AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

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How I treat high risck CML

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Disclosures

- Advisory Board: Novartis, Pfizer, Incyte
- Speaker Honoraria: Bristol-Meyers- Squibb, Novartis, Pfizer, Incyte

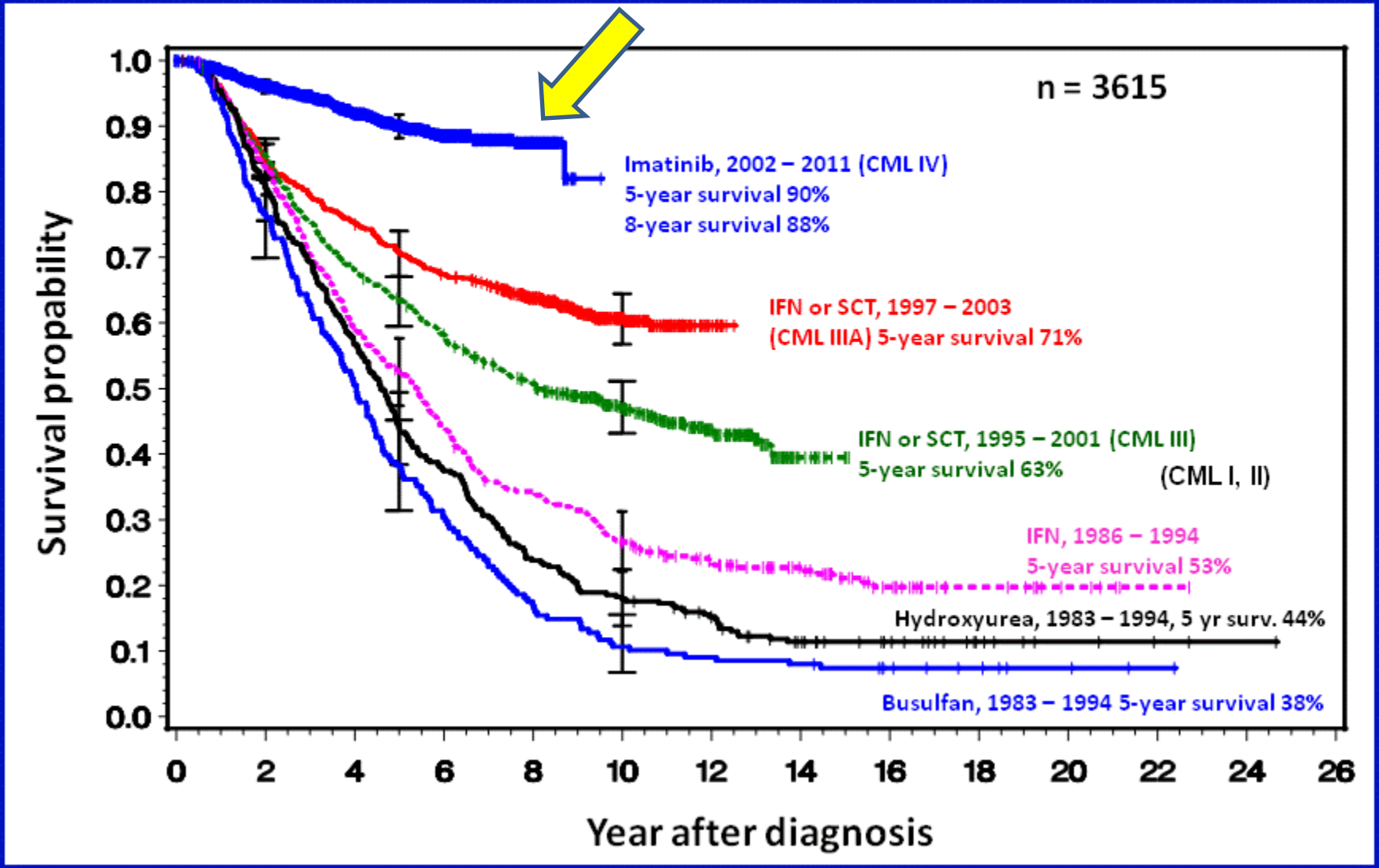
Incidence of CML /100,000 people

*) World Standard Population **) United States Standard Population ***) CML cases with known Ph/BCR-ABL positive status	Time of observation	Number of patients	Incidence crude	Incidence (WSP) *
SEER[1]	1998-2000	-	-	1.8 **
	2003-2007	4653	-	1.7 **
France[2]	1985-2006	906	-	0.8
Swedish Cancer Registry[3]	1998-2000	260	1	0.7
	2001-2008	704	1	0.7
Scotland Leukemia Registry[4] ***	1999-2000	64	0.6	-
Thames Registry[5]	1999-2000	180	1.09	0.8
Leukemia Research Fund[6]	1984-1993	1115	-	0.6
Cancer Registry of Saarland[7]	1998-2000	65	2	1
	2001-2007	142	1.9	0.9
Southwest Germany[8] ***	1998-2000	172	0.6	-
Southeast Germany[9]	2004	201	1.9	1.3

1. Altekruse et al. SEER Cancer Statistics Review, 1975-2007, http://seer.cancer.gov/csr/1975_2007/ Accessed May, 2010
2. Corm et al. J Clin Oncol 26: 2008 (May 20 suppl; abstr 7088).
3. Swedish Cancer Registry, 1998-2006. http://www.socialstyrelsen.se/Statistik/statistik_amne/Cancer. Accessed May, 2010
4. Harrison, et al. Scottish Medical Journal. 2004;49:87-90.
5. Phekoo et al. Haematologica; 2006;91:1400-1404.
6. McNally et al. Hematol Oncol. 1997;15:173-189.
7. Krebsregister Saarland, Germany. http://www.krebsregister.saarland.de. Accessed May, 2010
8. Rohrbacher et al. Leukemia. 2008;23:602-604.
9. Hasford et al. Blood (ASH Annual Meeting Abstracts) 2007, 110: Abstract 2964.

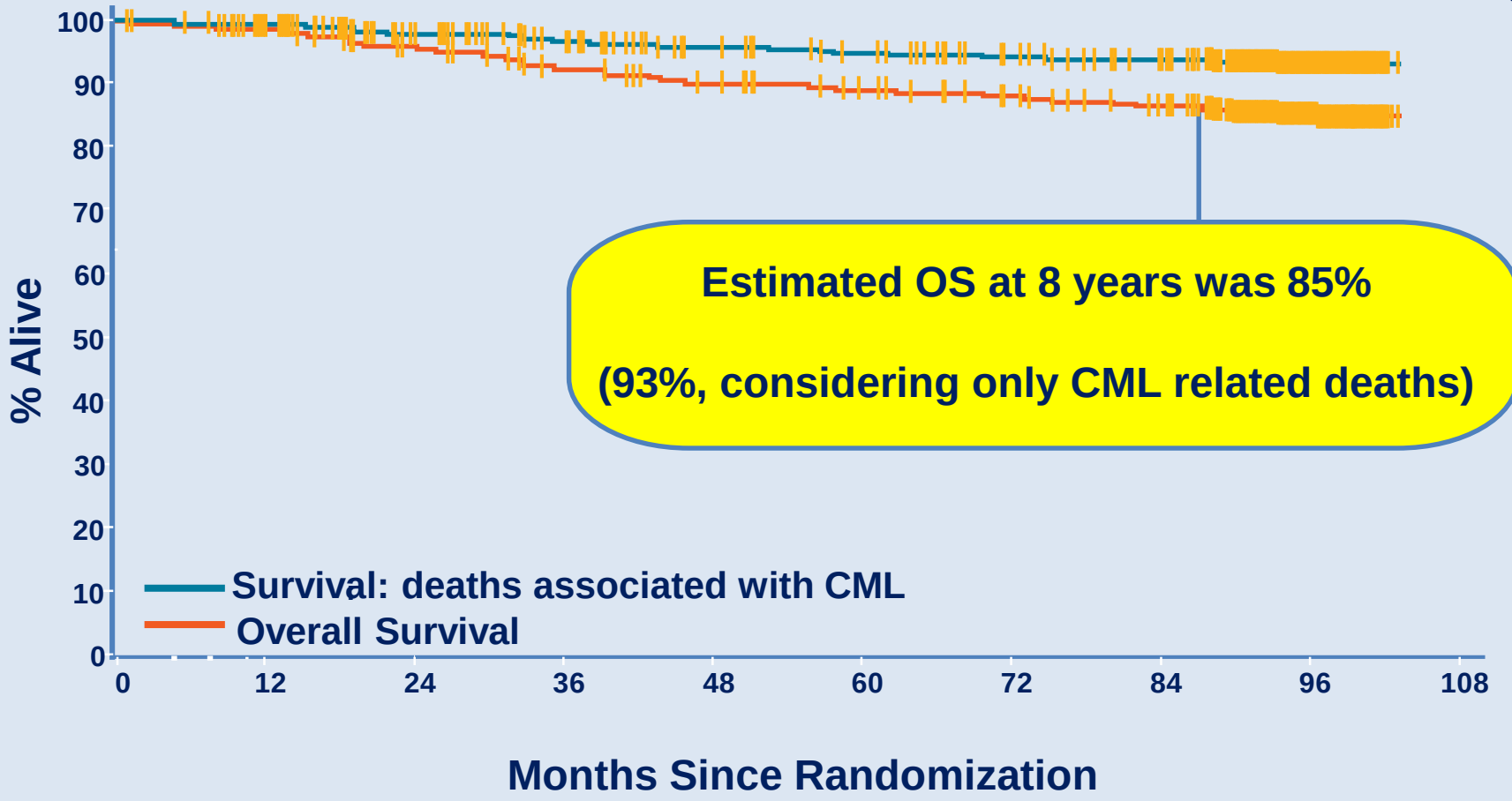
The EUTOS Registry reports that CML currently has an average incidence of 0.99/100,000, ranging from 0,69/100,000 (Poland) to 1,39/100,000 (Italy - Emilia-Romagna and Sicily).

