Cure of CML…Almost

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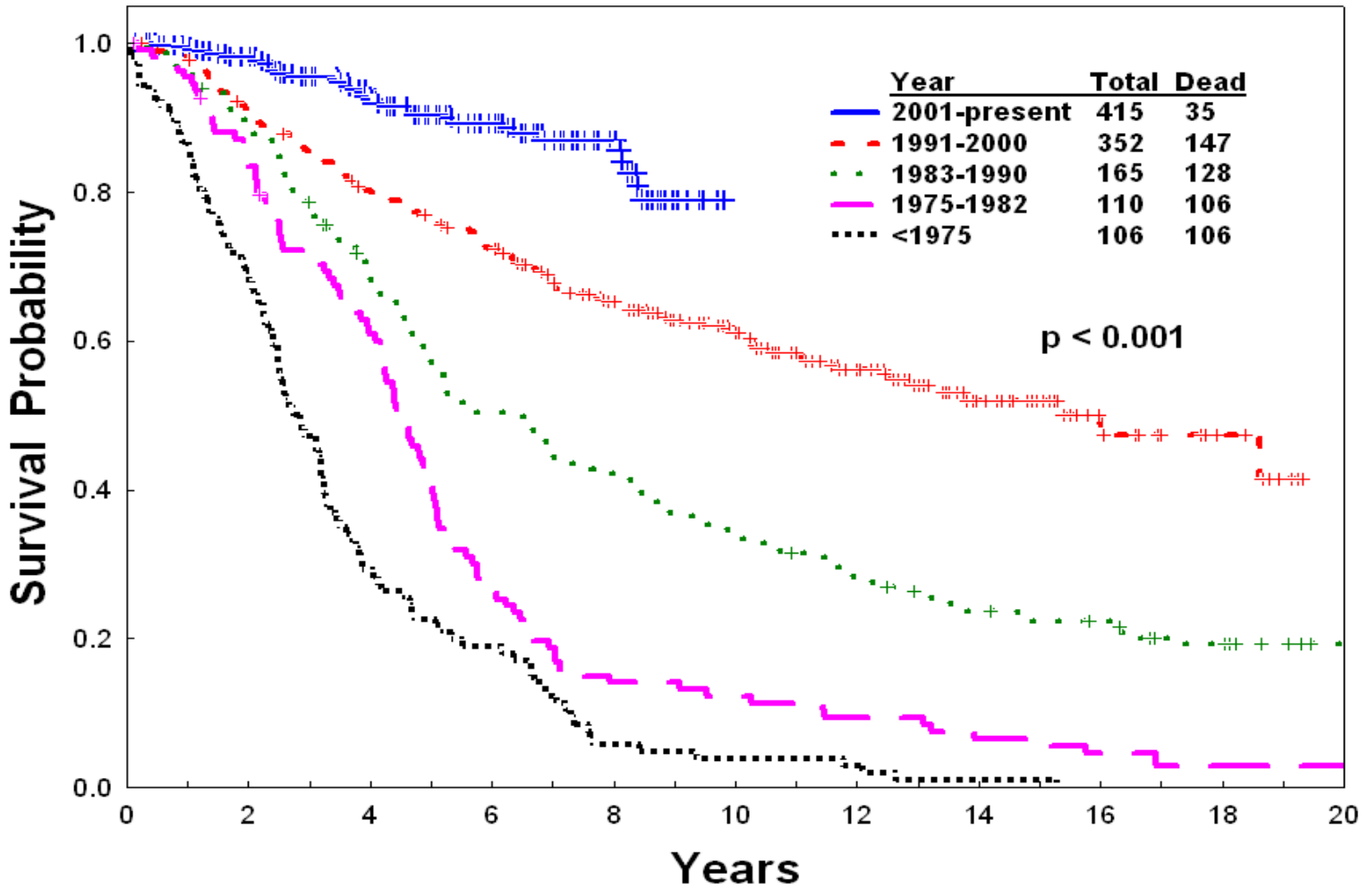
Hong Kong

CML. Historical vs. Modern Perspective

Parameter	Historical	Modern
• Course	Fatal	Indolent
• Prognosis	Poor	Excellent
• 10-yr survival	10%	84 - 90%
• Frontline Rx	Allo SCT; IFN-□	Imatinib; nilotinib; dasatinib
• Second line Rx	?	New TKIs; allo SCT

Improved Survival in Early Chronic Phase CML



Lee. Blood 118: abst 2750, 2011

Therapy of CML in 2012

- Frontline
  - imatinib 400 mg daily
  - nilotinib 300 mg BID
  - dasatinib 100 mg daily
- Second / third line
  - nilotinib, dasatinib, bosutiinib, ponatinib
  - allogeneic SCT
- Other
  - omacetaxine, decitabine, pegasys
  - hydrea, cytarabine, combos of TKIs and with TKIs
  - investigational: hedgehog inhibitors, JAK2 inhibitors, IL3-DT

CML. The Next Questions

- Frontline CML Rx: imatinib vs. second TKIs
- Can we cure CML molecularly? Is it necessary?
- Role and timing of allo SCT
- Monitoring of CML
- Others: prevalence, pregnancy CG

Results with Imatinib in Early CP CML – The IRIS Trial at 8-Years

- 304 (55%) patients on imatinib on study
- Projected results at 8 years:
  - CCyR 83%
    - 82 (18%) lost CCyR, 15 (3%) progressed to AP/BP
  - Event-free survival 81%
  - Transformation-free survival 92%
    - If MMR at 12 mo: 100%
  - Survival 85% (93% CML-related)
- Annual rate of transformation: 1.5%, 2.8%,

Deininger. Blood 114: abst 1126, 2009

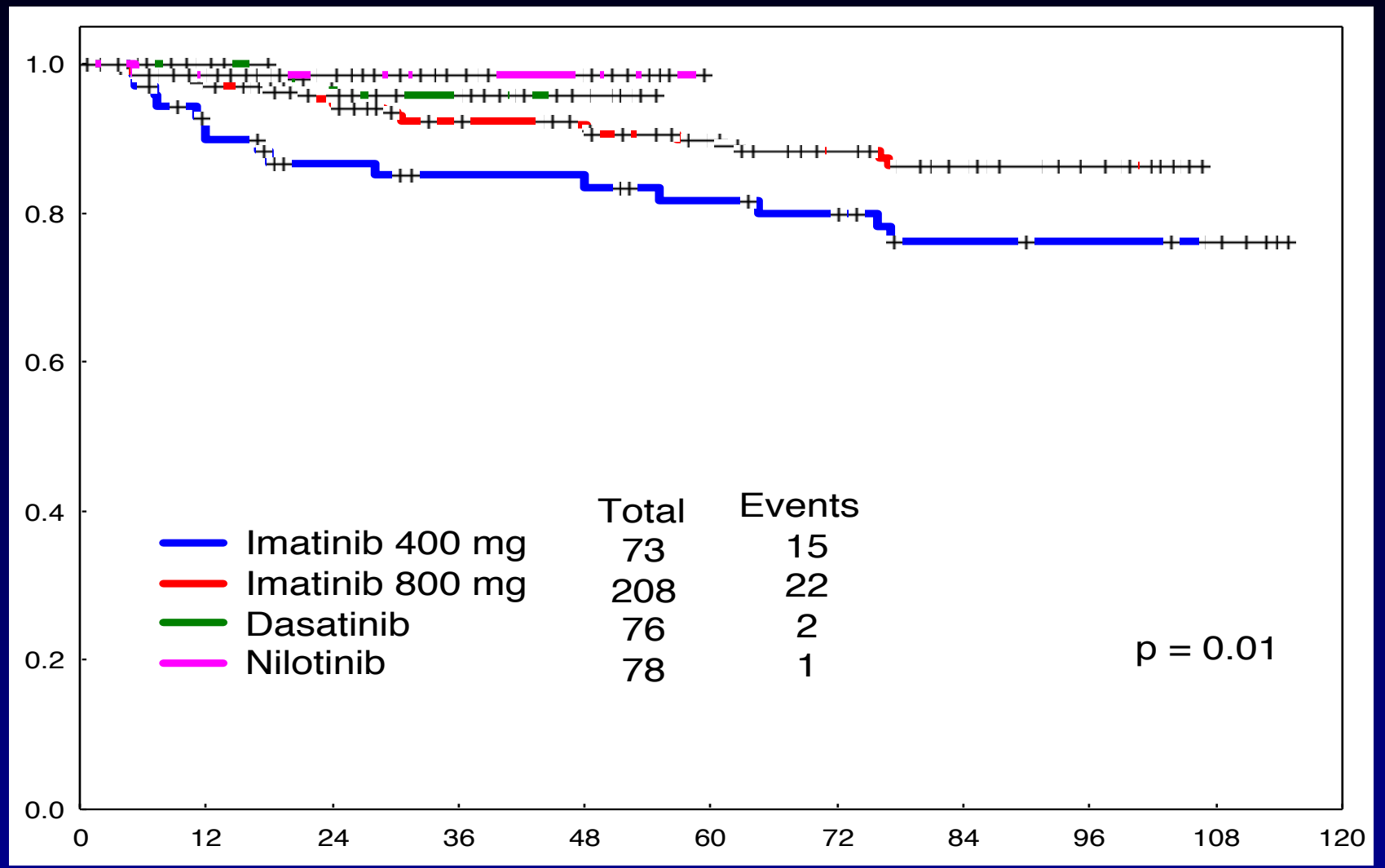
Frontline Rx with Dasatinib or Nilotinib at MDACC

- Parallel studies with nilotinib (400 mg BID) or dasatinib (100 mg QD or 50 mg BID)

% Response	Nilotinib N=100	Dasatinib N=93
CGCR by 12 mos	93	99
MMR by 12 mos	73	83
3-yr Survival	100	99
3-yr TFS	97	100
3-yr EFS	91	91
3-yr FFS	78	80
Rx discontinuation	11	9

Quintas-Cardama. Blood 118: abst 454, 2011. Pemmaraju. Blood 118; abst 1700; 2011

