CML HORIZONS 2016

CML AdvocatesNetwork

LJUBLJANA
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ELN Recommendations on treatment choice and response

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ELN 2013 – Response to Front-line Treatment

	OPTIMAL	WARNING	FAILURE
Baseline	NA	-**High risk**, -**CCA/Ph+** (Major route)	NA
3 months	Ph+ ≤ 35% and/or BCR-ABL ≤ 10%	Ph+ 36-95% and/or BCR-ABL > 10%	No CHR and/or Ph+ > 95%
6 months	Ph+ 0% and/or BCR-ABL ≤ 1%	Ph+ 1-35% and/or BCR-ABL 1-10%	Ph+ > 35% and/or BCR-ABL > 10%
12 months	BCR-ABL ≤ 0.1%	BCR-ABL > 0.1-1 %	Ph+ > 0% and/or BCR-ABL > 1%
Then	BCR-ABL ≤ 0.1%	BCR-ABL 0.1-1%	BCR-ABL > 1%

Baccarani et al, Blood 2013; 122: 885-892.

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ELN 2013 – Response to Front-line Treatment

Imatinib, Nilotinib, and Dasatinib

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2nd Generation TKIs in Early CP

Outcome and Responses By 5 Years

	ENESTnd[1]		Dasision[2]	
Treatment	Nilotinib	Imatinib	Imatinib	Dasatinib
Patient N.	282	283	260	259
5-year PFS[&]	96.5%	94.7%	85.5%	85.4%
5-year OS^	93.6%	91.6%	89.6%	90.9%
MMR	77%	60%	64%	76%
$MR^{4.5}$	54%	31%	33%	42%

Note: Data from different studies, please interpret with care.

[&] ENESTnd: death from any cause or progression to AP/BC. DASISION: doubling of WBC count, loss of CHR, increase in Ph-positive metaphases to >35%, transformation, or death from any cause

^ ENESTnd Including events occurring on core or extension treatment or during f/u after treatment discontinuation; DASISION Total n. of deaths on-study treatment and in follow-up after discontinuation of randomized treatment.

[1] Hughes et al., EHA 2014 Abstract S677
[2] Cortes J. et al. ESH, iCMLf 2104

2016, the weight of the choice of 1st line Treatment

Patient

- Risk, comorbidities
- Personal Expectations
- Education, compliance
- Advocacies

Drugs

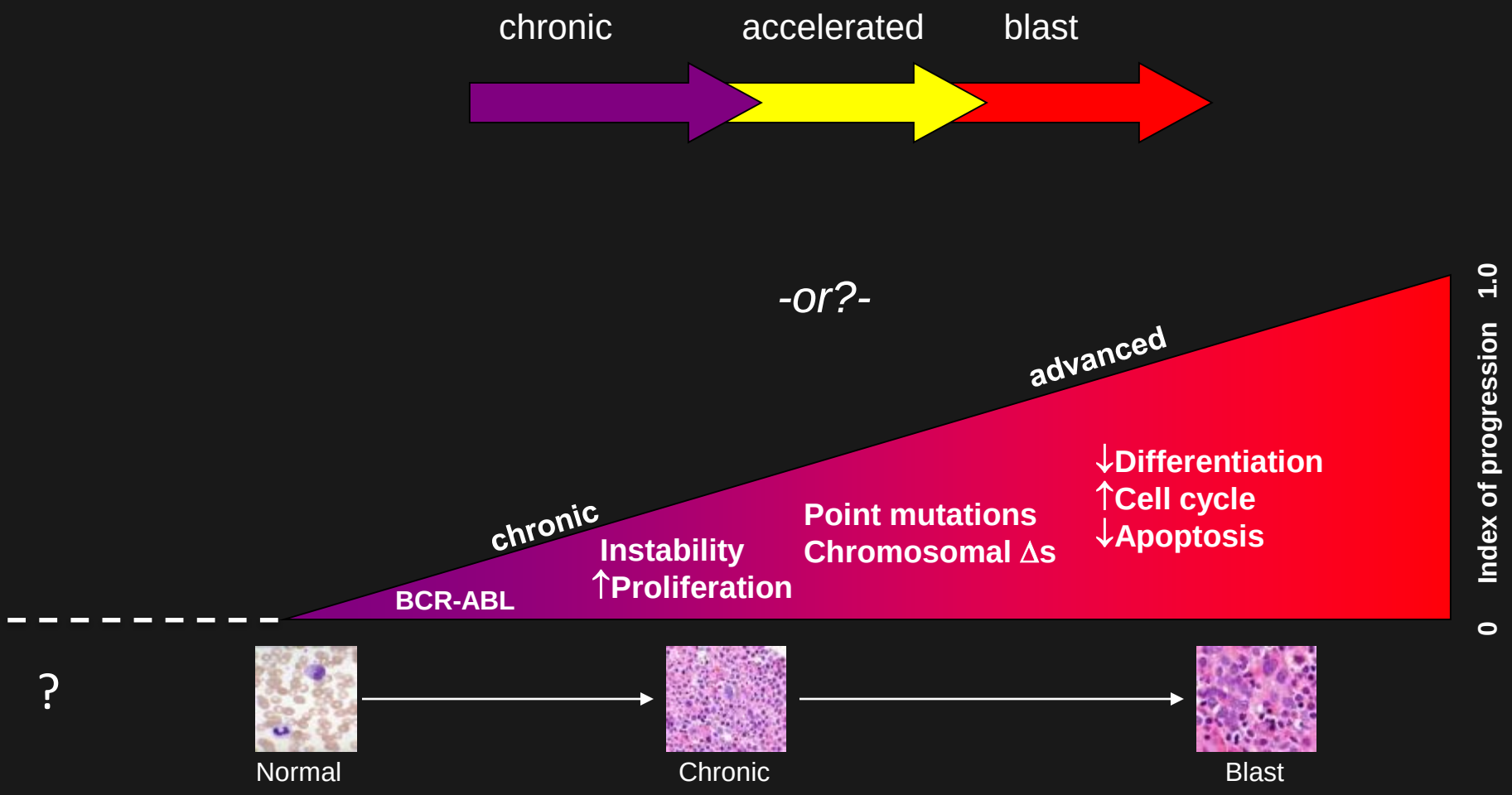
- Efficacy and time to response
- Side Effects / QOL
- Long term safety
- Costs

