J. Hematol. 2015; 90:910–914

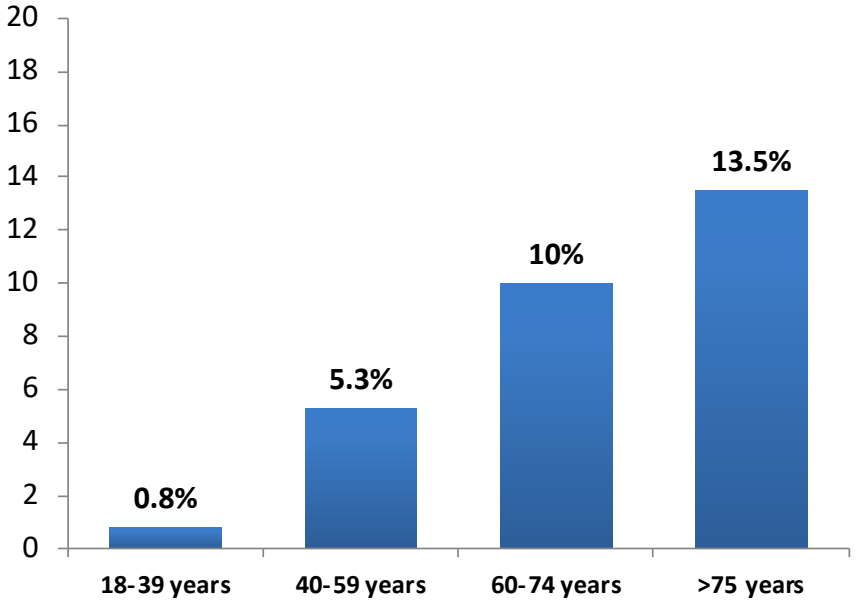
ENEST1st study

Efficacy and toxicity of frontline nilotinib across age groups

Rates of MR^4



CV events



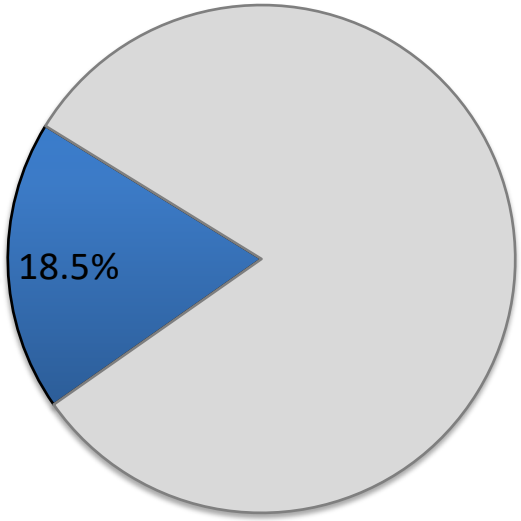
Giles et al. J Cancer Res Clin Oncol. 2017;143:1585-1596.

Frontline dasatinib in 65 CML patients older than 65 years

Response at different time points

	3rd Month	6th Month	12th Month
Too early	/	1	7
Evaluable	65	64	58
Not done	6 (9.3%)	6 (9.4%)	/
Discontinuation	2 (3.1%)	4 (6.2%)	7 (12.1%)
Less than CCyR	10 (15.3%)	5 (7.8%)	3 (5.1%)
CCyR*	47 (72.3%)	49 (76.6%)	48 (82.8%)
MMR	19 (29.2%)	36 (56.2%)	37 (63.8%)
MR 3.0	13	16	20
MR 4.0	4	13	9
MR 4.5	2	7	8

Pleural effusion



Latagliata et al. Neoplasia 2016;18:536-540.