Event-Free Survival by Treatment in ECP CML

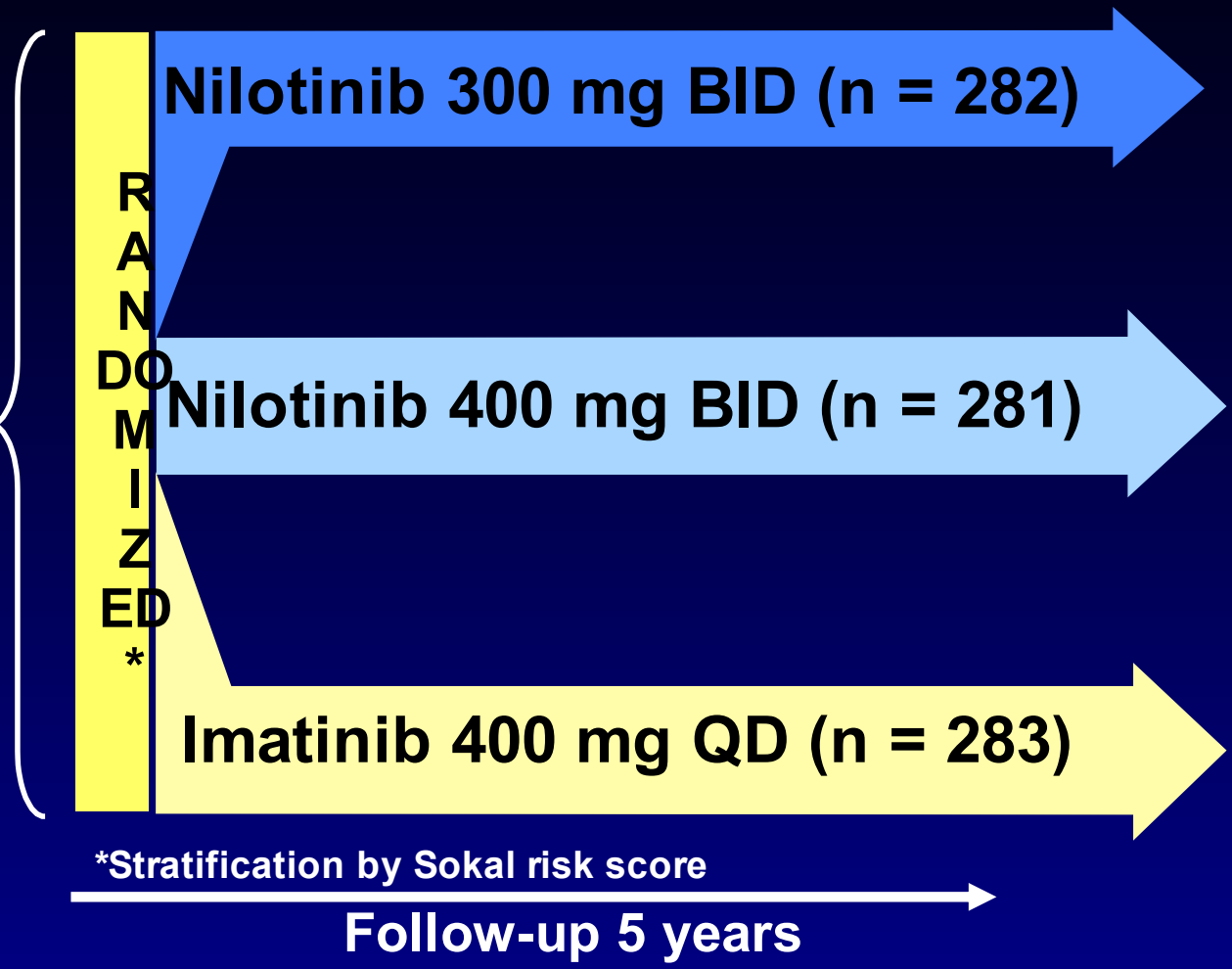


Months

Cortes. Blood 2009; abst 338 & 341; Updated October 2010

Nilotinib vs. Imatinib in CML (ENEST-nd). Study Design

- N = 846
- 217 centers
- 35 countries



Saglio. Blood 118: abst 452, 2011

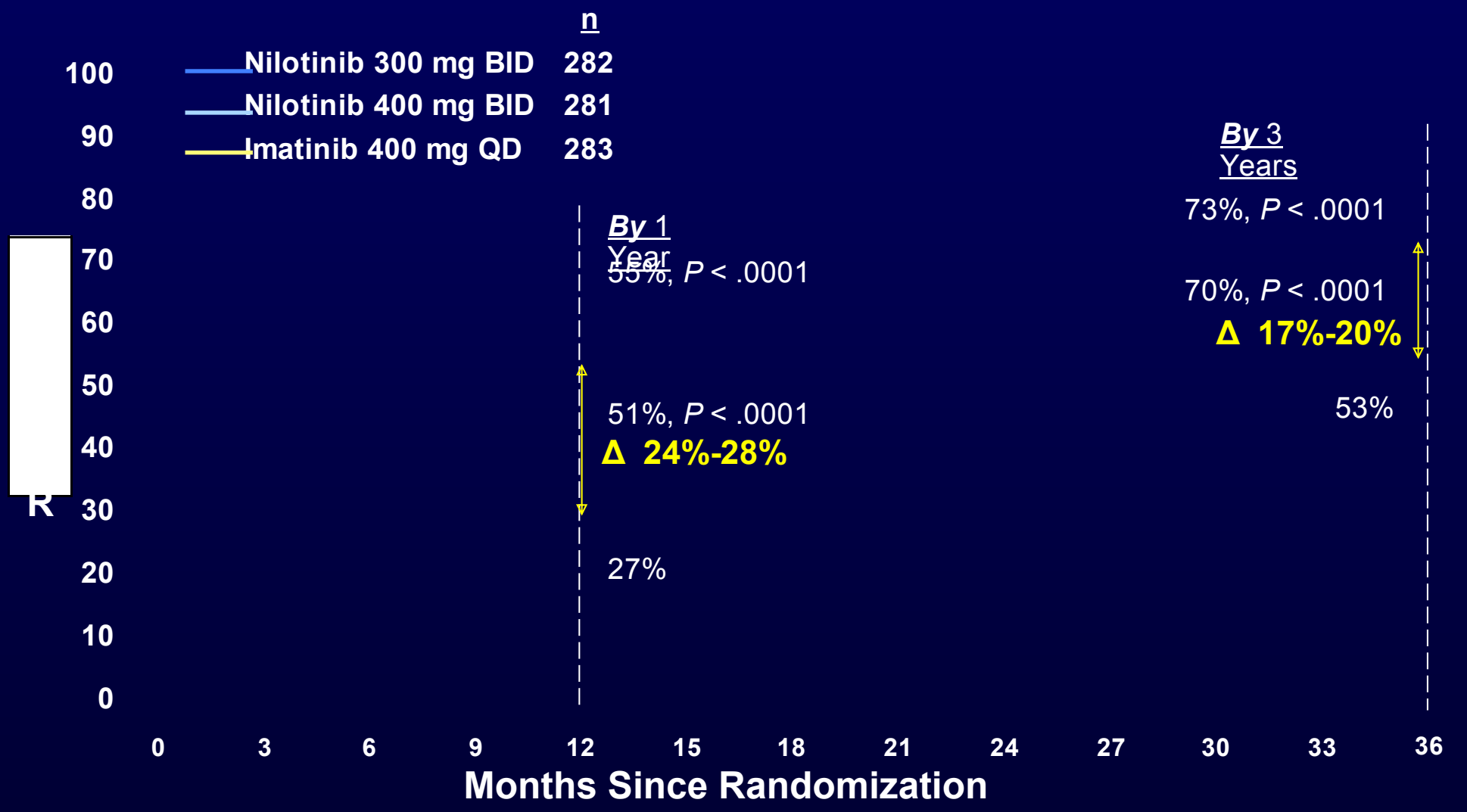
Nilotinib vs. Imatinib in Newly Dx CML (ENEST-nd)

- 846 pt randomized to nilotinib 300 mg BID (n=282), 400 mg BID (n=281), imatinib 400 mg daily

% Parameter	Nilo 300	Nilo 400	IM	P value
24-mo MMR low int-high	 73 74/65	 74 67/56	 53 44/32	
MR 4	44	36	20	< .001
MR 4.5	26	21	10	< .001
24-mo FFP	99	98	95	.02
24-mo PFS	98	98	95	.07
24-mo OS	97	98	96	NS