Physician

- Personal Experience
- Experience

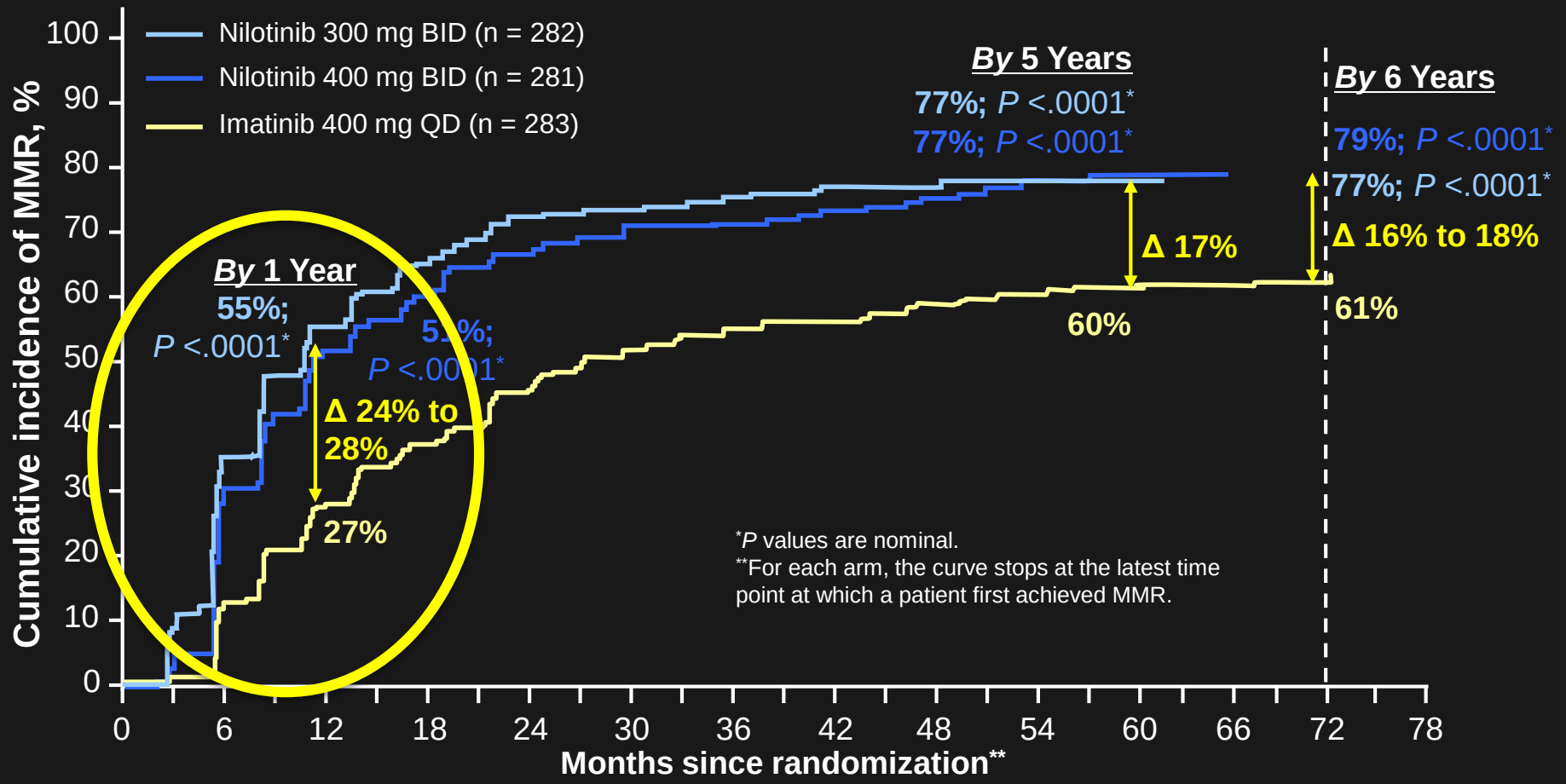
ENDPOINTS

CML, conceptual model of progression



Radich et al., PNAS 2006

ENESTnd: Cumulative Incidence of MMR



- Rates of MMR by 6 years remained higher in the nilotinib arms than in the imatinib arm (**Figure 2**)
- Nearly all patients still on core treatment at the data cutoff had achieved MMR; in each arm, 4 