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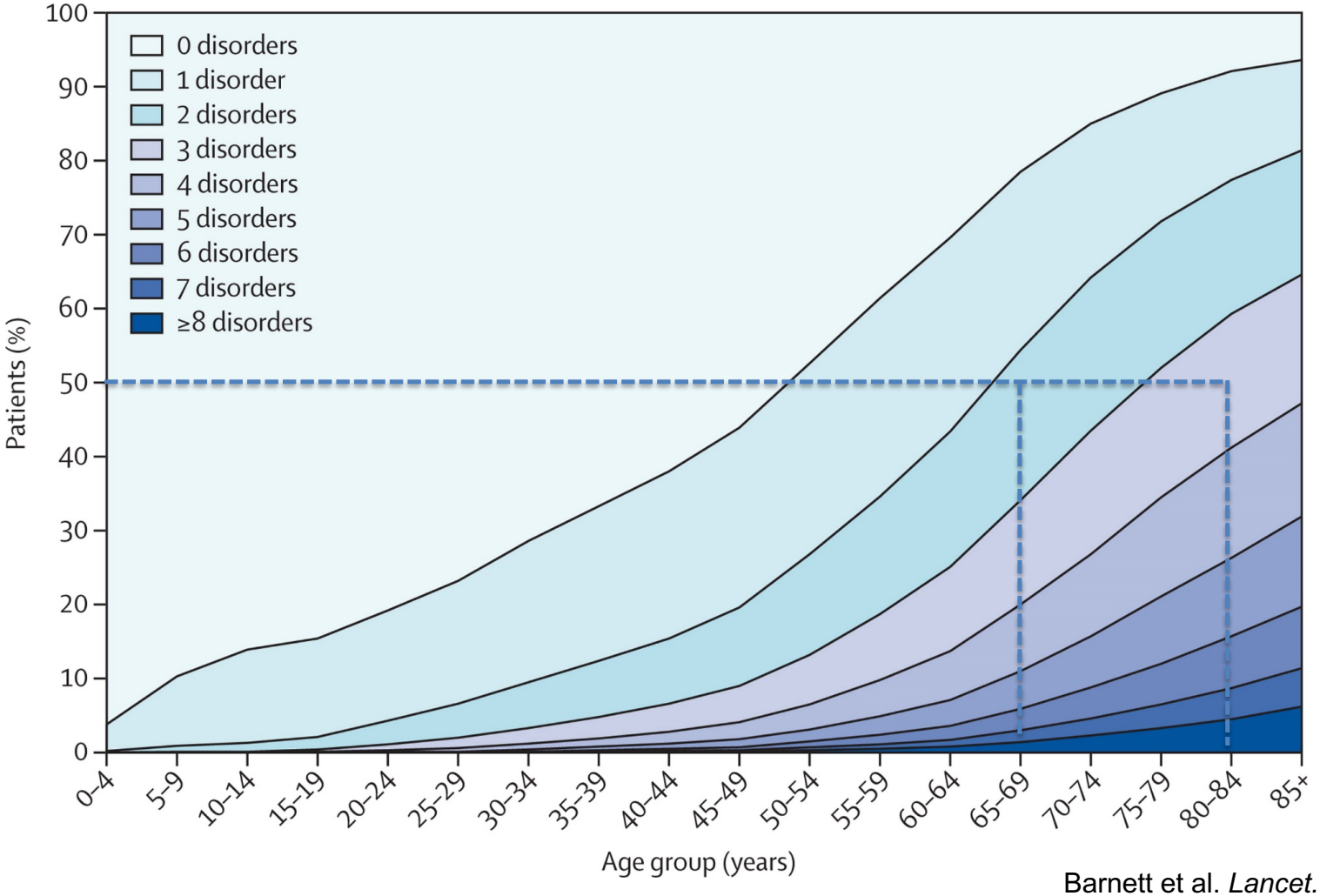