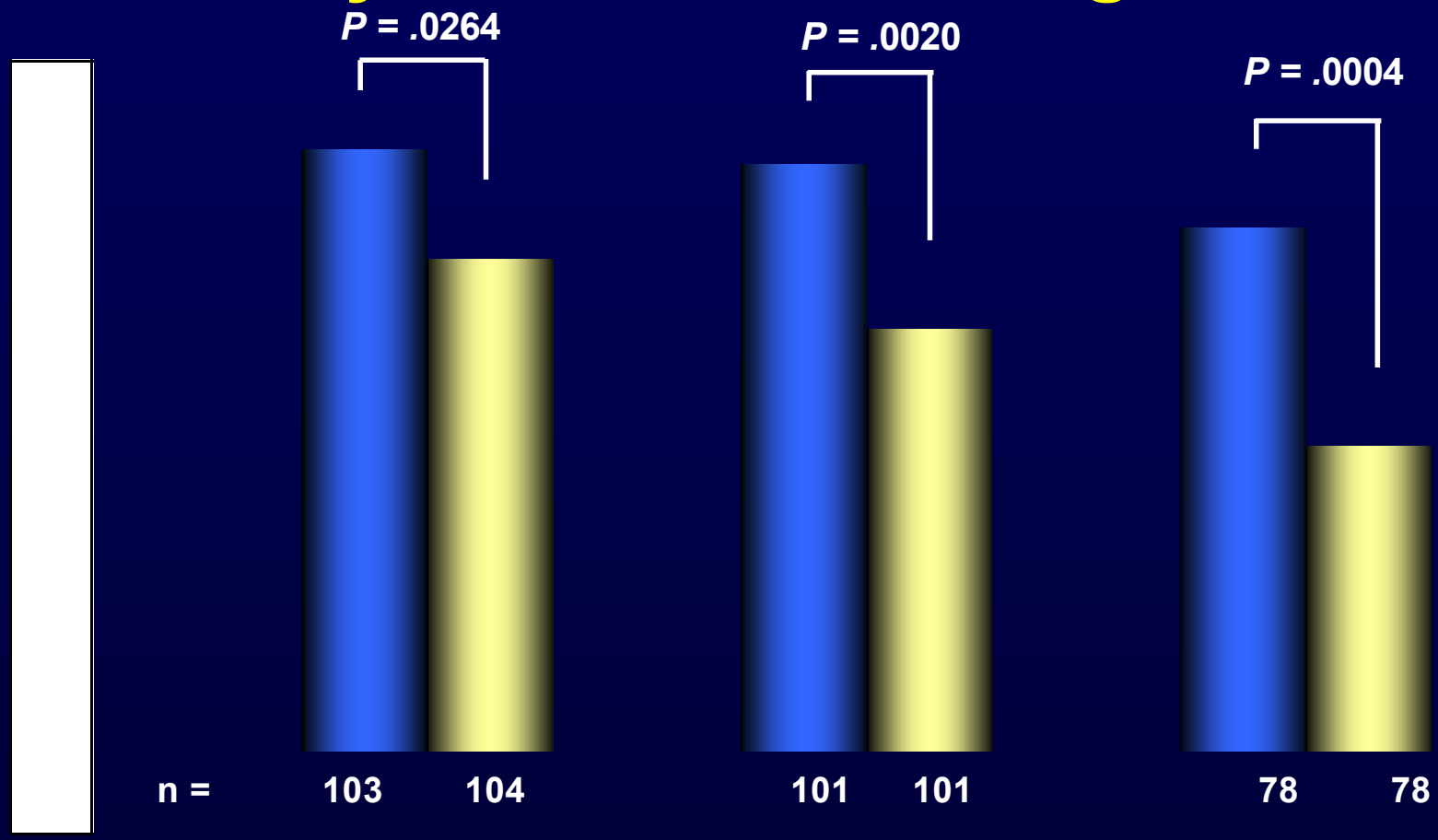
Saglio. Blood 118: abst 452; 2011

Nilotinib vs. Imatinib in CML (ENEST-nd). Cumulative Incidence of MMR



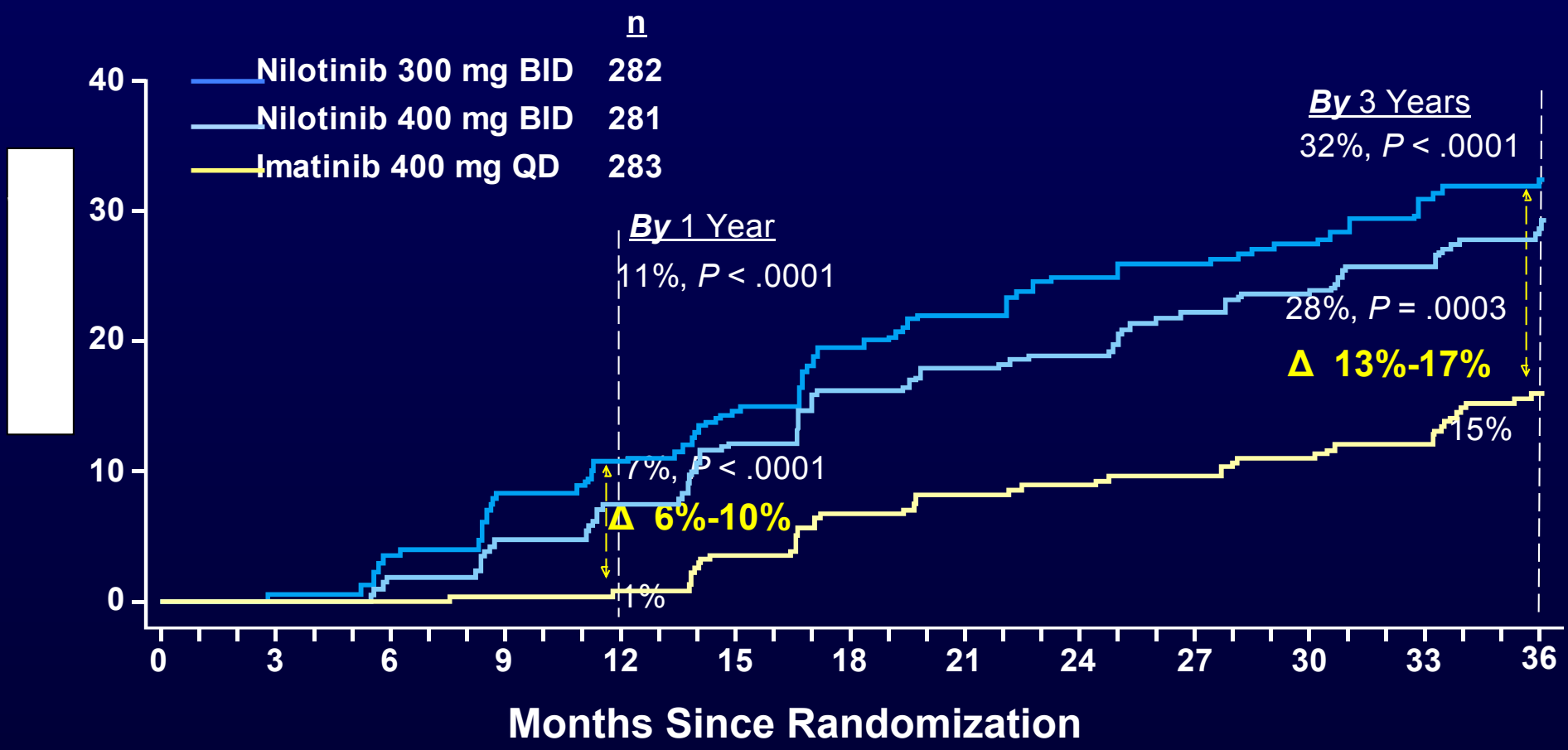
Saglio. Blood 118; abst 452, 2011

Nilotinib vs. Imatinib in CML (ENEST-nd). MMR by 3 Years According to Sokal Risk



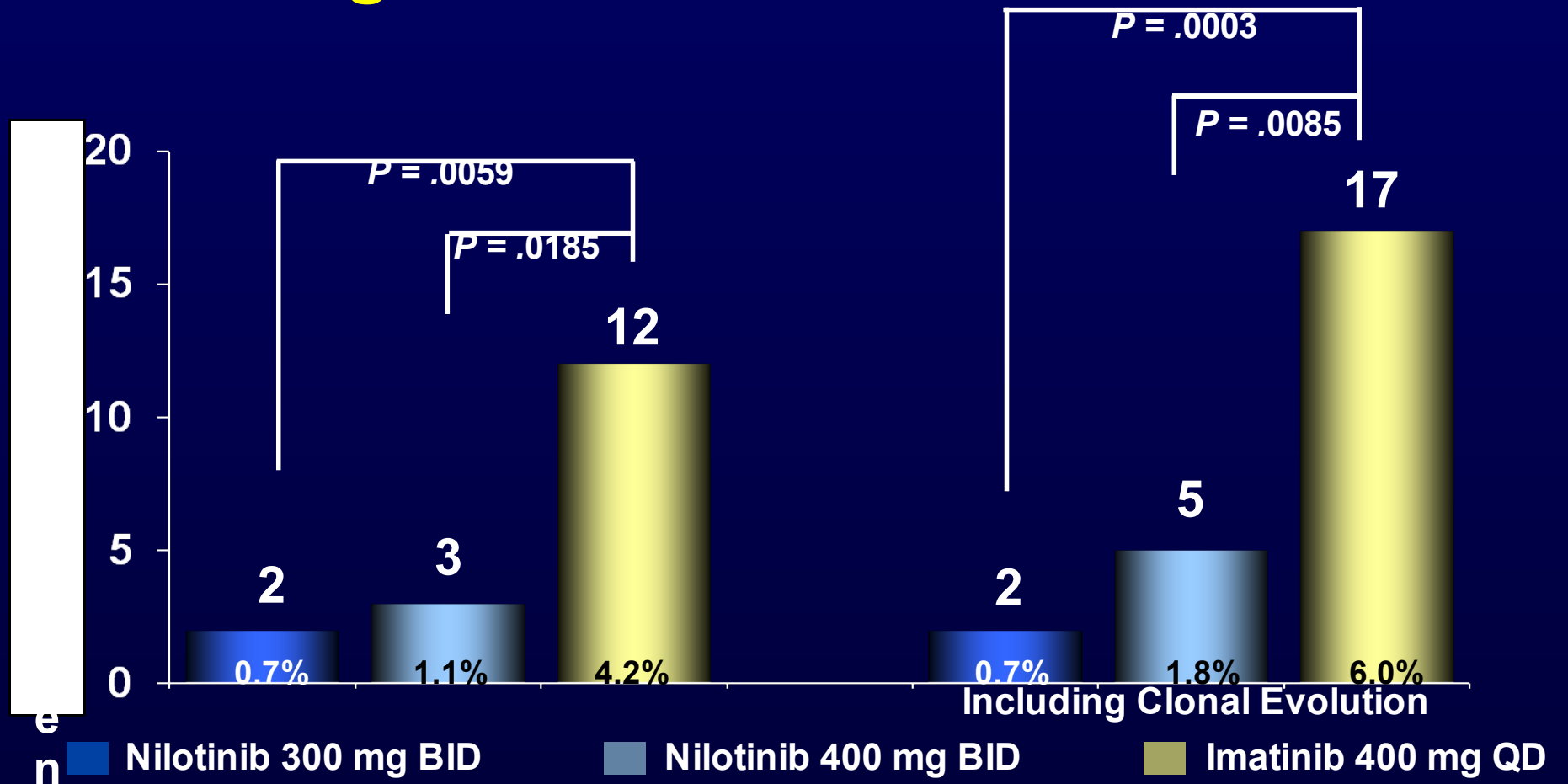
Saglio. Blood 118; abst 452, 2011

Nilotinib vs. Imatinib in CML (ENEST-nd). Cumulative Incidence of MR 4.5



Saglio. Blood 118; abst 452, 2011

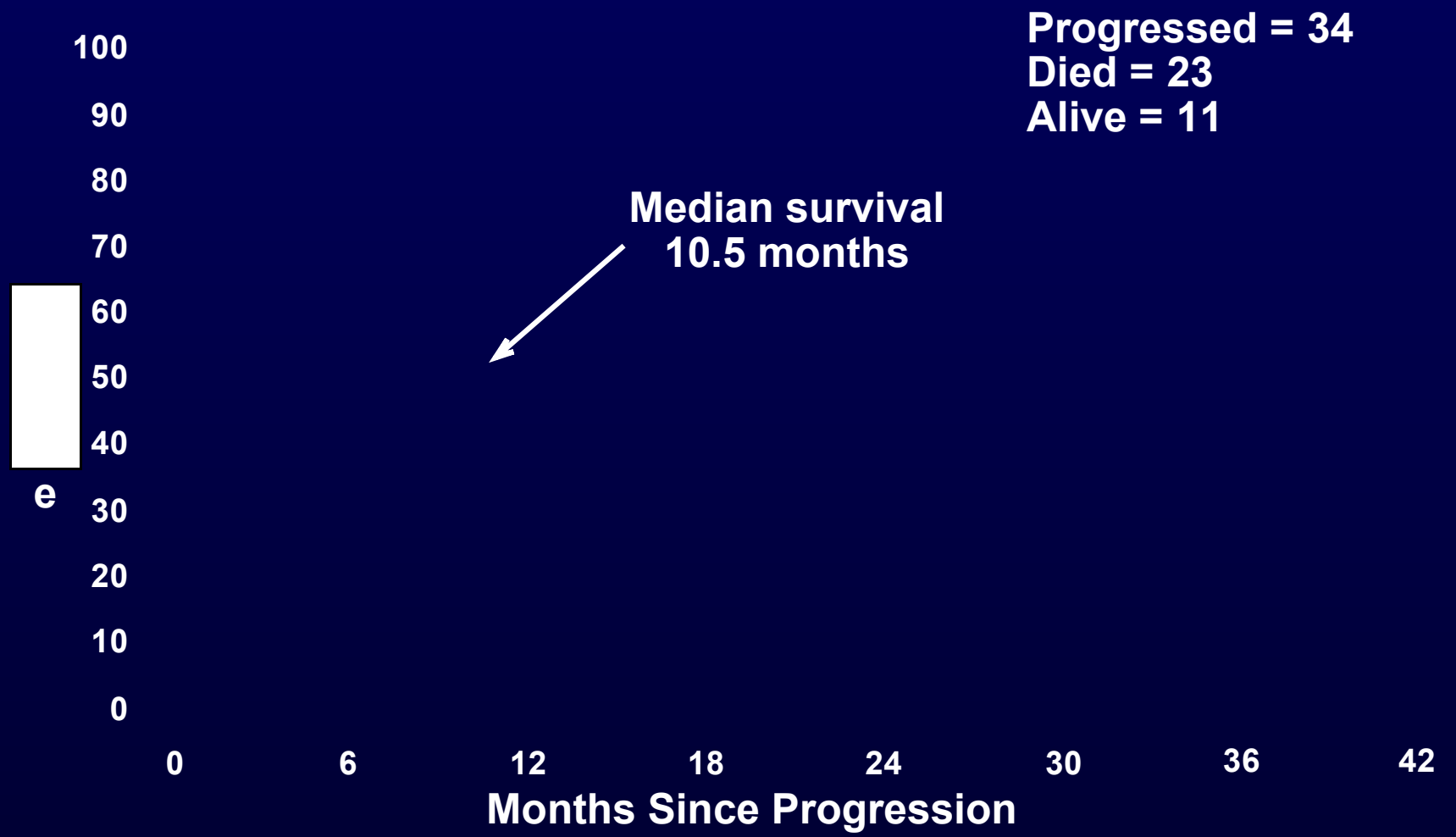
Nilotinib vs. Imatinib in CML (ENEST-nd). Progression to AP/BP on Core Rx