Improvement of survival of CML by therapy 1983 – 2011



IRIS Study 8 year Follow-up

Overall Survival (ITT Principle): Imatinib Arm



Deininger M, et al. *Blood*. 2009;114(22):462. Abs # 1126.

Treatment goals in CML in 2018

- Complete hematologic response, complete cytogenetic response and major molecular response
- Normal lifespan, normal quality of life
- Safe procreation
- Discontinuation of therapy?

Prognostic Significance of Molecular Response

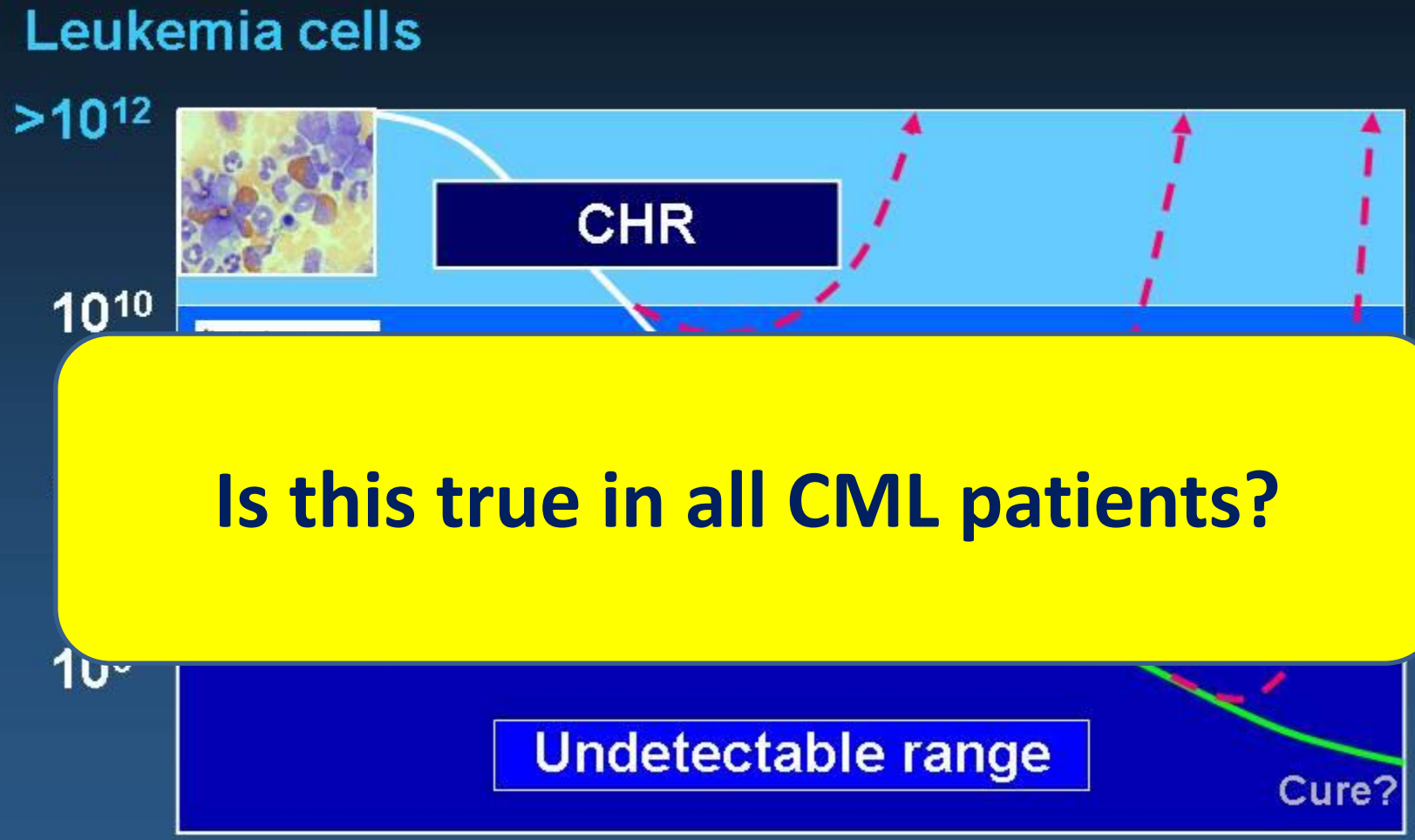
- Early molecular response (<10% IS BCR-ABL1) is associated with:
  - Higher probability of MMR (<0.1% IS BCR-ABL1)[1,2]
  - Higher rates of event-free survival (EFS)[2,3,4,5] and progression-free survival (PFS)[3]

- Achievement of MMR is associated with:
  - Higher rates of EFS[5] and PFS[6]
  - Longer duration of CCyR[7,8,9,10]
  - Deep MR achievement (≥ MR4.5)[12]

- Durable MMR is associated with prolonged PFS[11]

1. Branford S, et al. Leukemia. 2003;17:2401-2409; 2. Quintás-Cardama A, et al. Blood. 2009;113:6315-6321;
3. Müller MC, et al. Blood. 2008;112:129 [abstract 333]; 4. Osborn MP, et al. Blood. 2009;114:461-462 [abstract 1125];
5. Hughes TP, et al. Blood. 2008;112:129-130 [abstract 334]; 6. Press RD, et al. Blood. 2006;107:4250-4256;
7. Iacobucci I, et al, Clin Cancer Res. 2006;12:3037-3042: 8. Cortes J, et al, Clin Cancer Res;2005;11:3425-3432;
9. Paschka P, et al. Leukemia; 2003;17:1687-1694; 10. Press RD, et al. Clin Cancer Res. 2007;13:6136-6143;
11.Kantarjian H, et al. Cancer. 2008;112:837-845.

Goals of CML Therapy – Different Sensitivities of Methods



Is this true in all CML patients?

CML = chronic myelogenous leukemia; CHR = complete hematologic response; CCyR = complete cytogenetic response; MMR = major molecular response; CMR = complete molecular response.

Calculation of relative risk in CML

We have several ways to calculate the risk of the disease in each patient, with the meaning of a risk related to progression to advanced phases

Table 2. Calculation of relative risk

Study	Calculation	Risk definition by calculation
Sokal et al. 1984[7]	Exp 0.0116 × (age − 43.4) + 0.0345 × (spleen − 7.51) + 0.188 × [(platelet count ÷ 700)^2 − 0.563] + 0.0887 × (blast cells − 2.10)	Low risk: <0.8 Intermediate risk: 0.8-1.2 High risk: >1.2
Euro Hasford et al. 1998[8]	0.666 when age ≥50 y + (0.042 × spleen) + 1.0956 when platelet count >1500 × 10^9L + (0.0584 × blast cells) + 0.20399 when basophils >3% + (0.0413 × eosinophils) × 100	Low risk: ≤780 Intermediate risk: 781-1480 High risk: >1480
EUTOS Hasford et al. 2011[9]	Spleen × 4 + basophils × 7	Low risk: ≤87 High risk: >87

Age is given in years. Spleen is given in centimeters below the costal margin (maximum distance). Blast cells, eosinophils, and basophils are given in percent of peripheral blood differential. All values must be collected before any treatment. To calculate Sokal and Euro risk score, go to http://www.leukemia-net.org/content/leukemias/cml/cml_score/index_eng.html. To calculate EUTOS risk score, go to http://www.leukemia-net.org/content/leukemias/cml/eutos_score/index_eng.html.