patients who had not achieved MMR remained on core treatment at the data cutoff (among these 12 patients, 5 had atypical transcripts at baseline and 7 had a best response of *BCR-ABL*^{IS} >0.1% to ≤1%)

Larson RA, et al. ASH 2014. Abstract 4541.

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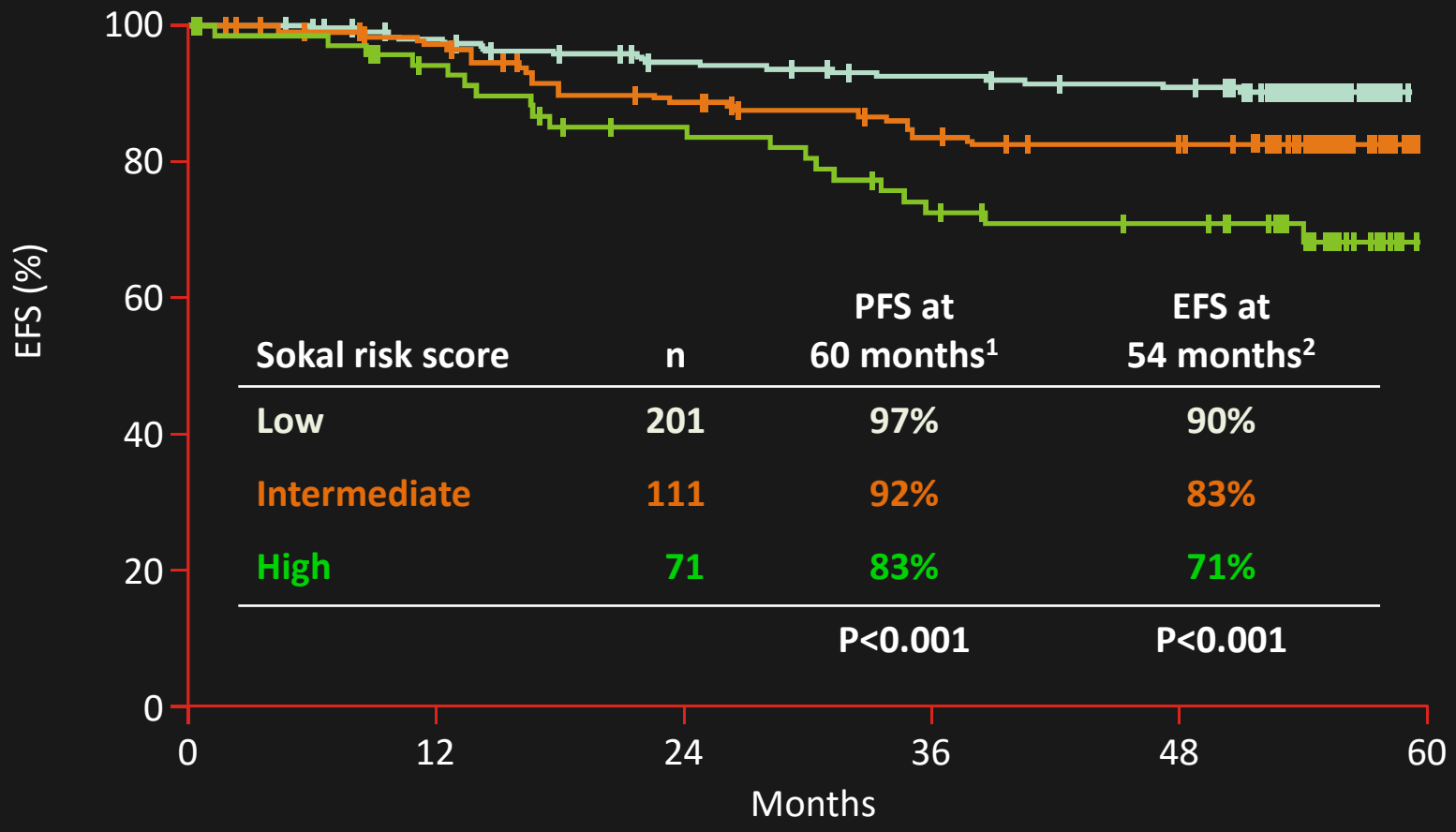
Sokal High-Risk Patients Had Significantly Worse Responses on Imatinib