- No new progressions on core Rx since 2-year analysis

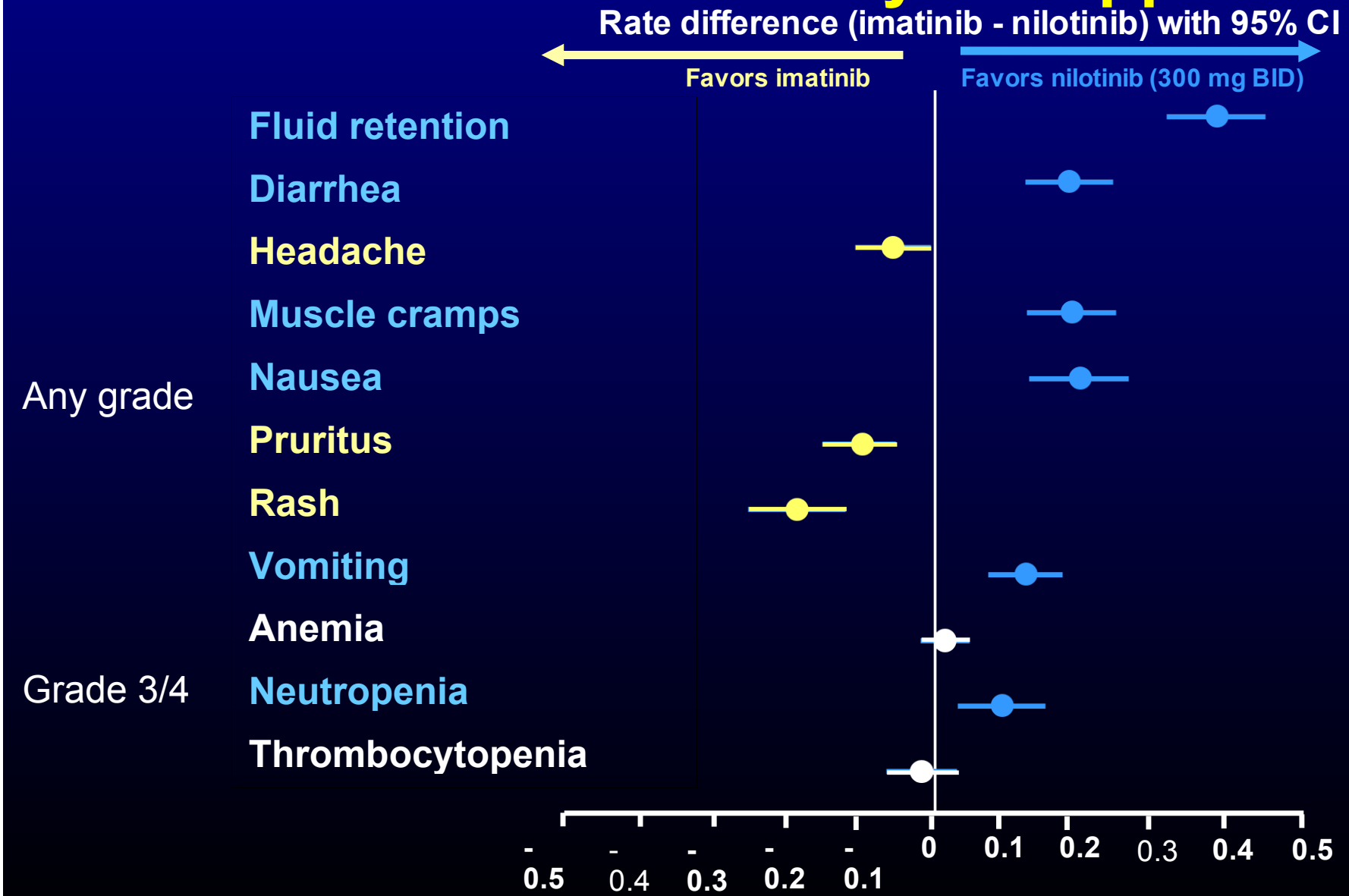
Saglio. Blood 118; abst 452, 2011

Nilotinib vs. Imatinib in CML (ENEST-nd). Survival After Progression to AP/BP



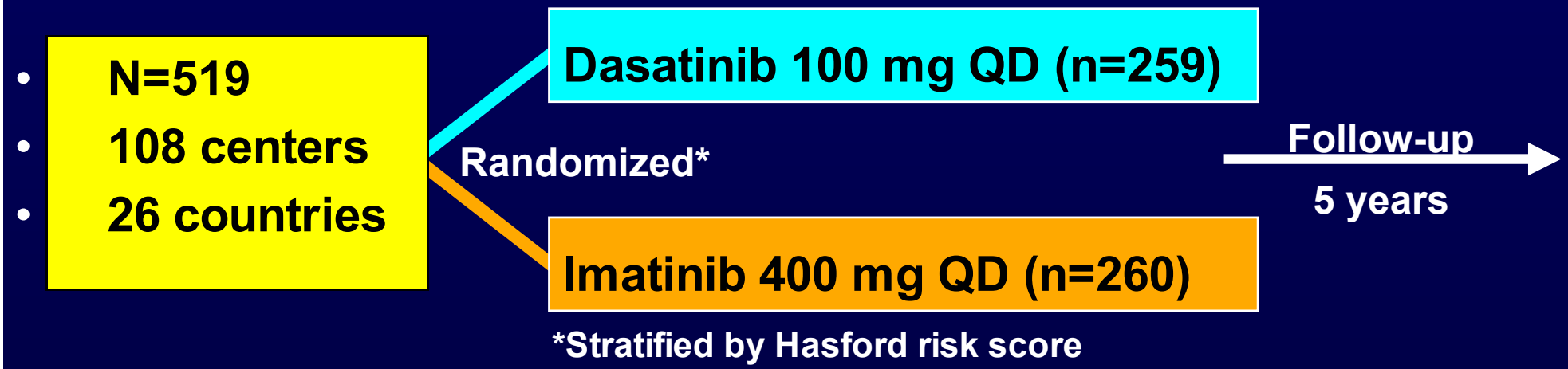
Saglio. Blood 118; abst 452, 2011

Nilotinib vs. Imatinib in CML-CP. Adverse Events and Grade 3/4 Myelosuppression



Hochhaus. Haematologica. 2010;95(s2):459 [abst 1113]

Dasatinib Versus Imatinib Study In Treatment-naïve CML (DASISION). Trial Design



- Primary endpoint: Confirmed CCyR by 12 months
- Secondary/other endpoints: Rates of CCyR and MMR; times to confirmed CCyR, CCyR and MMR; time in confirmed CCyR and CCyR; PFS; overall survival

Kantarjian. JCO. 29:abst 6510; 2011

Dasatinib vs Imatinib in Newly Diagnosed Chronic Phase CML

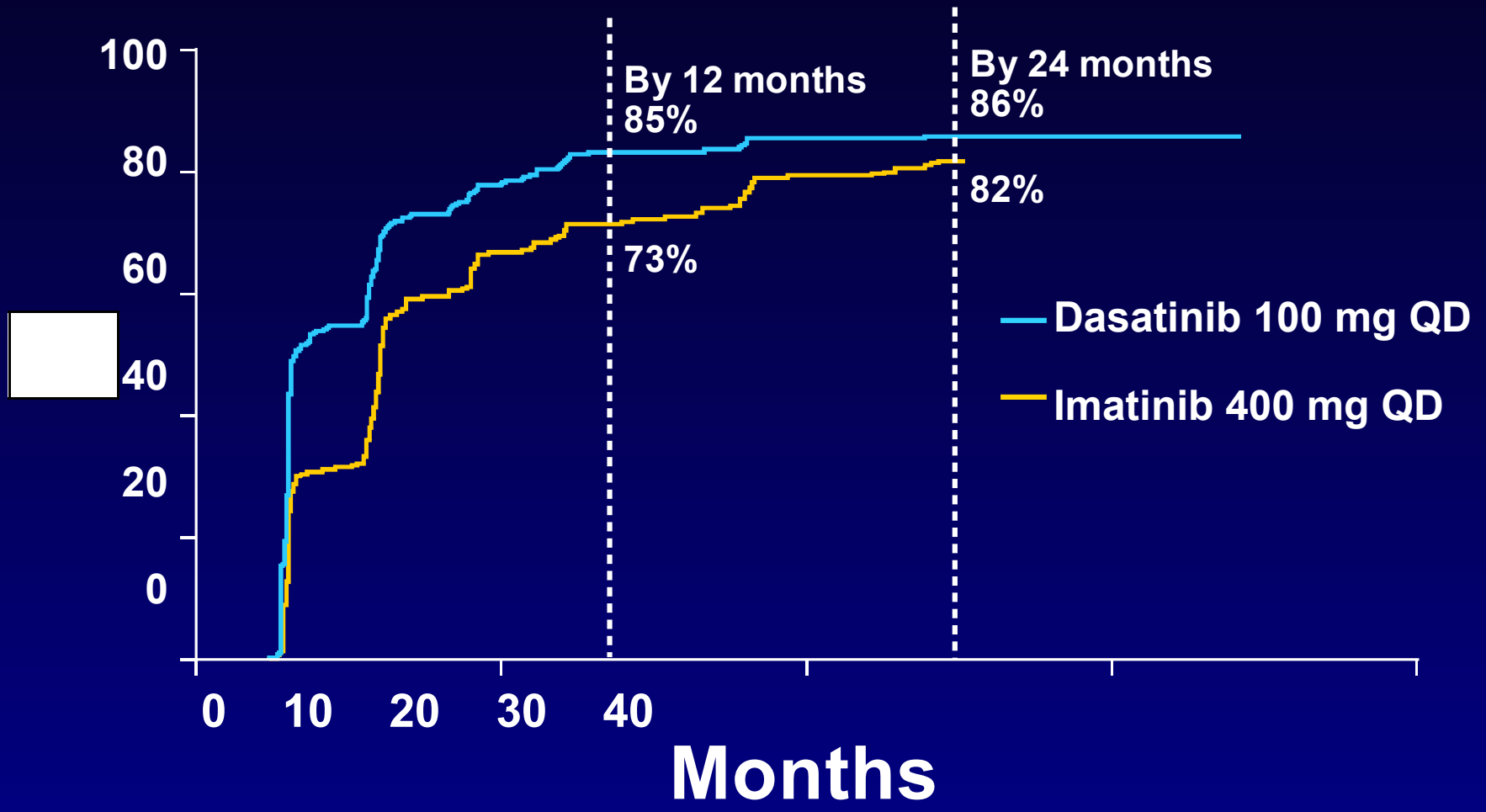
- 519 pts randomized to dasatinib 100 mg QD (n=259) or imatinib 400 mg QD (n=260)
- Median follow-up 28 mo

Outcome	Das 100	IM 400
% CCyR	86	82
% MMR	64	46
% BCR-ABL ≤0.0032%	17	8
% discontinued therapy	23	25
New mutations (No.)	10	10