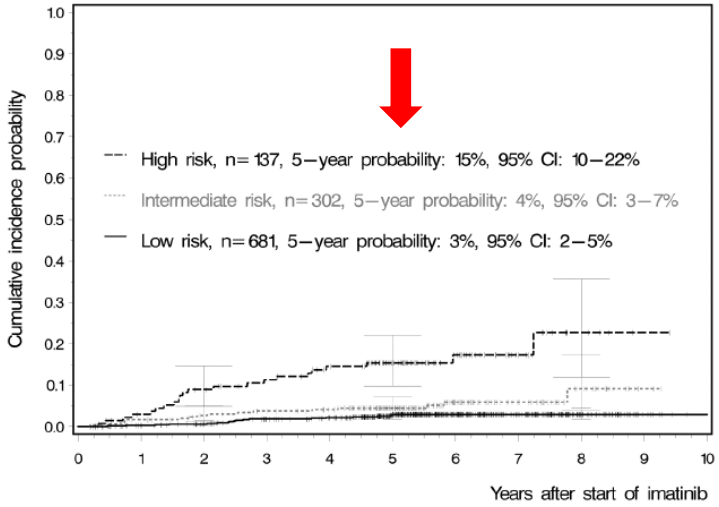
EUTOS long-term survival score

$0.0025 \times (age/10)^3 + 0.0615 \times$ spleen size $+ 0.1052 \times$ blasts in PB $+ 0.4104 \times (PLT\ count/1000)^{-0.5}$

LOW: < 1.5680

INTERMEDIATE: 1.568 - 2.2185

HIGH: > 2.2185



Baccarani M., Blood 2013; Sokal J. et al, Blood 1984; Hasford J. et al, Natl Cancer Inst. 1998; Hasford J. et al, Blood 2011; Pfirrmann M. Leukemia 2016.

Chromosomal Abnormalities in CML clones

- ✓ **Metaphase karyotyping may reveal additional clonal chromosomal abnormality in Ph+ cells (ACA/Ph+), a situation referred to as clonal cytogenetic evolution and defines TKI failure if emerging on treatment.**

- ✓ **CCA/Ph+ in case of so called «Major Route» abnormalities at the diagnosis have been reported to have an adverse prognostic value:**
  - **Trisomy 8**
  - **Trisomy Ph**
  - **Isochromosome 17**
  - **Trisomy 19**
  - **Ider22**

- ✓ **Others baseline factors, including gene expression profiles, specific polymorfism of gene coding for TKI transmembrane transporters or TKI-mediated apoptosis have been reported to have prognostic implication, but data are not yet sufficiently strong to use for planning treatment**

Castagnetti F. et al, J Clin Oncol 2010; Marzocchi G et al, Blood 2011; Fabarius A. et al, Blood 2011; Luatti S. et al Blood 2012; Verma D. et al, Cancer 2010

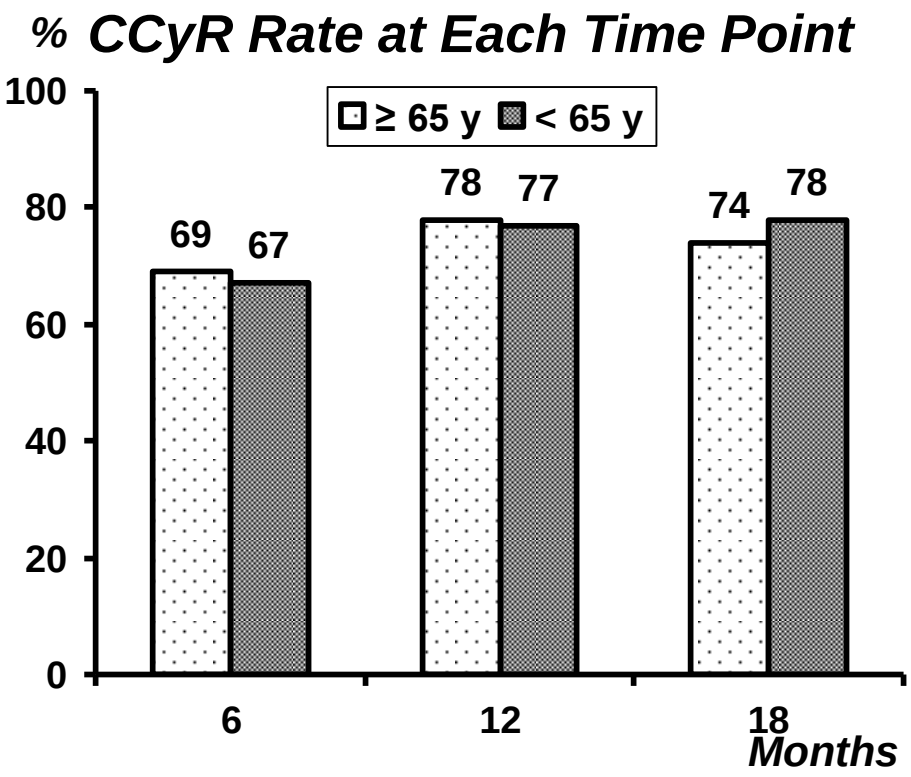
ICSG on CML 86-97 / 1114 patients

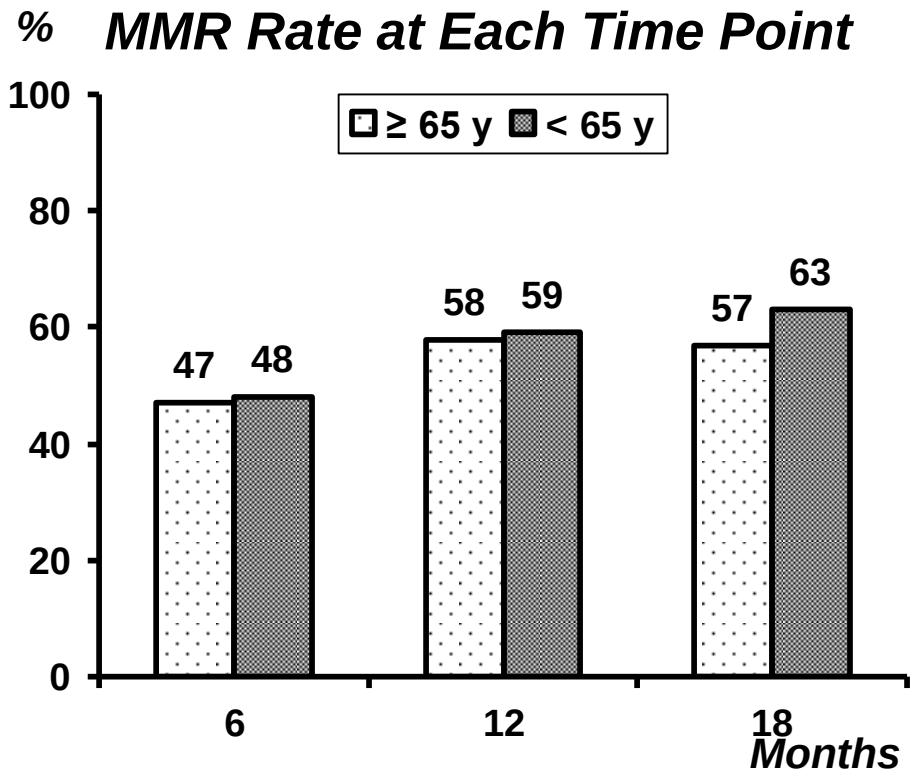
Distributions by age groups and Sokal Risk

Sokal Risk	<40 n. 421	41-60 n. 562	>61 n.131
Low	60%	41%	22%
Intermediate /High	40%	59%	78%