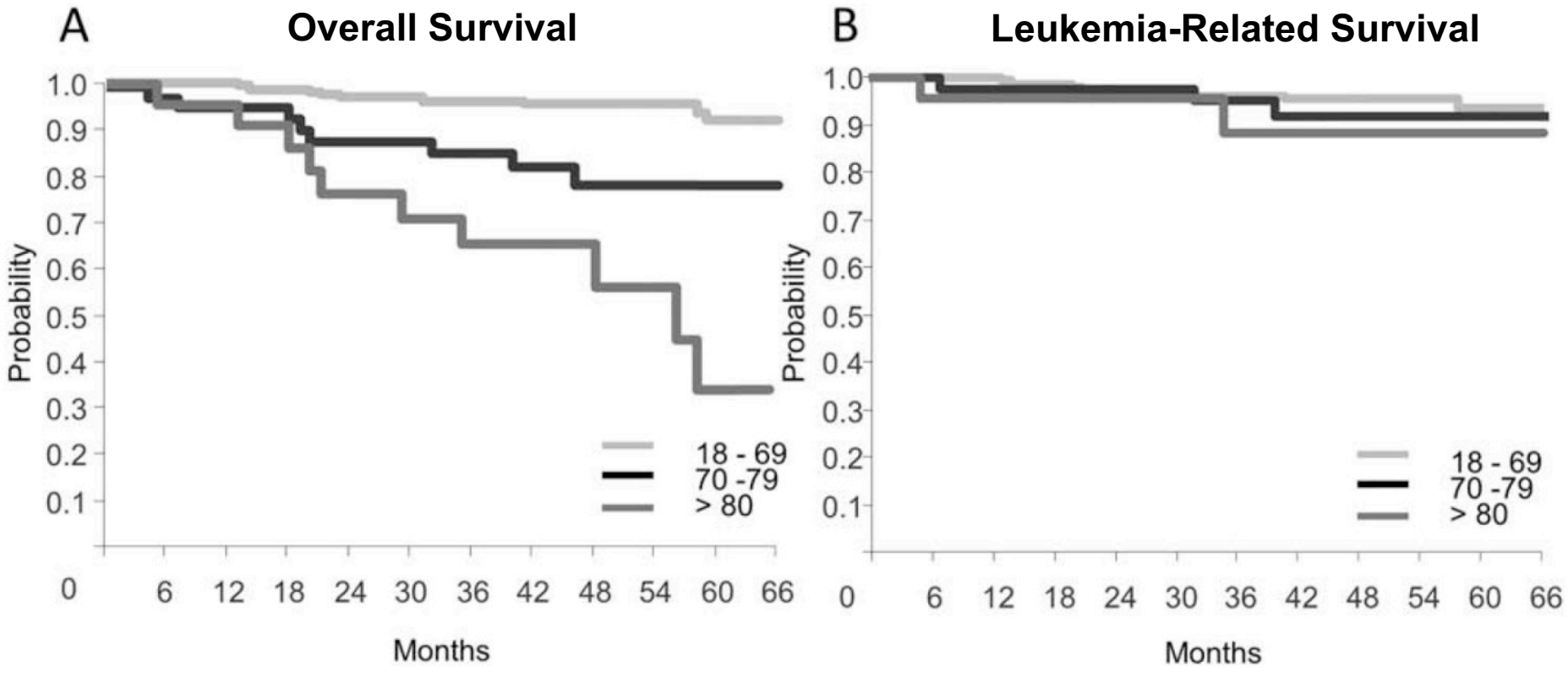
Age and multimorbidities