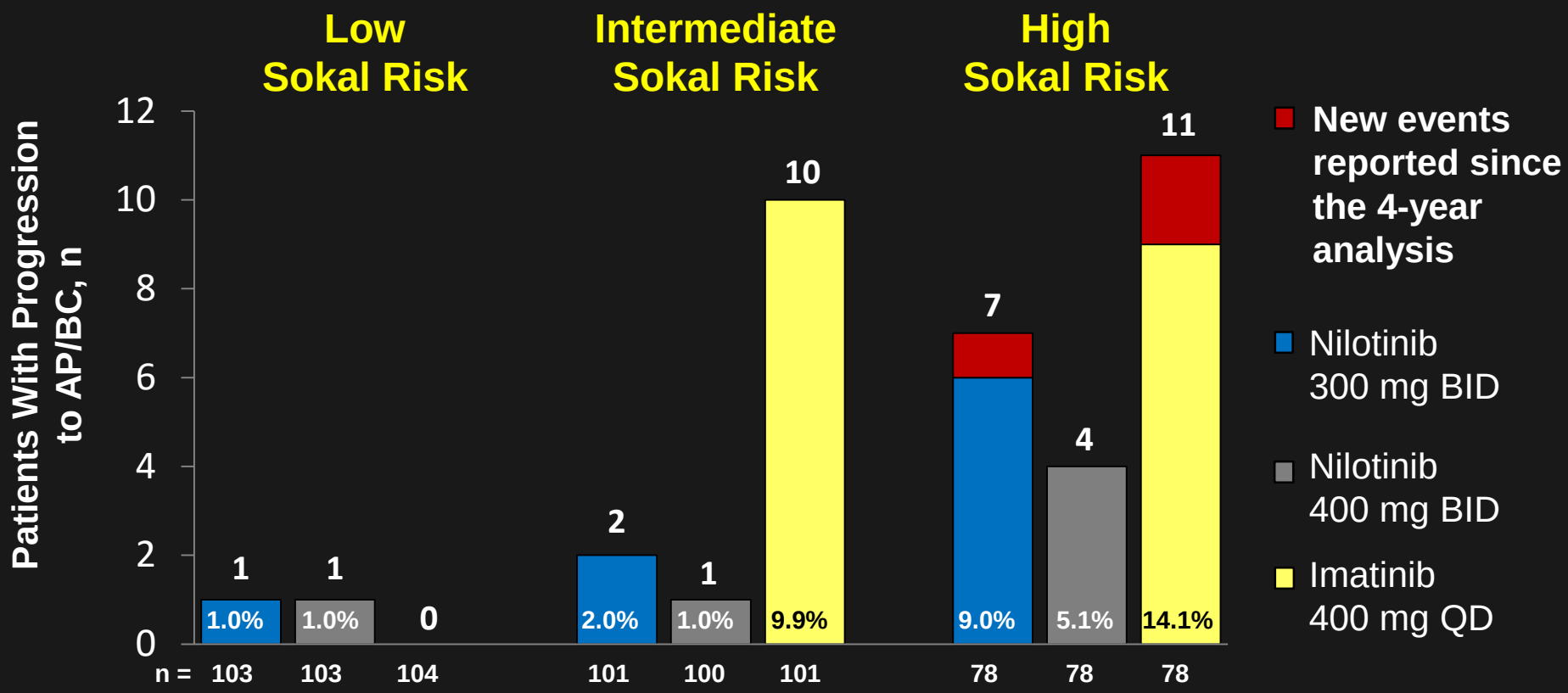


Sokal risk score	n	PFS at 60 months[1]	EFS at 54 months[2]
Low	201	97%	90%
Intermediate	111	92%	83%
High	71	83%	71%
		P<0.001	P<0.001