IMATINIB AND AGE – Early CP

RESPONSE



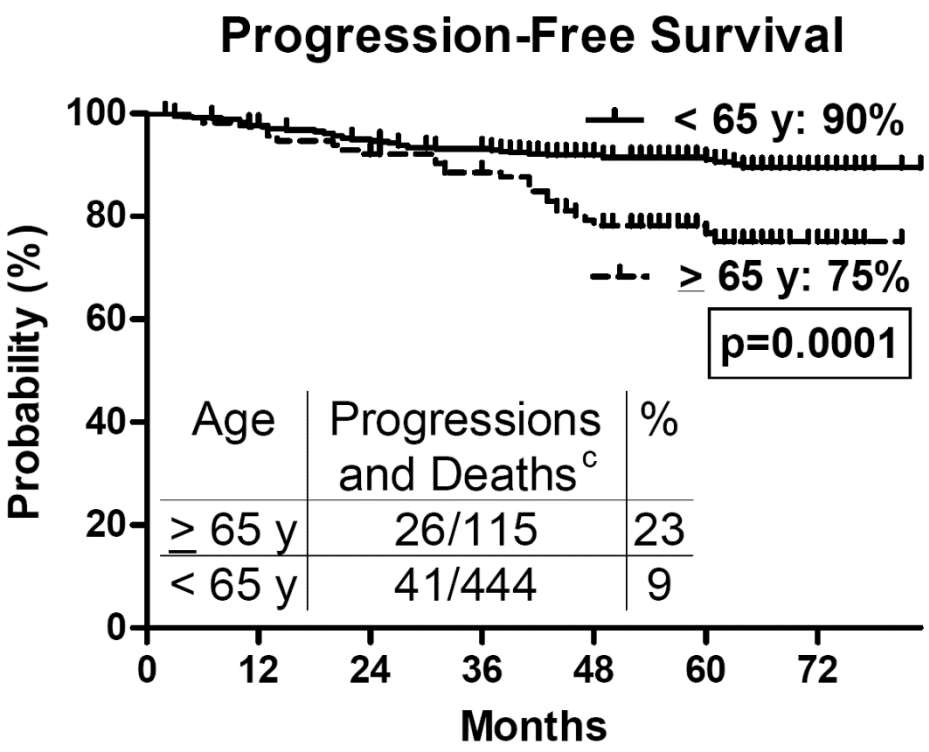


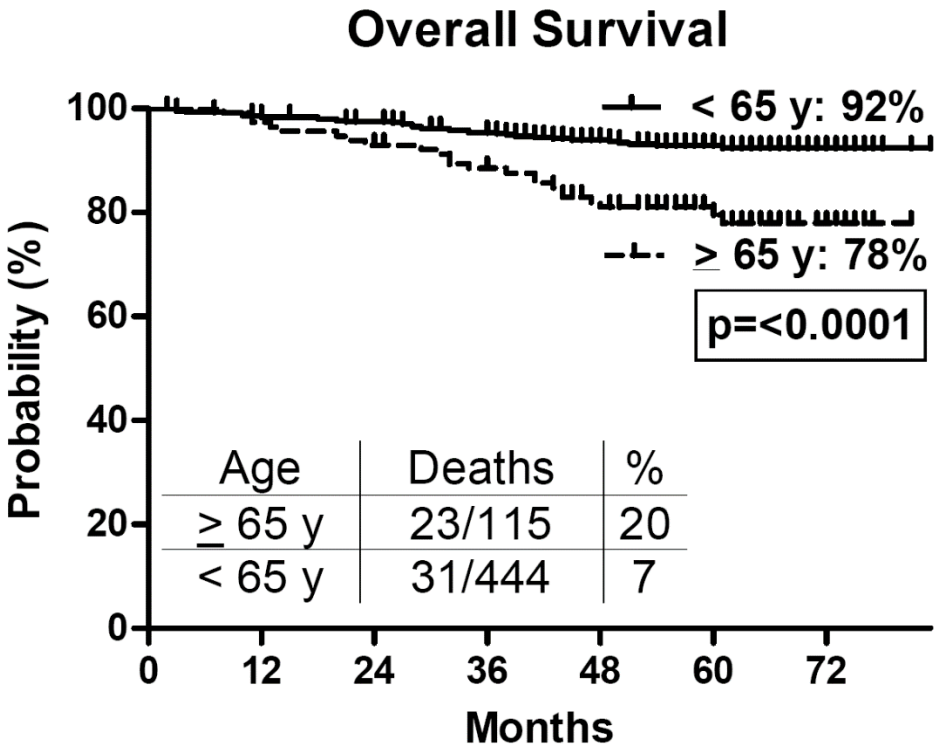
Gugliotta G et al. Blood 2011

GIMEMA CML WP

IMATINIB AND AGE - Early CP OUTCOME

GIMEMA CML 021-022-023 [1]



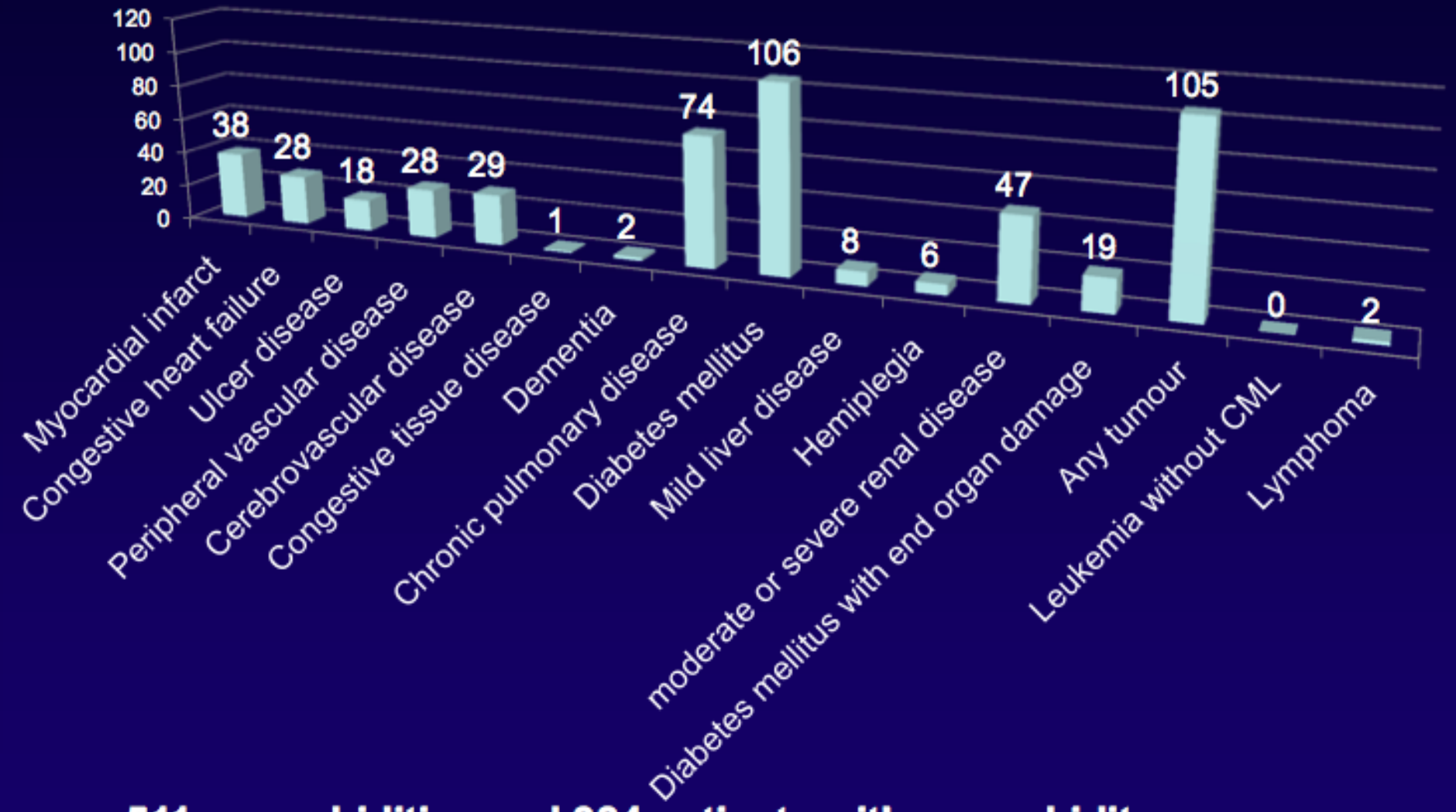


Considering all events, the 6-years survival rates are lower for older patients

Gugliotta G et al. Blood 2011

GIMEMA CML WP

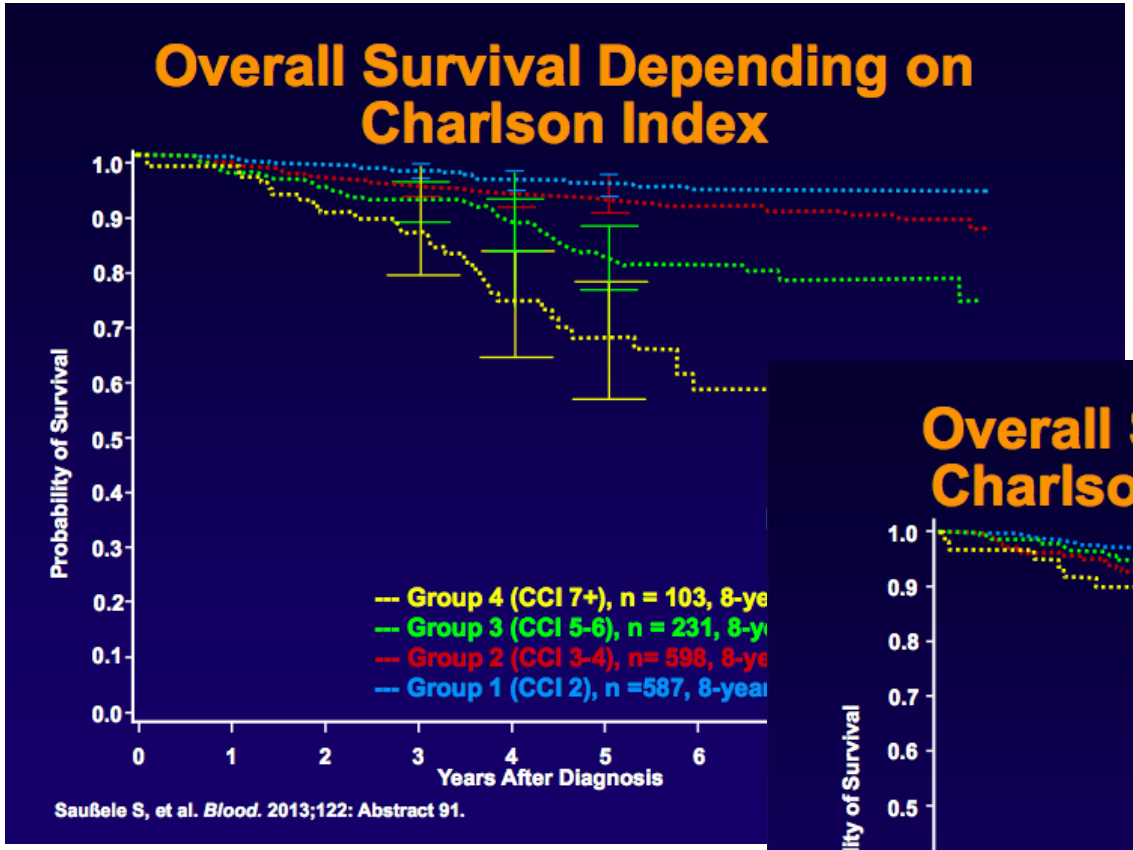
Documented Comorbidities (n = 511)