Barnett et al. *Lancet.* 2012;380:37-43.

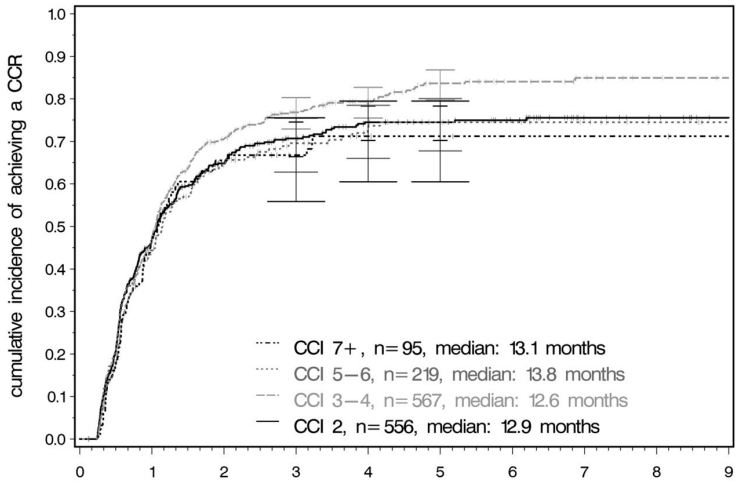
Survival of CML patients by age

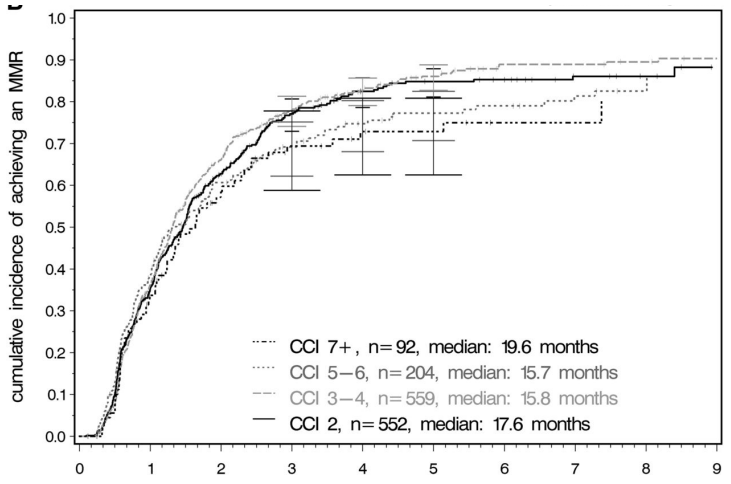


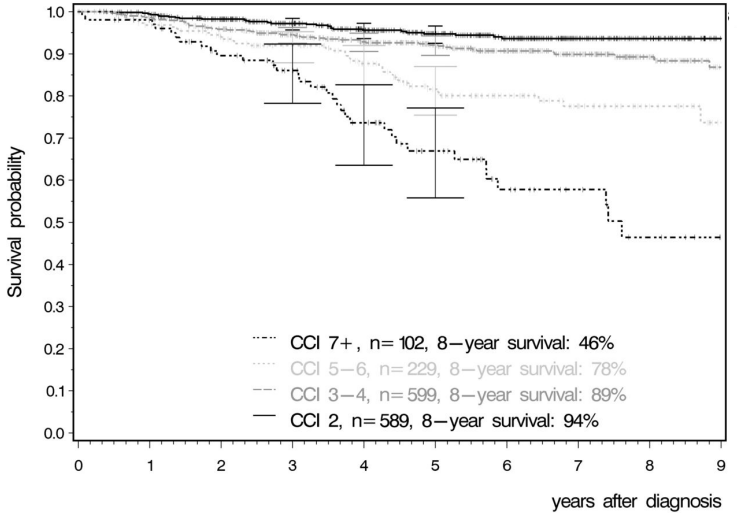
Castagnetti et al. Am. J. Hematol. 2017;92:82–87.

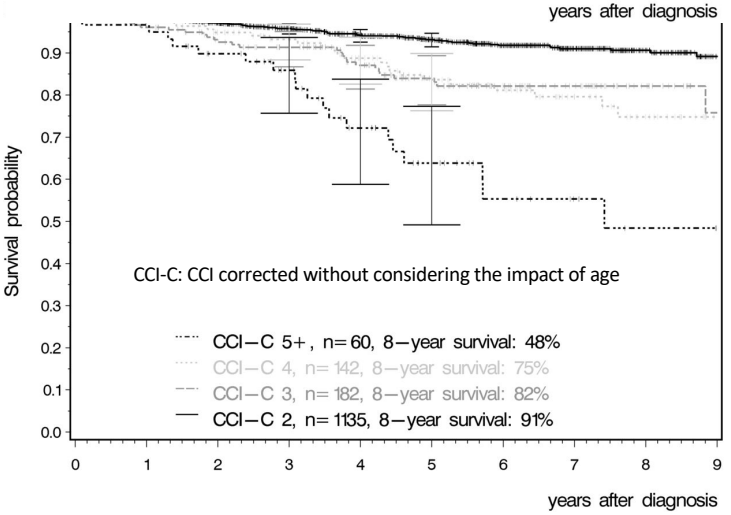
Comorbidities impact on CML survival, but not on response: German data

- There is no negative effect of comorbidities on remission rates and progression to advanced phases in CML.
- There is a strong negative association between comorbidities at diagnosis and overall survival.









Saussele et al. Blood. 2015;126:42-49.

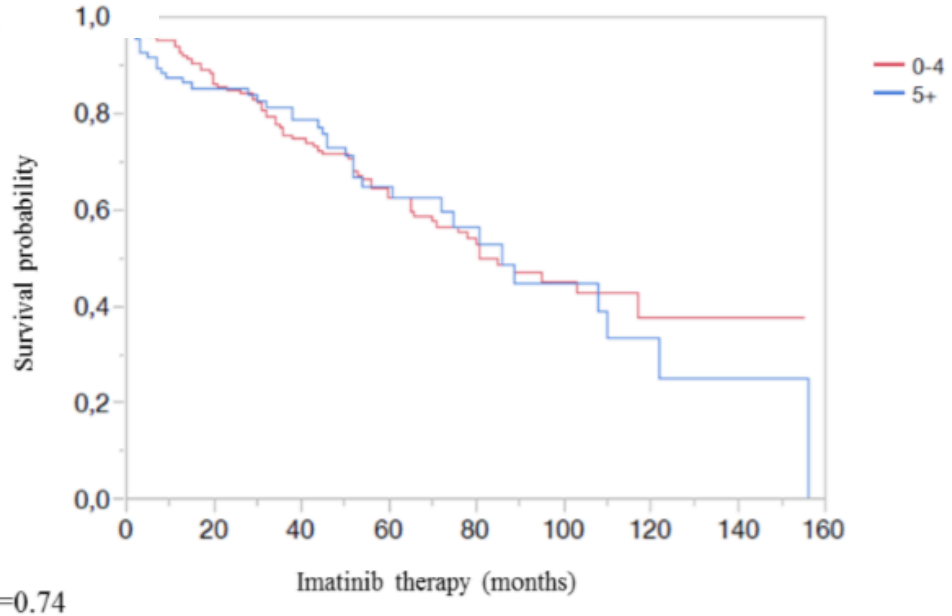
No impact of polypharmacy in elderly patients treated with imatinib