* by 24 months

Kantarjian. JCO. 29:abst 6510; 2011

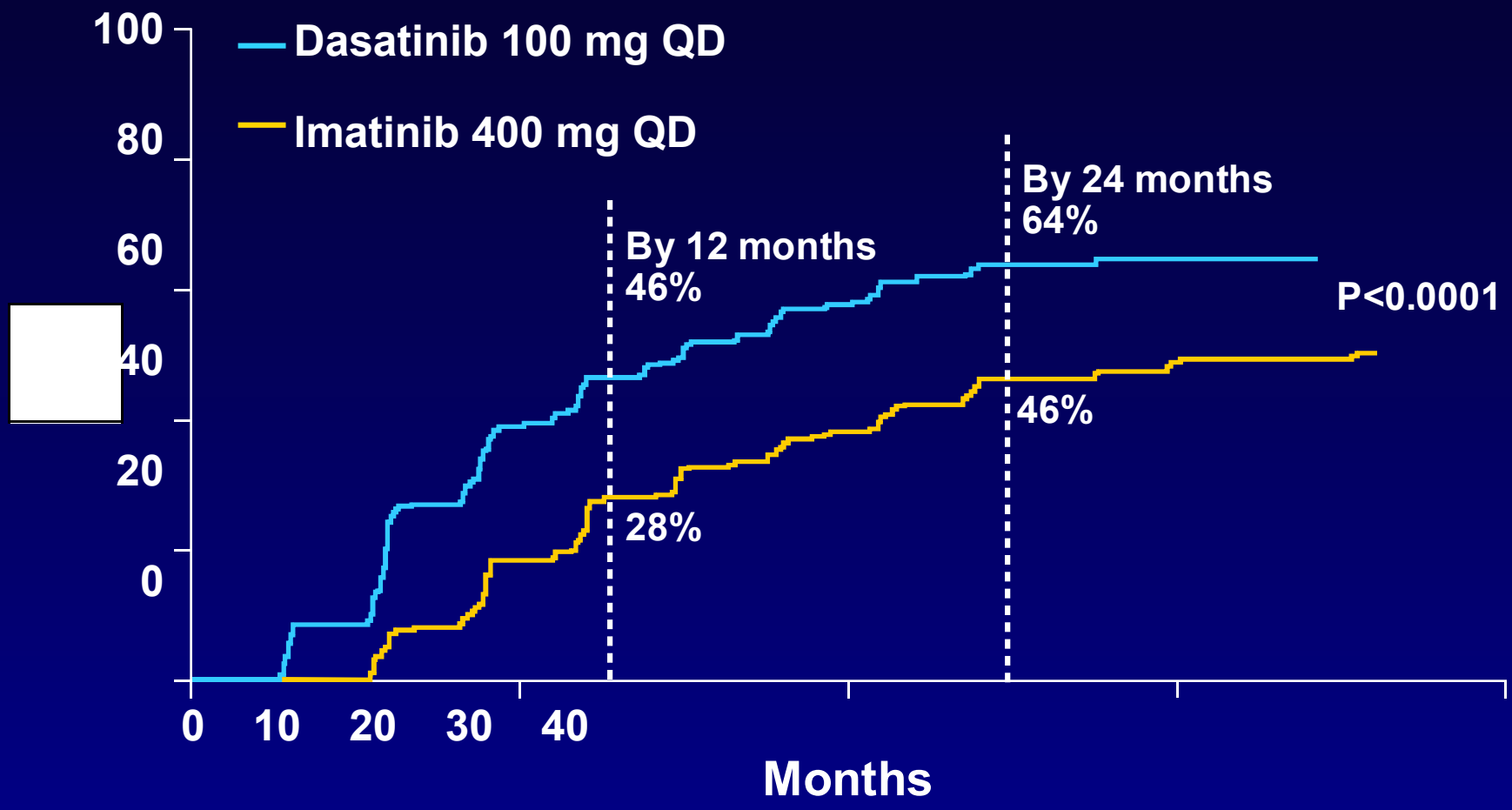
DASISION. Cumulative Incidence of CCyR



cCCyR rate by 24 months for dasatinib vs imatinib was 80% vs 74%

Kantarjian. JCO. 29:abst 6510; 2011

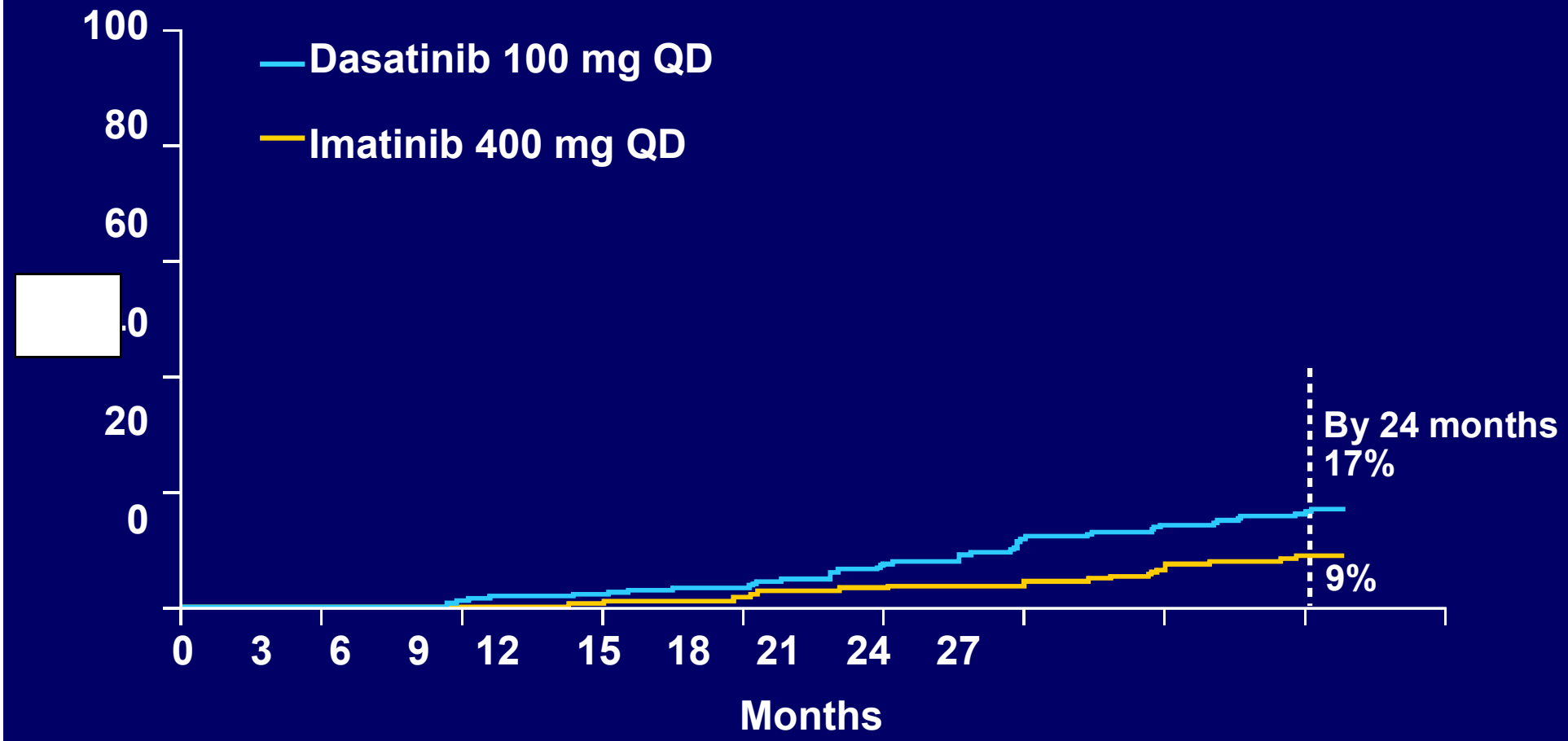
DASISION. Cumulative Incidence of MMR



Median time to MMR in all patients calculated by competing risk analysis was 15 months for dasatinib and 36 months for imatinib

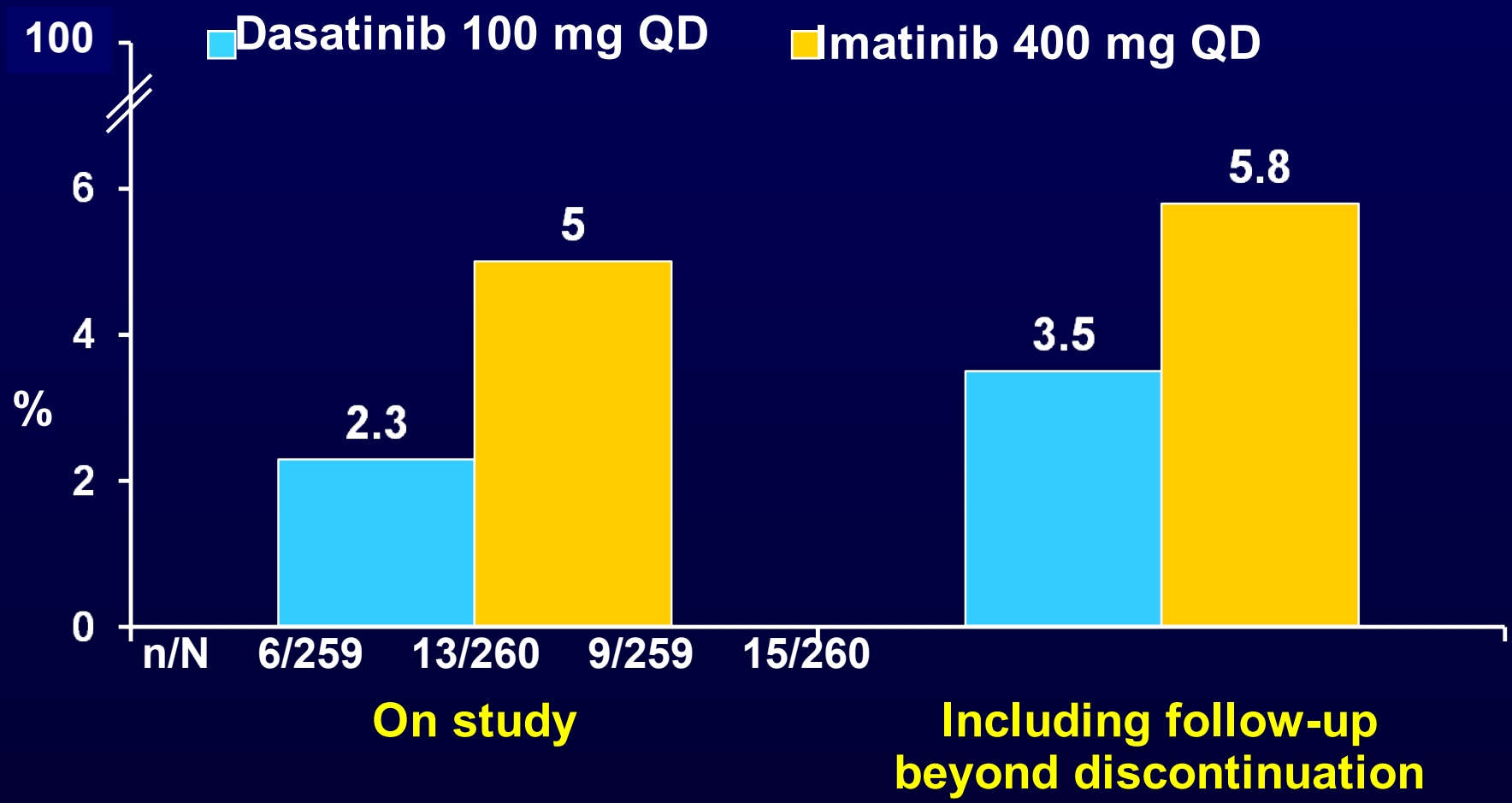
Kantarjian. JCO. 29:abst 6510; 2011

DASISION. Cumulative Incidence of BCR-ABL ≤0.0032% (MR4.5; ≥4.5-log reduction)*



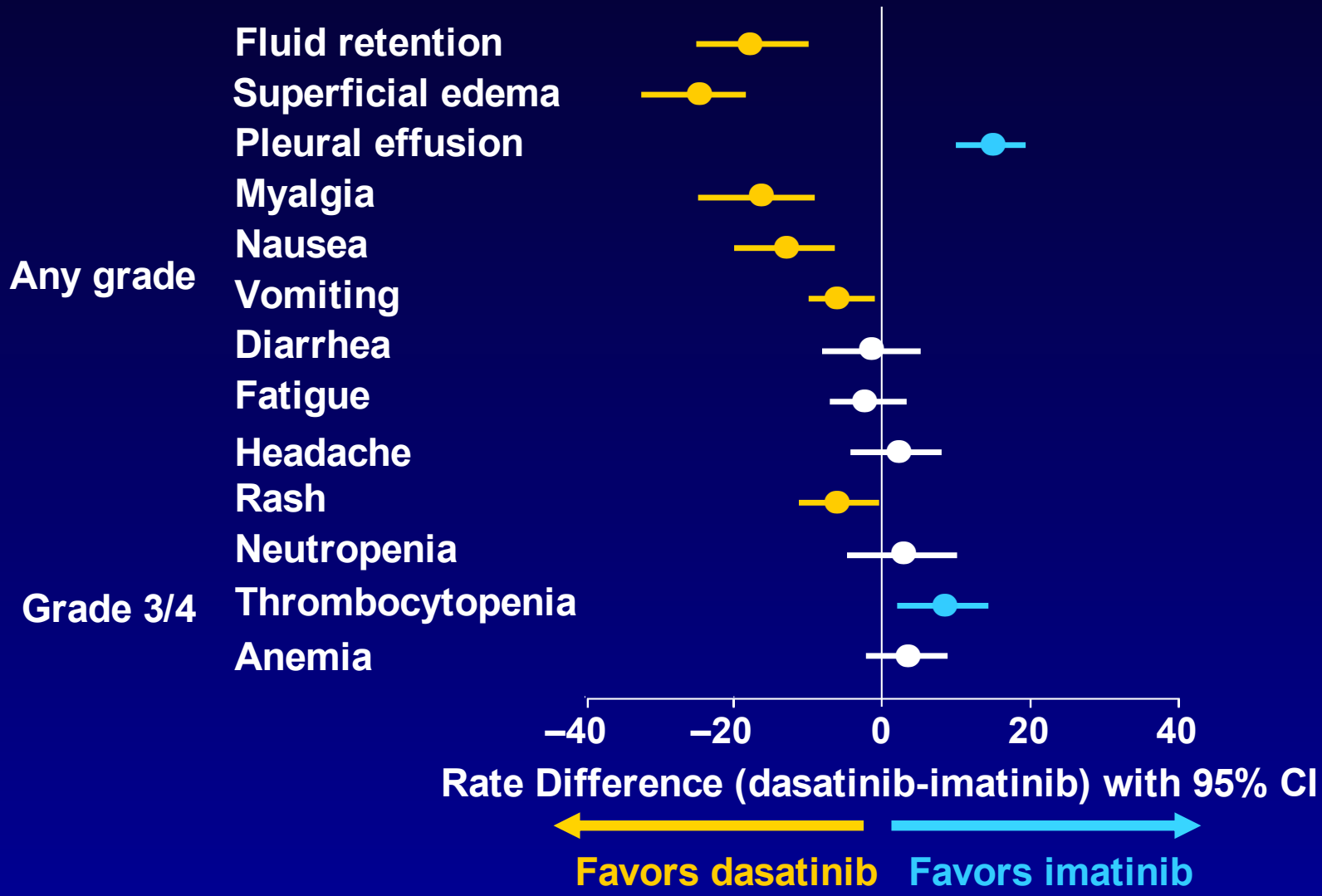
Hochhaus. ASH 2011

DASISION: Transformation To AP/BP CML (ITT)