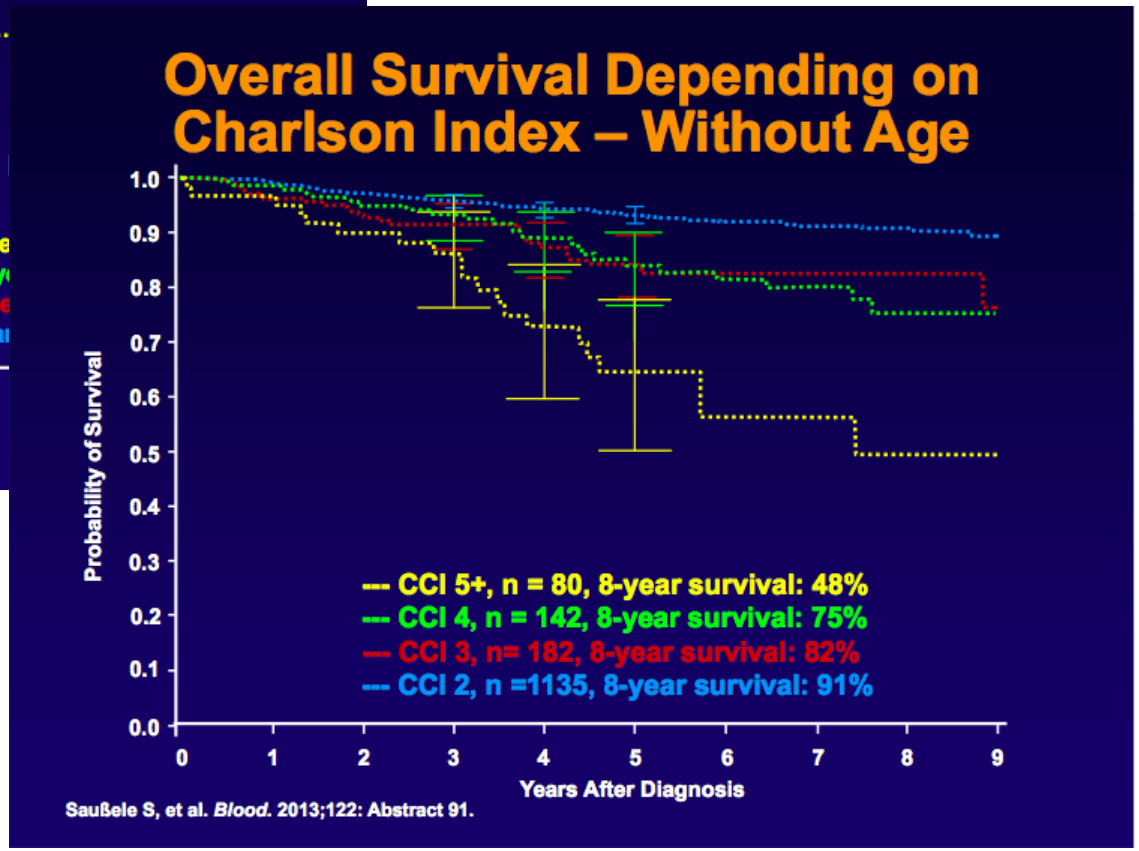


- **511 comorbidities and 384 patients with comorbidity**

Saußele S, et al. *Blood.* 2013;122: Abstract 91.

Outcome is influenced by comorbidities





Saußele S. et al, Blood 2013

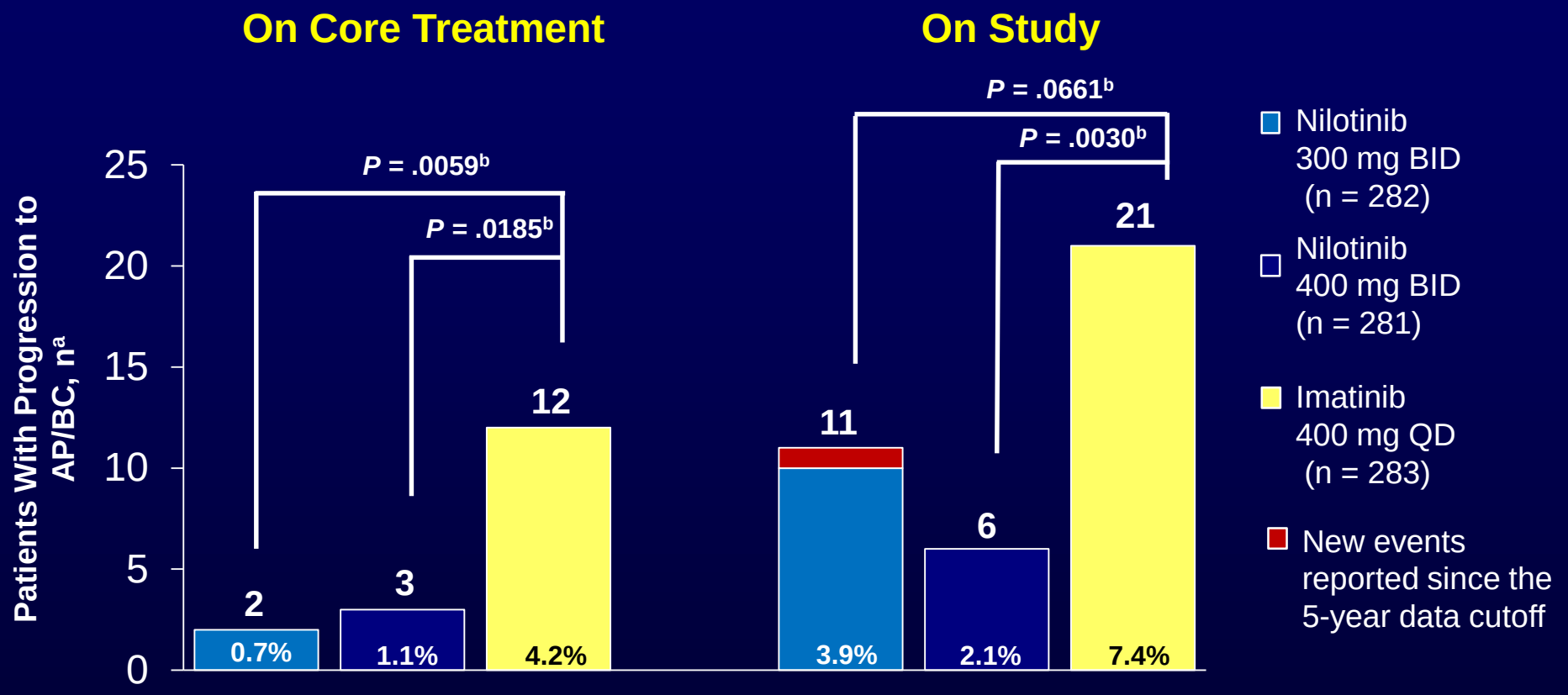
EUROPEAN LEUKEMIA NET 2013: TREATMENT RECOMMENDATIONS

Table 7. Chronic phase treatment recommendations for first, second, and subsequent lines of treatment

First line
Imatinib or nilotinib or dasatinib
HLA type patients and siblings only in case of baseline warnings (high risk, major route CCA/Ph+)
Second line, intolerance to the first TKI
Anyone of the other TKIs approved first line (imatinib, nilotinib, dasatinib)
Second line, failure of imatinib first line
Dasatinib or nilotinib or bosutinib or ponatinib
HLA type patients and siblings
Second line, failure of nilotinib first line
Dasatinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Second line, failure of dasatinib first line
Nilotinib or bosutinib or ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT
Third line, failure of and/or intolerance to 2 TKIs
Anyone of the remaining TKIs; alloSCT recommended in all eligible patients
Any line, T315I mutation
Ponatinib
HLA type patients and siblings; search for an unrelated stem cell donor; consider alloSCT