Table 2: Response rate and toxicity of 296 chronic-phase CML patients aged 75 years or older according to the exposure or not to polypharmacy.

Clinical outcomes	Patients (n. 296)			
	No polypharmacy (N of drugs 0-4) (n. 192)	Polypharmacy (N of drugs >5) (n. 104)	Univariate OR (95% CI)	Multivariable* OR (95% CI)
CCyR within 6 months, n (%)	50 (26)	28 (26.9)	0.81 (0.46-1.43)	0.96 (0.86-1.09)
CCyR 7 to 12 months, n (%)	43 (22.4)	20 (19.2)	0.91 (0.53-1.56)	0.96 (0.86-1.08)
MMR, n (%)	93 (48.4)	60 (57.7)	0.84 (0.51-1.38)	1.00 (0.90-1.11)
Hematological toxicity, n (%)	80 (41.7)	46 (44.2)	0.93 (0.57-1.52)	1.03 (0.93-1.14)
Extra-hematological toxicity, n (%)	108 (56.3)	59 (56.7)	1.33 (0.82-2.17)	1.05 (0.95-1.17)

Abbreviations: OR=Odds Ratio; CCyR=complete cytogenetic response; MMR=major molecular response.
* Adjusted for age and sex.

b



p=0.74

Iurlo et al. Oncotarget. 2016;7:80083-80090.

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EUTOS long-term survival (ELTS) score

Same variables included in the Sokal score (differently weighted)

	SOKAL Overall Survival CHT	EURO Overall Survival α – IFN	EUTOS CCyR at 18M IMATINIB	EUTOS Long-term Survival CML-related Survival IMATINIB
Age (yrs)	**0,0166 x (Age-43,4)**	0.666 x Age (> 50)	-	**0.0025 x (Age/10)^3**
Spleen (cm)	**0,0345 x (Spleen-7,51)**	0.042 x Spleen	4 x Spleen	**0.0615 x Spleen**
Platelets (10^3/µL)	**0,188 x [(PLT/700)^2-0,563]**	1.0956 x PLT (> 1500)	-	**0.4104 x (PLT count/1000)$^{-0.5}$**
Myeloblast (%)	**0,0887 x (MB-2,1)**	0.0584 x MB	-	**0.1052 x MB**
Eosinophils (%)	-	0.20399 x Bas (> 3)	7 x Bas	
Basophils (%)	-	0.0413 x Eos	-	

Relative risk				
Low	≤ 0.80	≤ 780	≤ 87	< 1.5680
Intermediate	0.81 – 1.20	781-1480	-	1.568 - 2.2185
High	> 1.21	> 1481	> 87	2.2185

SOKAL et al. Blood 1984; 63: 789-799
HASFORD et al. JNCI 1998; 90: 850-858
HASFORD et al. Blood 2011; 118: 686-692
PFIRRMANN M et al, LEUKEMIA 2016;30:48-56

Sokal score of patients classified by ELTS score

All patients
N = 904

		Sokal		
		LOW	INT	HIGH
ELTS	**LOW**	**64.3%**	28.3%	7.4%
	INT	10.8%	**64.3%**	24.9%
	HIGH	0.8%	28.3%	**70.8%**

≥ 65 years
N = 202

		Sokal		
		LOW	INT	HIGH
ELTS	**LOW**	**8%**	**80%**	**12%**
	INT	12%	**74%**	14%
	HIGH	**2%**	**50%**	**48%**

One third of patients stratified by ELTS score have a different Sokal score (any risk)
Discrepancies were more evident in elderly patients