Kantarjian. JCO. 29:abst 6510; 2011

DASISION. Forest Plot Comparing Differences in AE Rates for Dasatinib and Imatinib



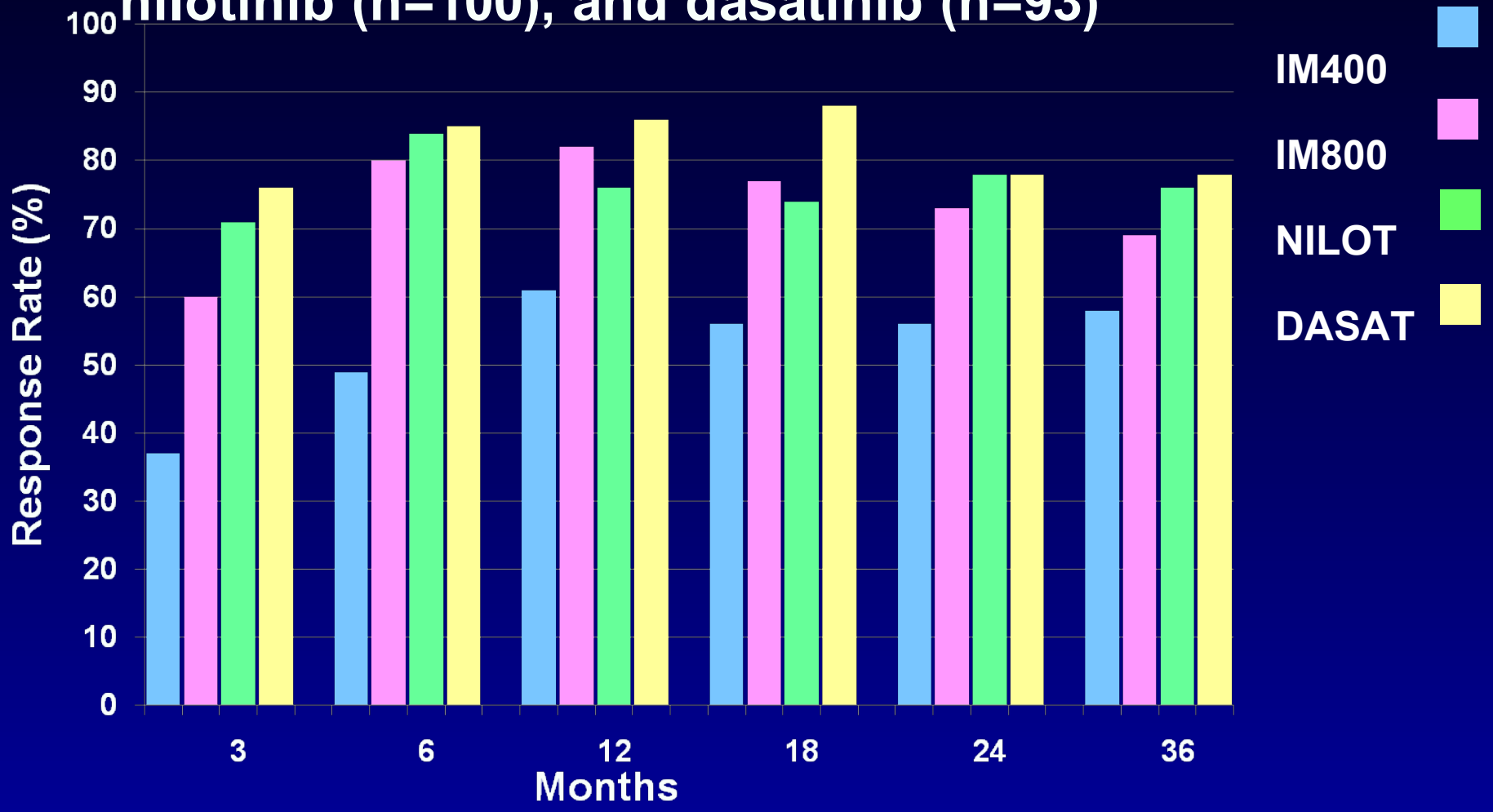
Kantarjian. JCO. 29:abst 6510; 2011

CML Frontline Rx. Toxicities of TKIs

- Bothersome chronic side-effects less frequent with nilotinib than with imatinib: nausea, cramps, aches, weight gain, fluid retention, periorbital edema
- Rashes, headaches more frequent with nilotinib
- Pleural effusions; cytopenias more frequent with dasatinib

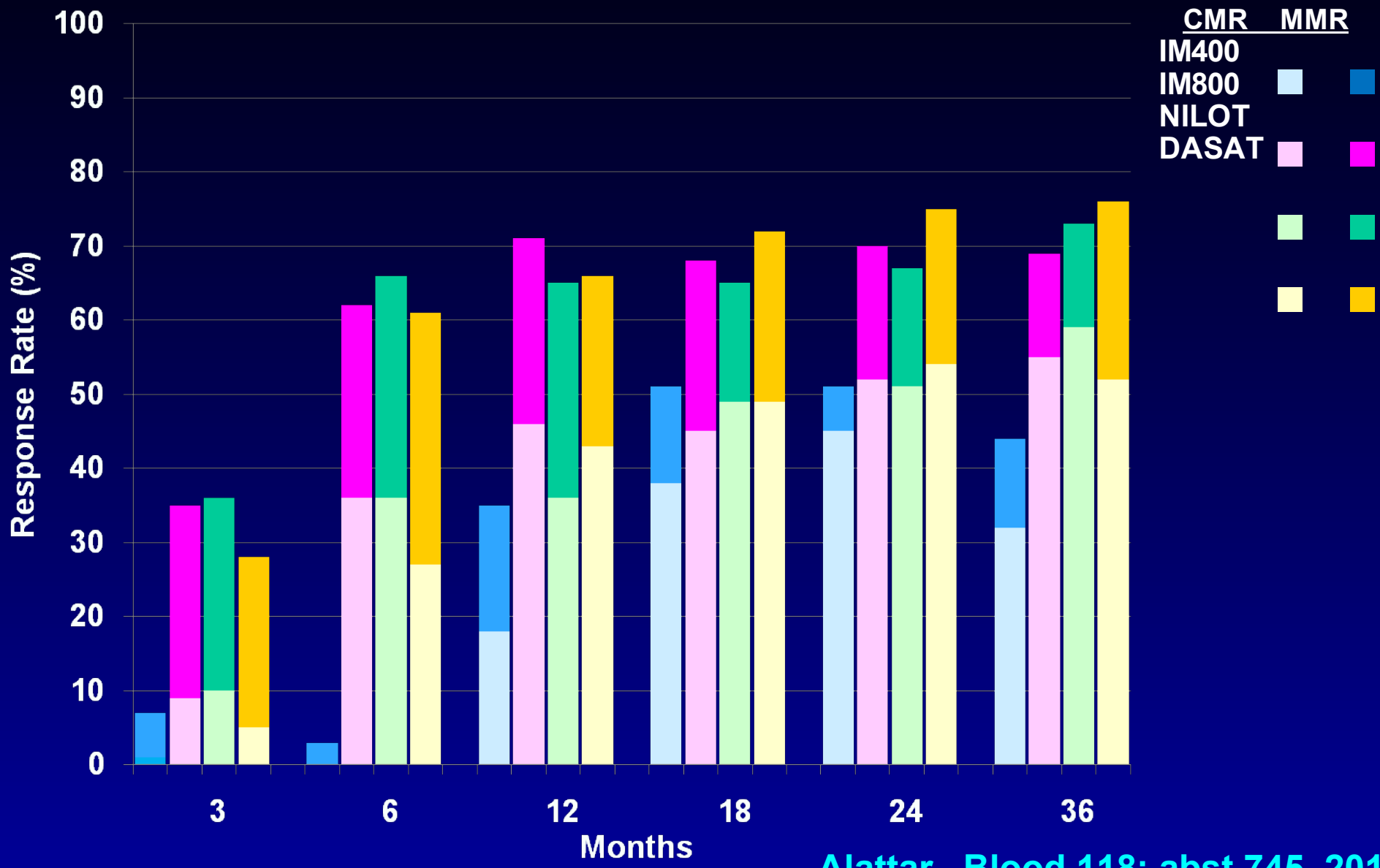
TKI Frontline Therapy in CML
CCyR AT Time Periods (ITT)

- 465 patients with CML frontline therapy
  - Imatinib 400 mg (n=71), imatinib 800 mg (n=201), nilotinib (n=100), and dasatinib (n=93)



Alattar . Blood 118; abst 745, 2011

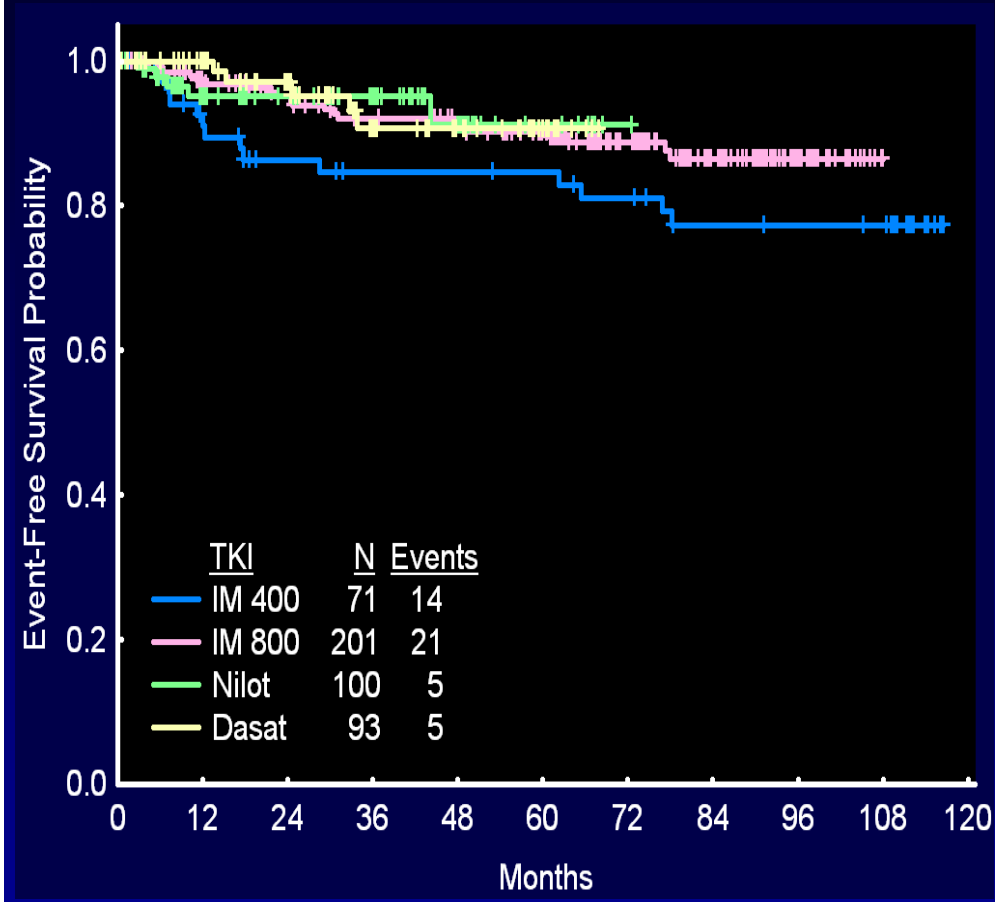
TKI Frontline Therapy in CML
Response AT Time Periods (ITT)