Baccarani M, et al. Blood. 2013;122(6):872-884

Figure 5. Progression to AP/BC

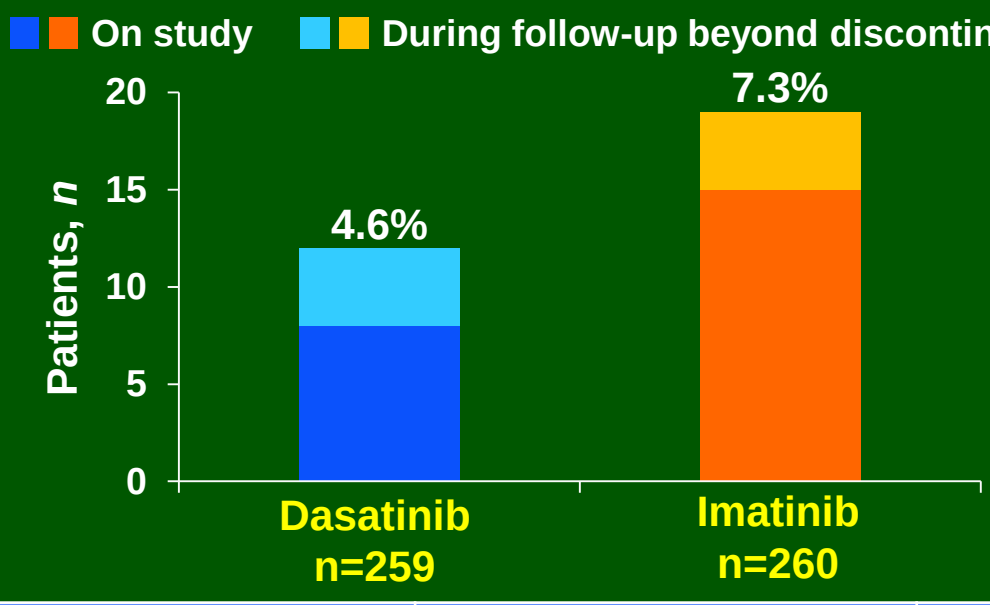


[a] Defined as progression to AP/BC or death due to advanced CML. [b] *P* values are nominal, were provided for descriptive purposes only, and were not adjusted for multiple comparisons

Hughes TP, et al. *Haematologica*. 2015;100:[abstract P228].

Transformation to AP/BP CML by 5 Years

Overall transformations to AP/BP



	Dasatinib 100 mg QD (n=259)		Imatinib 400 mg QD (n=260)	
BCR-ABL at 3 Months[a]	≤10% n=198	>10% n=37	≤10% n=154	>10% n=85
Transformation to AP/BP[b], n (%)	6 (3)	5 (14)	5 (3)	13 (15)

- **One imatinib patient and no dasatinib patients transformed between 4 and 5 years**

[a]One dasatinib and one imatinib patient transformed but did not have 3-month molecular assessments.

[b]Including follow-up beyond discontinuation (intent to treat).

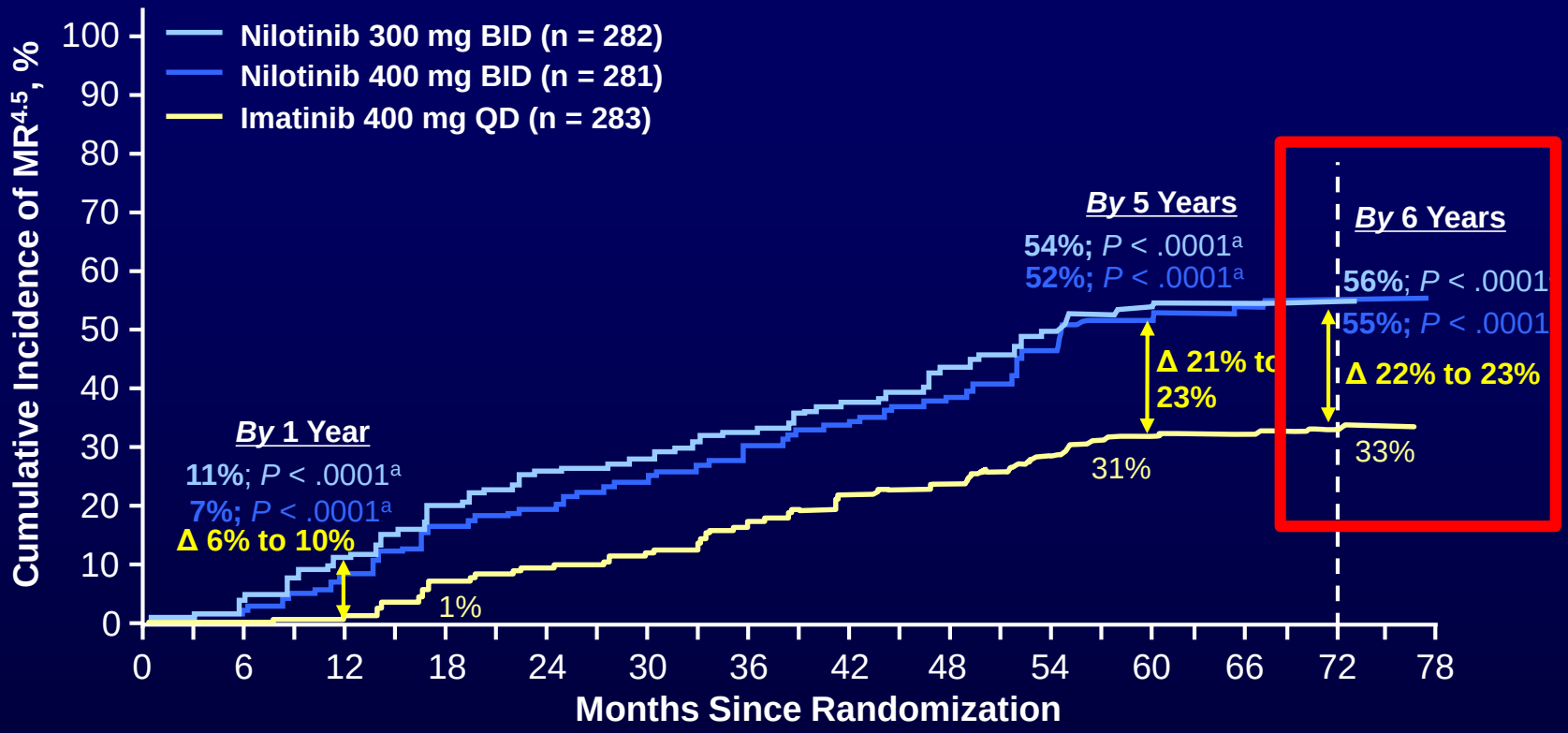
First line Tki therapy for CP-CML: Long-term FU data from phase III studies

Trial	Study Arms	N° pts	Median FU	CCyR %	MMR%	Disease progression n (%)	PFS %	OS %
IRIS[1]	Imatinib 400	553	11 ys	83	-	38 (37)	92	83
	α-IFN+LD ARA-C	553		-	-	71 (13)	-	79
DASISION[2]	Dasatinib 100	259	5 ys	-	76 P=.002	12 (5)	85	91
	Imatinib 400	260		-	64	19 (7)	86	90
ENESTnd[3]	Nilotinib 600	282	5 ys	-	77 P vs IMA <.0001	10 (4)	92	94
	Nilotinib 800	281		-	77 P vs IMA <.0001	8 (2)	96	96
	Imatinib 400	283		-	60	21 (7)	91	92
BFORE[4]	Bosutinib 400	268	12 ms	77 P=.0075	47 P=.02	4 (2)	-	-
	Imatinib 400	268		66	37	6 (3)	-	-

1. Hochhaus A et al, N Engl J Med, 2017 2. Cortes JE et al J Clin Oncol 2016
3. Hochhaus A et al, Leukemia 2016 4. Cortes JE et al, J Clin Oncol 2018