GIMEMA CML WP

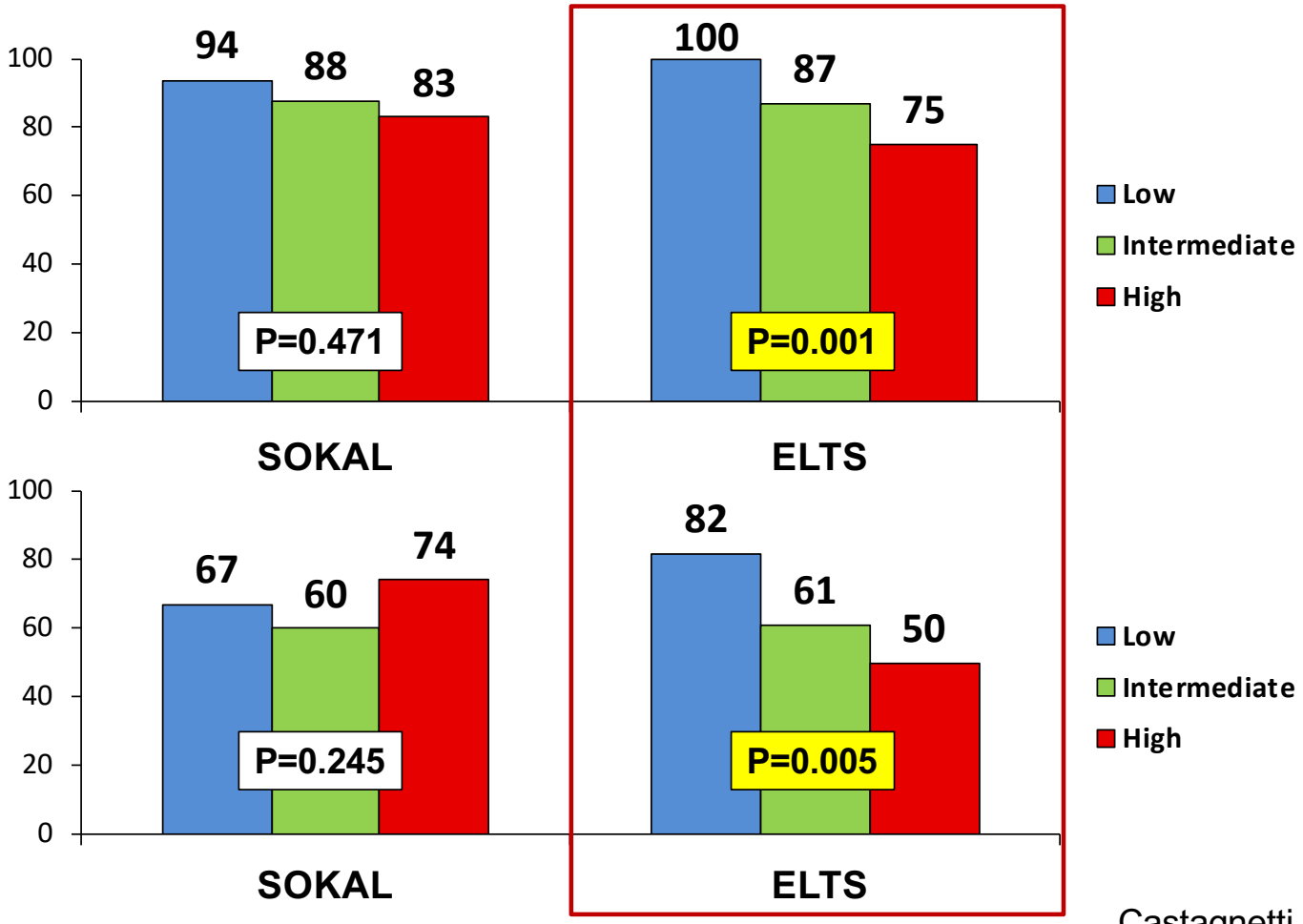
Castagnetti et al. ASH 2018

ELTS score - Strongly advised in elderly patients (≥ 65 yrs)