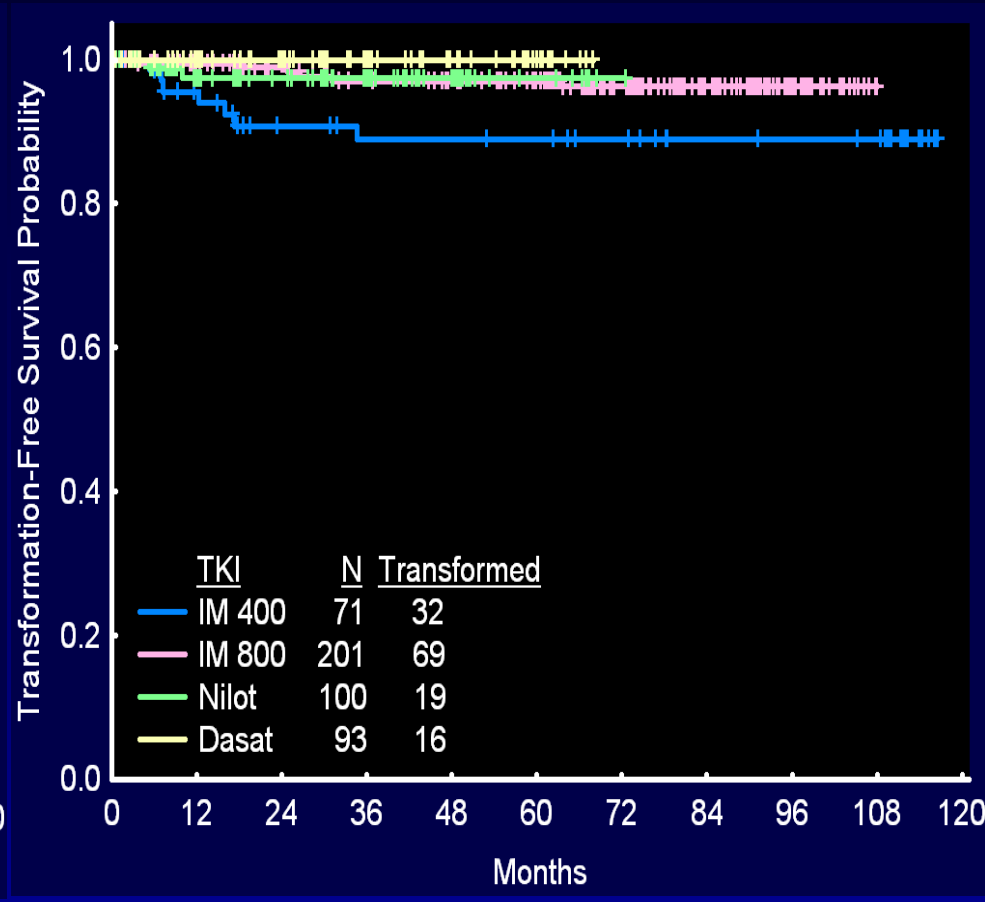
Alattar . Blood 118; abst 745, 2011

TKI Frontline Therapy in CML
Long-Term Outcome By Response Time

Event-Free Survival



Transformation-Free Survival



Alattar . Blood 118; abst 745, 2011

Frontline Rx with Imatinib vs. Second Generation TKIs

Parameter	Imatinib	2nd TKIs
•Efficacy	excellent	even better
• %12-mo CGCR	65-70	80-85
MMR	20-25	40-45
AP- BP	3.5	0.4-2
•Tolerances	excellent	even better
•Follow up (yrs)	10	6-7
•Cost ($/yr)	54,000	90,000 – 96,000

CML. What Happens in 2015?

Parameter	Imatinib	2nd TKIs
•Efficacy	excellent	even better
• Tolerance	excellent	even better
•Cost ($/yr)	2-10,000	90-96,000
•%5 – 10 yr survival		
survival	80 – 90	? > 90
EFS	50-60	???

→ the difference at 5 yrs in EFS and OS determines frontline Rx

CML. Role and Timing of allo SCT

Status	TKIs	Allo SCT
AP-BP	Interim Rx to MRD	ASAP
IM failure in CP, T315I	Ponatinib interim Rx to MRD	ASAP
IM failure in CP – no CE, no mutations, good initial response	Long-term second line TKIs	Third line post second TKI failure
IM failure in CP – CE, bad mutations, no CG response	Interim Rx to MRD	Second line
Older ≥65 – 70 post IM failure	Long-term	May forgo allo SCT for many yrs of QOL

CML Monitoring

- Establish confirmed CGCR in first year (BM at 6-12 mo)
- In CGCR
  - FISH and QPCR every 6 mos
  - If MMR (QPCR < 0.1%), may monitor with QPCR only (watch for false results)
  - If QPCR ↑ by 0.5 – 1 log and/or loss of MMR (PCR> 0.1%) → monitor more frequently
- Mutations studies if resistance / need to change TKIs
- Change TKI only for loss of CGCR, not based on MMR/QPCR

How Do I Use FISH and QPCR Monitoring in CGCR?

FISH	QPCR	Interpretation
Neg	<0.1%	Excellent response; FU 6 mos
Pos	<0.1%	FISH and QPCR false + or false -; FU 3 mos
Neg	>1%	
Neg	0.1-1%	FU 6 mos, FU 3 mos if one log
Pos	>1%	Check marrow + CG; ? relapse

Criteria for Failure and Suboptimal Response to Imatinib

Time (mo)	Response		
	Failure	Suboptimal	Optimal
3	No CHR	No CG Response	< 65% Ph+
6	No CHR >95% Ph+	≥35% Ph+	≤35% Ph+
12	≥35% Ph+	1-35% Ph+	0% Ph+
18	≥5% Ph+	No MMR	MMR
Any	Loss of CHR Loss of CCgR Mutation CE	Loss of MMR Mutation	Stable or improving MMR

Baccarani. JCO 2009; 27: 6041-51

Criteria for Failure and Suboptimal Response to Imatinib

Time (mo)	Response		
	Failure	Suboptimal	Optimal
3	No CHR	No CHR	<65% Ph+
6	No CHR >95% Ph+	>35% Ph+	≤35% Ph+
12	≥35% Ph+	1-35% Ph+	0% Ph+
18	≥5% Ph+	No MMR	MMR
Any	Loss of CHR Loss of CgR Mutation CE	Loss of MMR Mutation	Stable or improving MMR

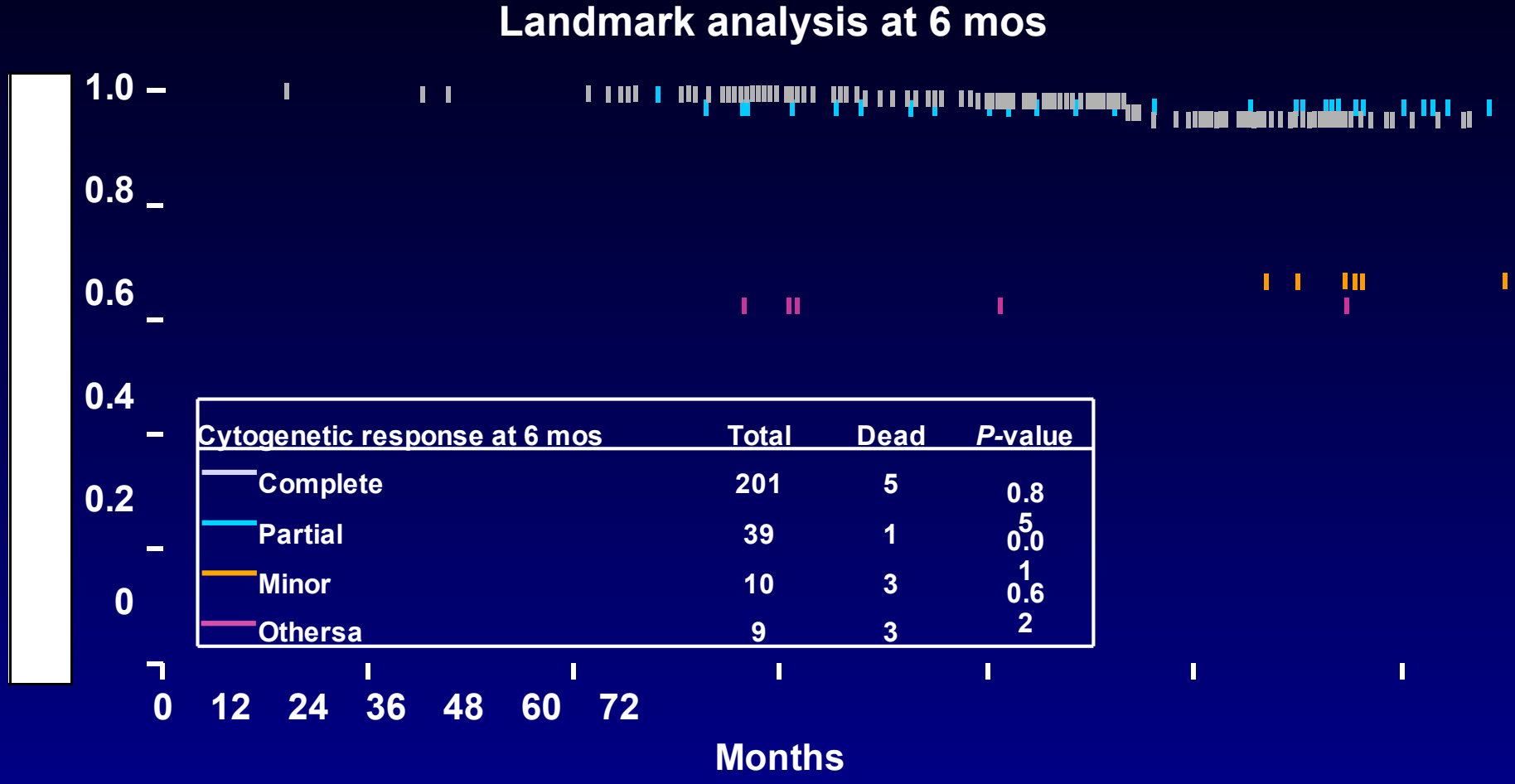
Baccarani. JCO 2009; 27: 6041-51

CML. Criteria For Failure On Imatinib

- No major CG response at 6 mos (Ph 100%) (Ph > 35%)
- No major CG CR at 12 mos
- No CGCR in Year 2+
- CG relapse or hematologic relapse
- Not failure criteria
  - suboptimal CG response
  - QPCR □ in CGCR

Baccarani. Blood 108:1809-20, 2006

MDACC Retrospective Analysis: MCyR at 6 Months Associated With OS



Patients with MCyR have better OS than patients that do not

Kantarjian H. Cancer. 2008;112:837–845.