NCCN Guidelines 1/19, August 2018 modified

Figure 3. Cumulative Incidence of MR$^{4.5}$ and Time to First MR$^{4.5}$

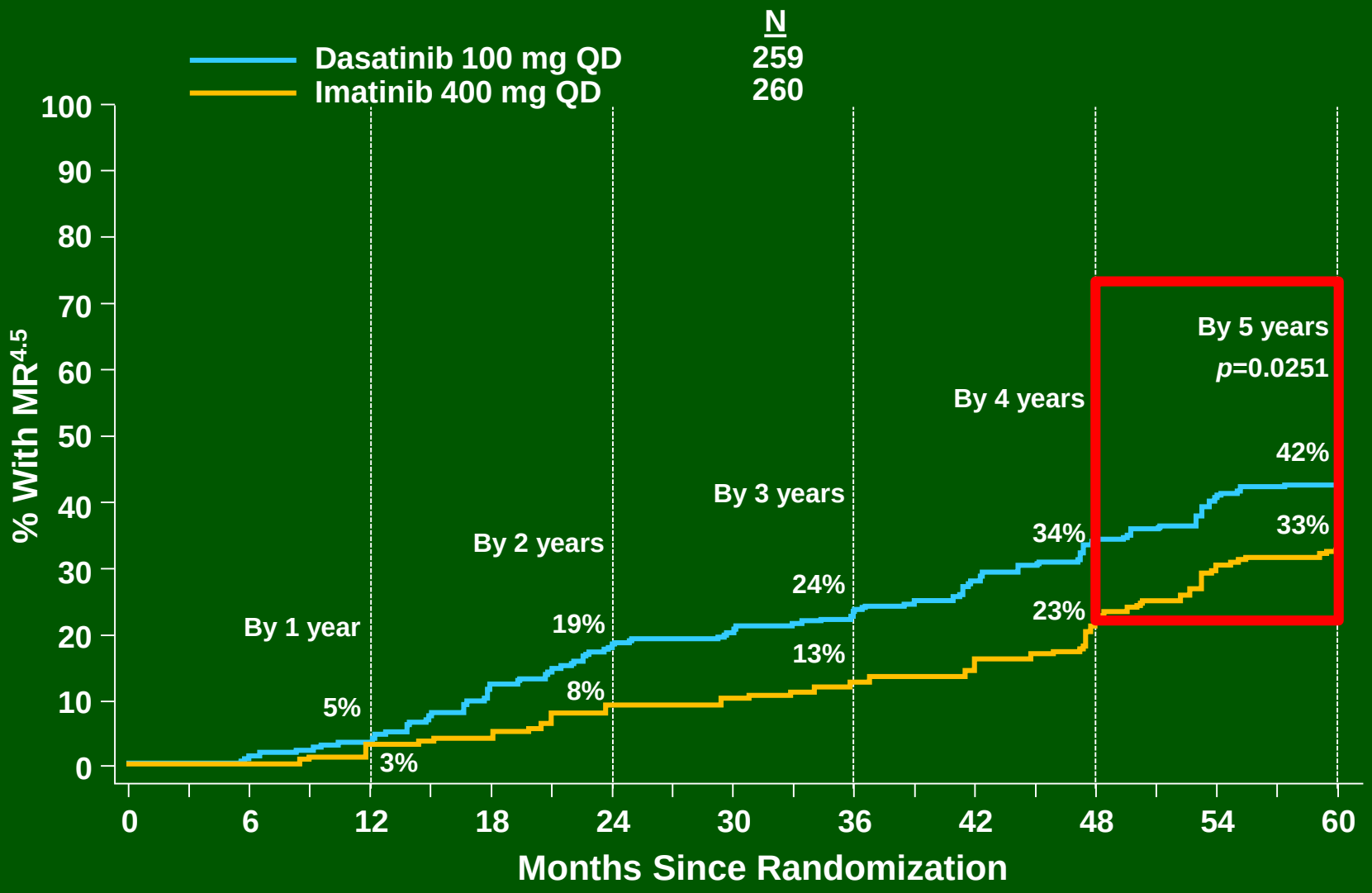


Treatment Arm	Kaplan-Meier Estimated Median Time to First MR$^{4.5}$, months	Hazard Ratio vs Imatinib (95% Confidence Interval)	*P* value[a]
Nilotinib 300 mg BID	45.5	2.0387 (1.5807-2.6295)	< .0001
Nilotinib 400 mg BID	49.8	1.7770 (1.3780-2.2915)	< .0001
Imatinib 400 mg QD	61.1	–	–

[a] *P* values are nominal, were provided for descriptive purposes only, and were not adjusted for multiple comparisons.

Hughes TP, et al. *Haematologica*. 2015;100:[abstract P228].

Cumulative MR$^{4.5}$ Rates Over Time



MR$^{4.5}$, BCR-ABL (IS) ≤0.0032% (for subjects with B2a2 and B3A2 transcripts).

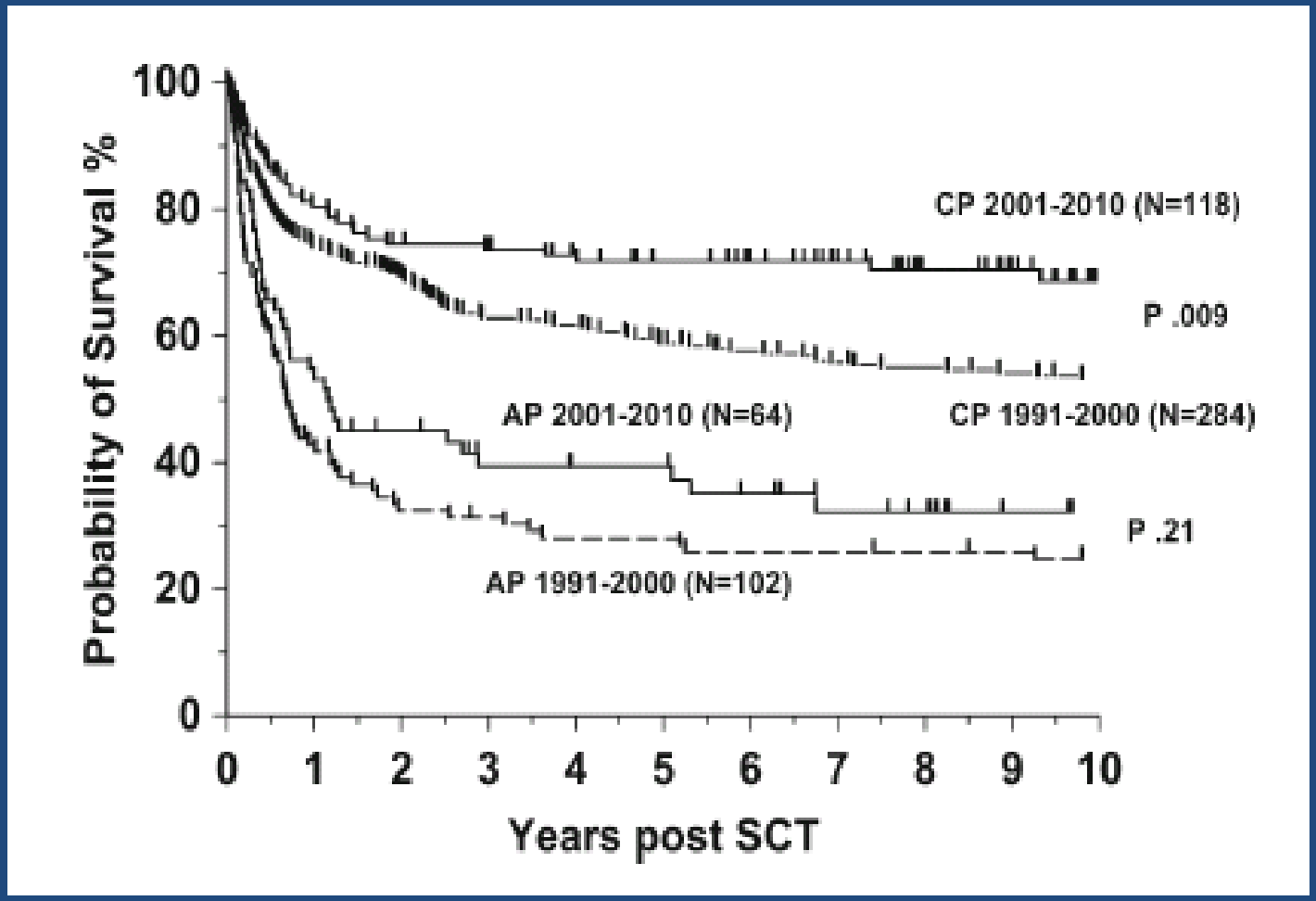
First line II Gen-TKI therapy for CP-CML: Molecular Response (MR) according to Sokal or Euro Risk Score

Trial	Study Arms (mg/daily)	Low-risk		Intermediate- risk		High-risk	
		MMR%	MR4.5%	MMR%	MR4.5%	MMR%	MR4.5%
DASISION[1]	Dasatinib 100	90	55	71	43	67	31
	Imatinib 400	69	44	65	28	54	30
ENESTnd[2]	Nilotinib 600	-	53	-	60	-	45
	Nilotinib 800	-	62	-	50	-	42
	Imatinib 400	-	38	-	33	-	23
BFORE[3]	Bosutinib 400	58	-	45	-	34	-
	Imatinib 400	46	-	39	-	17	-