Better prediction of molecular response

MR3

MR4

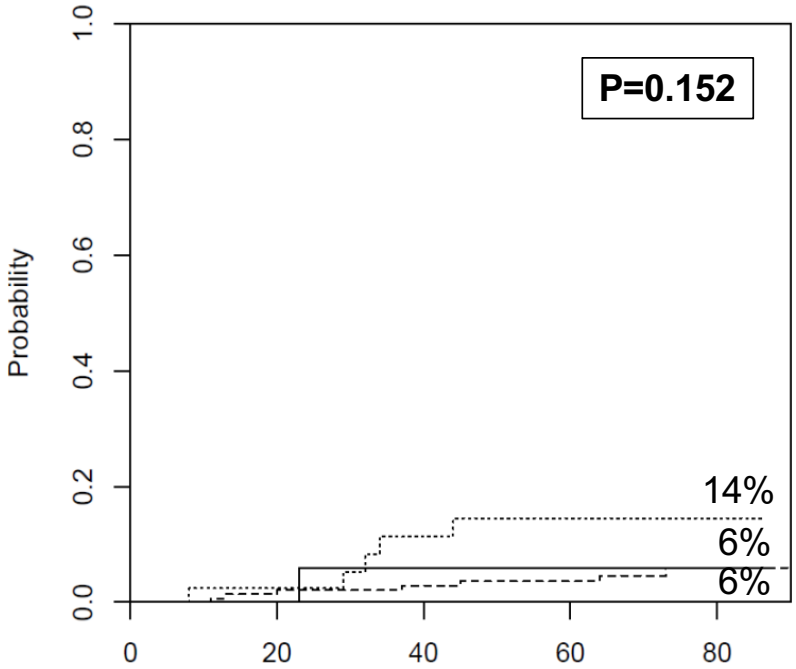


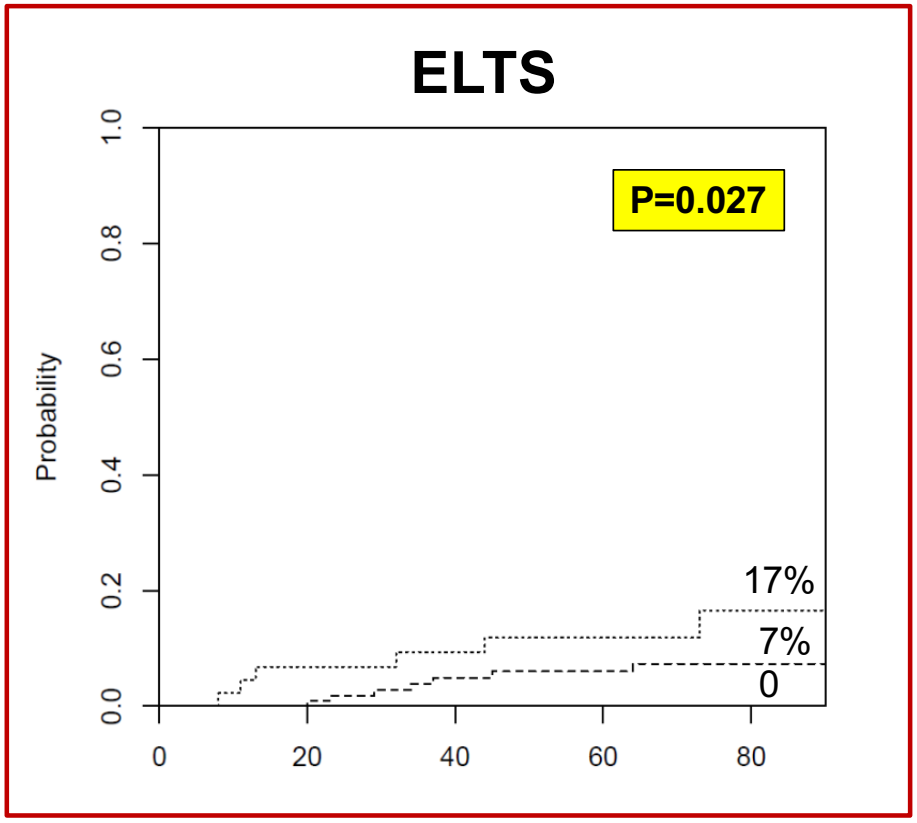
GIMEMA CML WP

Castagnetti et al. ASH 2018

ELTS score - Strongly advised in elderly patients (≥ 65 yrs)

Better prediction of leukemia-related death





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FIRST-LINE TREATMENT CHOICE

OLD PATIENTS (≥ 80 years)