Data from the IRIS trial

1. Hochhaus A, et al. Leukemia 2009;23:1054–61
2. Baccarani M. Relative Risk (Sokal & Hasford)
Available at: http://www.leukemia-net.org/content/leukemias/cml/research/research/

Progression to AP/BC on Study[a] According to Sokal Risk Score



- All 3 progressions to AP/BC on study reported since the 4-year analysis occurred in patients with high Sokal risk scores at baseline; all 3 patients also had BCR-ABL^{IS} > 10% at 3 months
- All progressions in patients with low/intermediate Sokal risk scores occurred during the first 2 years on study

Data cutoff: September 30, 2013

[a] Progression to AP/BC or death due to advanced CML on core treatment or during follow-up after discontinuation of core treatment.

Long-term benefits and risks of frontline nilotinib vs imatinib for chronic myeloid leukemia in chronic phase: 5-year update of the randomized ENESTnd trial

	Nilotinib 300 mg twice daily	*Nilotinib 400 mg twice daily*	*Imatinib 400 mg once daily*
Low Sokal risk, *n*	103	103	104
$MR^{4.5}$ by 5 years, *n* (%)	55 (53.4)	64 (62.1)	38 (36.5)
Progression to AP/BC on study, *n* (%)	1 (1.0)	1 (1.0)	0
Estimated 5-year PFS on study, %[a]	96.0	99.0	100
Estimated 5-year OS on study, %[a]	97.0	99.0	100
Treatment-emergent mutations, *n* (%)[b]	1 (1.0)	2 (1.9)	1 (1.0)
Intermediate Sokal risk, *n*	101	100	101
$MR^{4.5}$ by 5 years, *n* (%)	61 (60.4)	50 (50.0)	33 (32.7)
Progression to AP/BC on study, *n* (%)	2 (2.0)	1 (1.0)	10 (9.9)
Estimated 5-year PFS on study, %[a]	92.9	96.9	87.9
Estimated 5-year OS on study, %[a]	93.8	96.9	88.5
Treatment-emergent mutations, *n* (%)[b]	5 (5.0)	3 (3.0)	8 (7.9)
High Sokal risk, *n*	78	78	78
$MR^{4.5}$ by 5 years, *n* (%)	35 (44.9)	33 (42.3)	18 (23.1)
Progression to AP/BC on study, *n* (%)	7 (9.0)	4 (5.1)	11 (14.1)
Estimated 5-year PFS on study, %[a]	86.2	90.0	82.6
Estimated 5-year OS on study, %[a]	88.8	91.5	84.2
Treatment-emergent mutations, *n* (%)[b]	6 (7.7)	6 (7.7)	13 (16.7)

Hochhaus et al, Leukemia 2016

Defining Molecular Response Requirements for Potential Treatment Discontinuation[1]

Response at Time of Treatment Discontinuation	Patients with Molecular and/or Cytogenetic Relapse, %
CCyR[2]	100%
MMR[3]	100%
MMR, CCyR, MCyR[4]	100%
CMR for ≥2 years on imatinib[5-8]	~30%–65%

CCyR, complete cytogenetic response; CMR, complete molecular response; MCyR, major cytogenetic response; MMR, major molecular response.

1. Milojkovic D et al. *Blood.* 2011;118(21): abstract 605; 2. Goh HG, et al. *Leuk Lymphoma.* 2009;50(6):944-951; 3. Koskenvesa P, et al. *Blood.* 2008;112(11):738. Abstract 2121; 4. Kuwabara A, et al. *Blood.* 2010;116(6):1014-1016; 5. Mahon FX, et al. *Blood.* 2011;118(21): abstract 603; 6. Rousselot P, et al. *Blood.* 2011;118(21): abstract 3781; 7. Goh HG, et al. *Blood.* 2011;118(21): abstract 2763; 8. Matsuki E, et al. *Blood.* 2011;118(21): abstract 3765.

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CML Potential Molecular “Cures”

	Imatinib (%)	Nilo/Dasa (1,2) (%)
$MR^{4.5}$ at 5 yr	40	60–70
“CMR” ≥2–3 yr	30	50+
Molecular “cures”	15	25–30

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