1. Cortes JE et al J. Clin Oncol. 2016
2. Hochhaus A et al, Leukemia 2016
3. Cortes JE et al, J. Clin Oncol. 2018

NCCN Guidelines 1/19, August 2018, modified

Outcome of stem cell transplantation



Pavlu J. Curr Hematol Malig Rep 2013

DISCONTINUATION OF TKI THERAPY

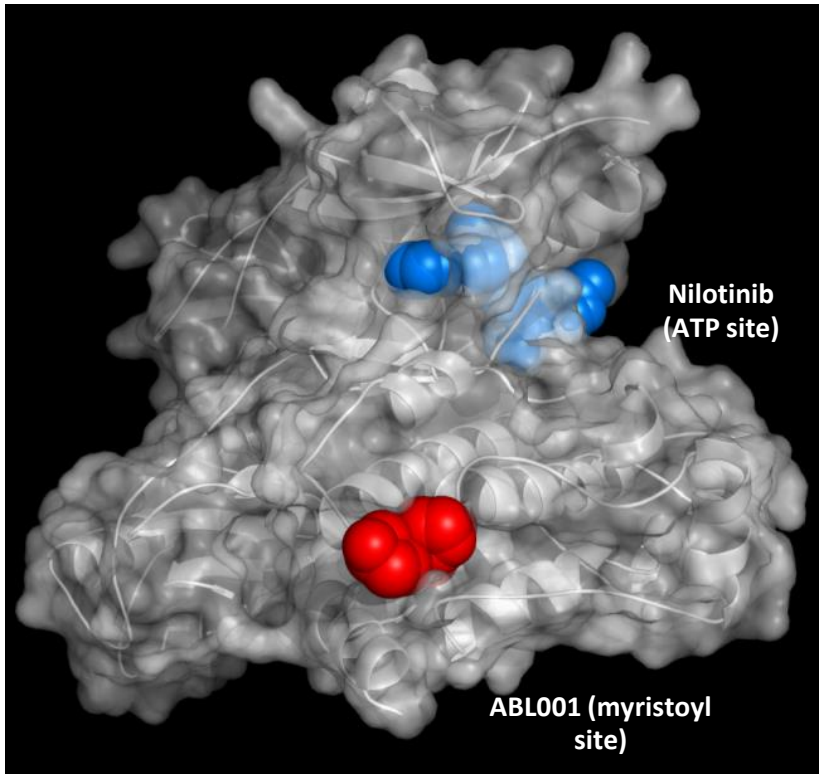
Criteria	Green	Yellow	Red
Institutional criteria met (per table 1)	Yes	-	No
Sokal score at diagnosis	Non-high	High	-
BCR-ABL transcript at diagnosis	Typical - B2A2 or B3A2 (e13a2 or e14a2)	Atypical, but can be accurately quantified	Not quantifiable
CML past history	CP only	Resistance or KD mutation	Prior AP or BC
Response to first line TKI therapy	Optimal	Warning	Failure
Duration of all TKI therapy	> 8 years	3–8 years	< 3 years
Depth of deep molecular response	MR4.5	MR4.0	Not in MR4.0
Duration of deep molecular response monitored in a standardized laboratory	> 2 years	1–2 years	< 1 year

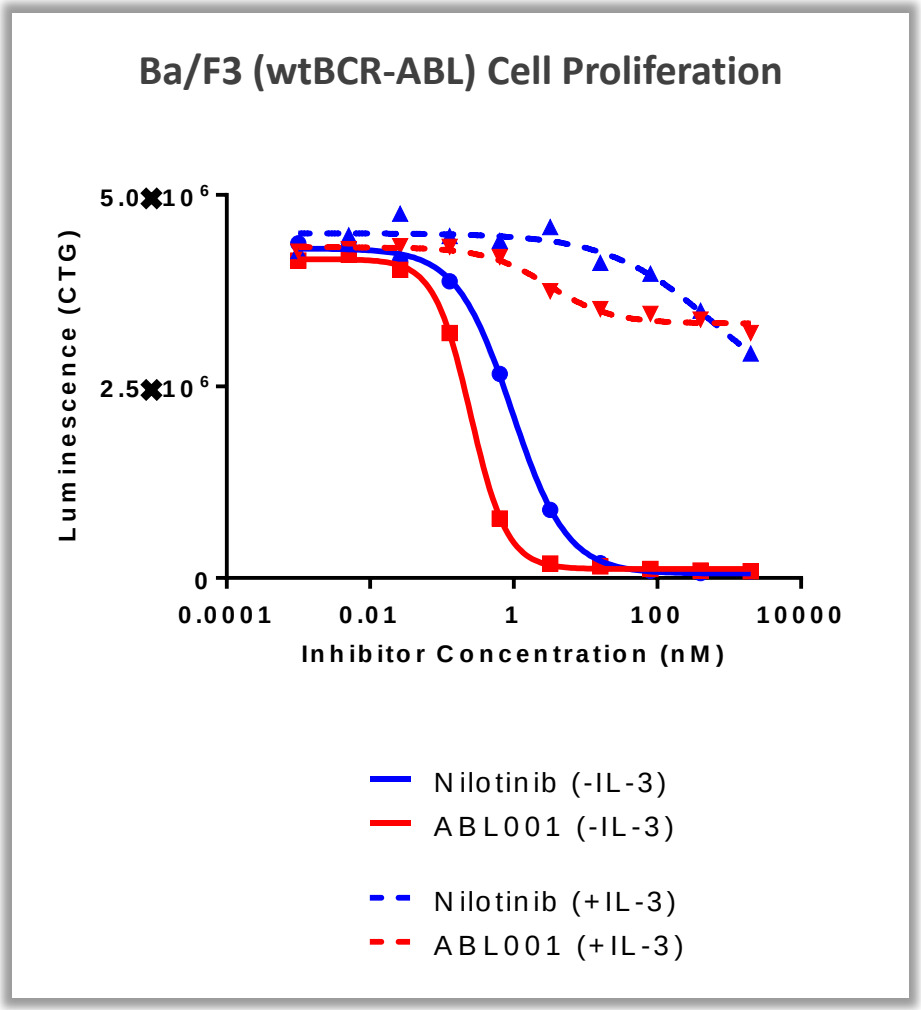
All green lights: strong recommendation to consider TKI withdrawal

Any yellow lights: only consider TKI withdrawal in high priority circumstances (e.g. significant toxicity or planned pregnancy)

Any red lights: TKI withdrawal not recommended except in clinical trial

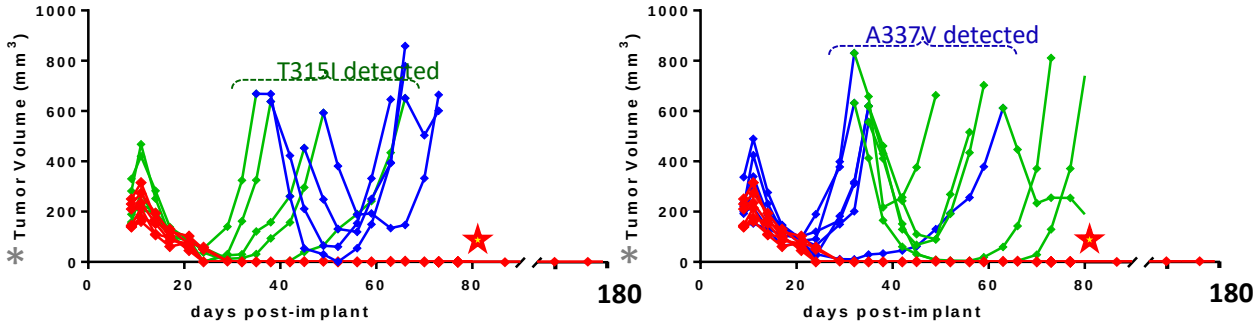
ABL001 is a potent, selective inhibitor of ABL1



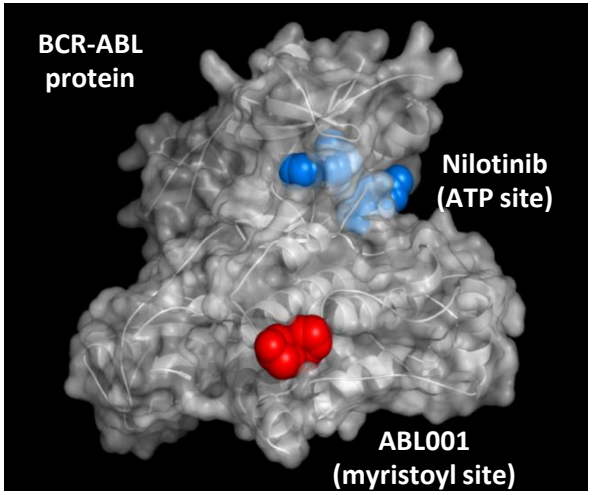


Wylie A, et al. *Blood*. 2014:[abstract 398].

Combination of ABL001 and Nilotinib prevents the emergence of resistance



KCL-22 CML Xenograft



- Nilotinib (75mg/kg) BID
- ABL001 (30mg/kg) BID
- Nilotinib (75mg/kg) BID + ABL001 (30mg/kg) BID
- Dosing stopped on day 77, all mice remain disease free >176 days

A Multicenter, Open-Label, Randomized, Phase 3 Study of Oral Asciminib (ABL001) vs Bosutinib in Patients With Chronic Myeloid Leukemia in Chronic Phase Previously Treated With ≥ 2 Tyrosine Kinase Inhibitors
ClinicalTrials.gov NCT03106779

*Each line represents individual animals

Wylie A, et al. *Blood*. 2014:[abstract 398].

Andreas Hochhaus[1] et al

Conclusions

- ✓ **The selection of first-line TKI therapy (IMA, NILO or DAS) in a given patient shold be based on the risk score, toxicity profile of TKI, patient' age and comorbidity.**
- ✓ **IMA and II Gen-TKI are all appropriate options for patients across all risk scores.**
- ✓ **The prevention of disease progression to AP-CML or BC-CML is the primary endopoint of TKI therapy in CP-CML patients and disease progression is more frequent in patients with intermediate-or high-risk score.**
- ✓ **II Gen-TKI are associated with lower risk of disease progression than IMA and are therefore preferred for patients with an intermediate- or high-risk score.**
- ✓ **Moreover, II Gen TKI can induce higher rates of deeper (MMR and MR4.5) and faster responses in patients across all risk scores, which may facilitate subsequent discontinuation of TKI Therapy in selected patients. Particular caution should be needed in high-risk patients**
- ✓ **IMA may be preferred for older patiens with comorbidities especially cardiovascular diseases.**

SALUS SCIENTIA
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Città della Salute e della Scienza di Torino

THANK YOU