Patient

Risk

Comorbidities

Personal Expectations
Compliance

Drugs

Efficacy
Time to response

Side Effects

(Long term) safety

Costs

Physician

Personal Experience

ENDPOINTs

Overall survival

Progression-free survival
Major molecular response

Deep MR
TFR

QoL

blood advances

MANAGING CML FOR TREATMENT-FREE REMISSION. A PROPOSAL FROM THE GIMEMA CML WP

Michele Baccarani[1] and the members of the GIMEMA CML WP;

Elisabetta Abruzzese (2); Vincenzo Accurso (3); Francesco Albano (4); Mario Annunziata (5); Sara Barulli (6); Germana Beltrami (7); Michela Bergamaschi (7); Gianni Binotto (8); Monica Bocchia (9); Giovanni Caocci (10); Isabella Capodanno (11); Francesco Cavazzini (12); Michele Cedrone (13); Marco Cerrano (14); Monica Crugnola (15); Mariella D'Adda (16); Chiara Elena (17); Carmen Fava (14); Paola Fazi (2); Claudio Fozza (18); Sara Galimberti (19); Valentina Giai (20); Antonella Gozzini (21); Gabriele Gugliotta (1); Alessandra Iurlo (22); Gaetano La Barba (23); Luciano Levato (24); Alessandro Lucchesi (25); Luigia Luciano (26); Francesca Lunghi (27); Monia Lunghi (28); Michele Malagola (29); Roberto Marasca (30); Bruno Martino (31); Angela Melpignano (32); Cristina Miggiano (33); Enrico Montefusco (34); Caterina Musolino (35); Fausto Palmieri (36); Patrizia Pregno (37); Davide Rapezzi (38); Giovanna Rege-Cambrin (14); Serena Rupoli (39); Marzia Salvucci (40); Rosaria Sancetta (41); Simona Sica (42); Raffaele Spadano (43); Fabio Stagno (44); Mario Tiribelli (45); Simona Tomassetti (46); Elena Trabacchi (47); Massimiliano Bonifacio (48), Massimo Breccia (2), Fausto Castagnetti (1), Fabrizio Pane (26), Domenico Russo (29), Giuseppe Saglio (14), Simona Soverini (1), Paolo Vigneri (44), and Gianantonio Rosti (1)

ABSTRACT

Several papers authored by international experts have proposed recommendations on the management of BCR-ABL1+ chronic myeloid leukemia (CML). Following these recommendations, survival of CML patients has become very close to normal. The next, ambitious, step is to bring as many patients as possible into a condition of treatment-free remission (TFR). The GIMEMA CML Working Party (WP) has developed a **project aimed to** select the treatment policies that may **increase the probability of TFR, taking into account four variables: the need for TFR, the tyrosine kinase inhibitors, the characteristics of leukemia, and the patient.** A Delphi-like method was used to reach a consensus among the representatives of **50 centers of the CML WP**. **A consensus was reached on the assessment of disease risk (ELTS score), on the definition of the most appropriate age boundaries for the choice of first-line treatment, on the choice of the TKI for firstline treatment, and on the definition of the responses that do not require a change of the TKI** (BCR-ABL1≤10% at 3 months, ≤1% at 6 months, ≤0.1% at 12 months, ≤0.01% at 24 months), and of the responses that require a change of the TKI, when the goal is TFR (BCR-ABL1>10% at 3 and 6 months, >1% at 12 months, and >0.1% at 24 months). These suggestions may help optimizing the treatment strategy for TFR.

GIMEMA Gruppo Italiano Malattie EMatologiche dell'Adulto

Accepted November 2019

First-line treatment of CML patients

	18-40 yrs	41-65 yrs	66-80 yrs	**> 80 yrs**
Low risk	2GTKIs	IM – 2GTKIs	IMATINIB	**IMATINIB**
Intermediate risk	2GTKIs	2GTKIs	IM – 2GTKIs	**IMATINIB**
High risk	2GTKIs	2GTKIs	IM – 2GTKIs	**IMATINIB**

Baccarani et al. Blood Advances 2019

Take home messages

- Comorbidities increase with age
- High efficacy of TKIs in elderly patients, but comorbidities have an impact on life expectancy and CML-unrelated deaths.
- The use of ELTS score is strongly advised in elderly patients
- GIMEMA recommendations taking into account the age of patients have been published: imatinib should be preferred in very elderly patients (> 80 years old), irrespectively of disease risk

Thank you for attention!

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