German Experience. CGCR at 12 Months Associated with PFS and Survival

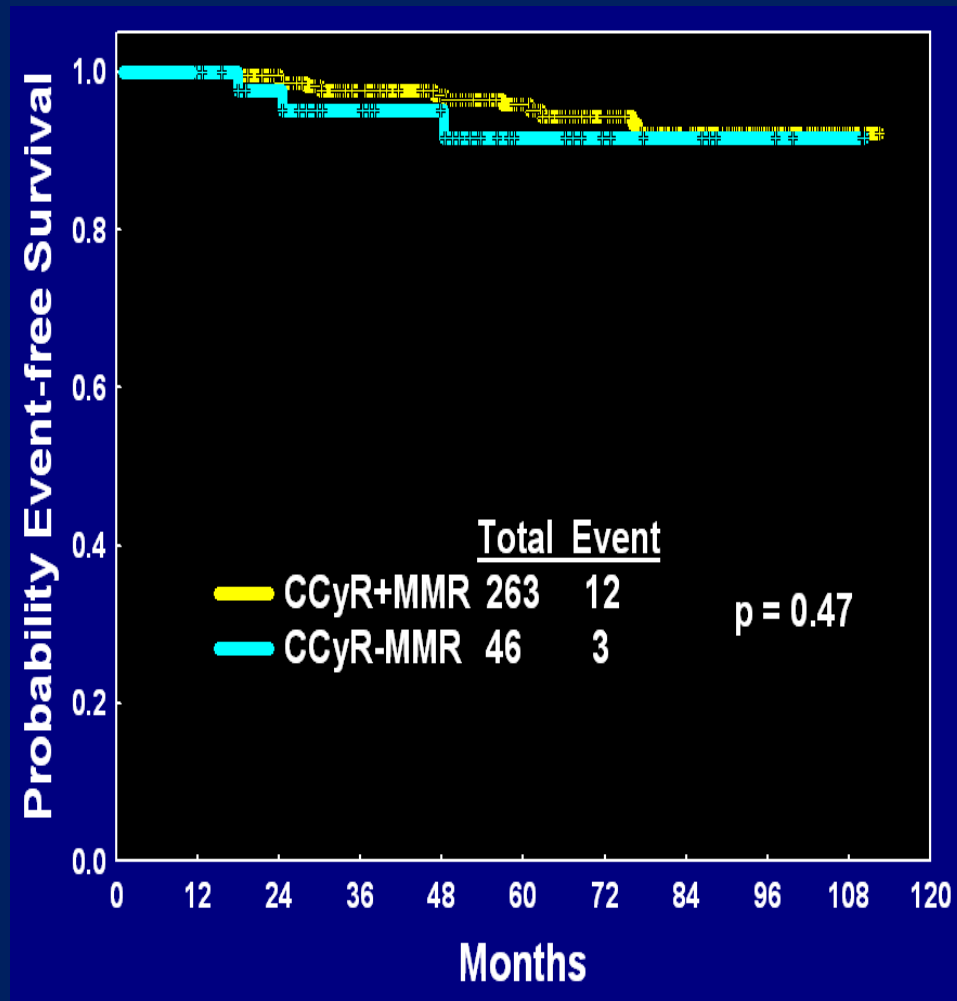
- 848 pts randomized to IM 400mg, IM 800mg, or IM 400 + IFN
- Median F/U: 40 months

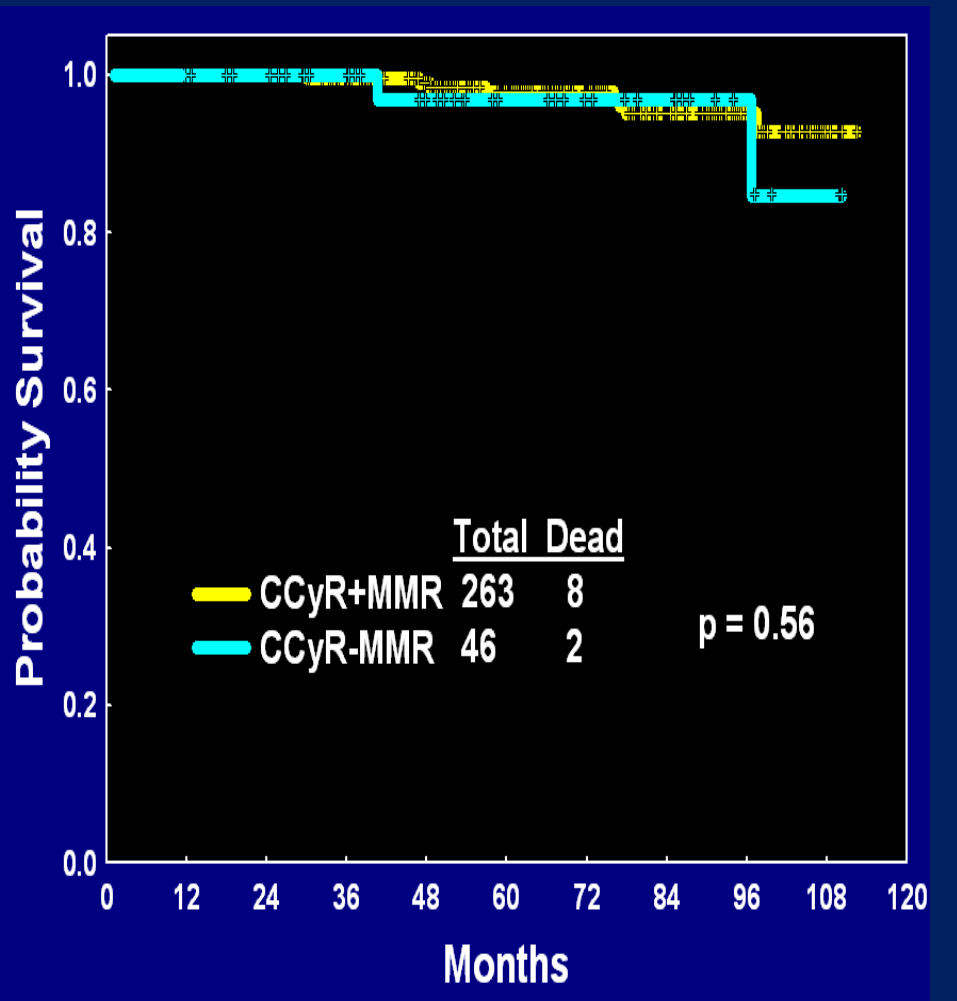
12-month BCR-ABL/ABL (IS)		N	Percentage PFS	Percentage OS
<0.1%	CCyR	341	99	99
0.1-1%		240	97	98
>1%		267	94	93
P value			.0023	.0011

Outcome independent of treatment arm

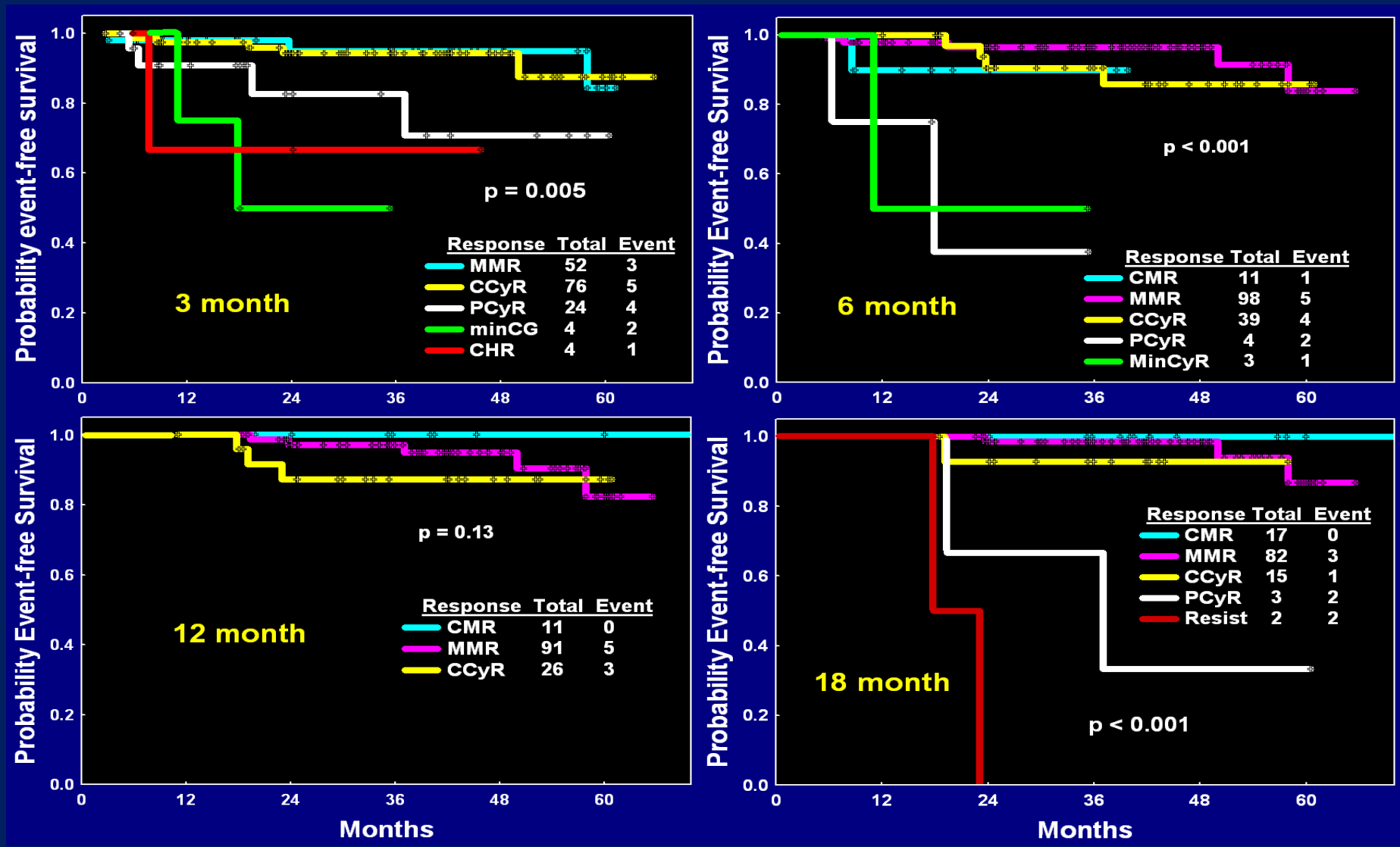
Hehlmann R. J Clin Oncol. 2011;29(12):1634-1642.

EFS and Survival by 12-month Response-CCyR with vs without MMR with TKI Frontline Rx (Landmark)





EFS by Response at 3, 6, 12, 18 Months with 2nd TKI Frontline Rx (Landmark)



Imatinib Discontinuation with Prolonged CMR (STIM Trial)

- 100 pts (49 de novo) in CMR > 2 yrs on imatinib stopped Rx
- 58 mlecular relapses; 48 reinduced into CMR
- 3-yr CMR 39%
- MVA: higher relapse if high Sokal (HR 2.56; p=.008) and short imatinib duration ≤ 60 yrs (HR 0.58; p=.047)

Mahon. Blood 118: abst 603; 2011

Imatinib and Pregnancy

- Rare syndrome of fetal malformations (exomphalos, kidneys, bones) in 3/125
- Stop imatinib if pregnancy
- Female partners of males on TKIs →no problems
- If pregnancy / children highly desired: achieve durable CMR on TKIs then hold TKI and proceed with pregnancy / delivery under closer monitoring (e.g. FISH/QPCR every 2-3 mos)

Inhibition of Bcr-Abl

ATP-binding		T315I-active	Non-kinase Inhibition
Bcr-Abl	Abl & Src		
Imatinib	Dasatinib	Ponatinib	Omacetaxine
Nilotinib	Bosutinib	DCC-2036	Decitabine
	INNO-406	XL228	
	AZD 0530	PHA-739358	
		KW-2449	

PACE Initial Results
Response CP-CML Cohorts

449 pts resistant or intolerant (R/I) to dasatinib or nilotinib OR with T315I mutation after any TKI

Median follow-up 6 months

Response	n Response / N Evaluable (%)		
	Overall	R/I Cohort	T315I Cohort
CHR	248/271 (92)	193/207 (93)	55/64 (86)
MCyR*	116/248 (47)	79/191 (41)	37/57 (65)
CCyR	96/248 (39)	63/191 (33)	33/57 (58)
MMR	51/265 (19)	31/205 (15)	20/60 (33)

*MCyR is the primary endpoint

Cortes. Blood 118: abst 109, 2011

Omacetaxine for CML CP After Failure to ≥2 TKI

- 122 pts with CML CP (n=81) or AP (n=41) with ≥2 prior TKI
- Omacetaxine 1.25 mg/m2 BID x14d, then x7d

Response, %	CP N=81	AP N=41
Primary endpoint	MCyR 20%	MaHR 27%
	CCyR 10%	CHR 24%
Median duration, mo	17.7	9
Median PFS, mo	9.6	4.7
Median OS, mo	33.9	16

Cortes. Blood 118: abst 3761, 2011

CML. Eradication of MRD

- Older agents: pegasys, decitabine, omacetaxine
- Sexy agents: hedgehog inhibitors, JAK2 inhibitors, IL3-DT toxins

CML 2012- Summary

- Frontline Rx: new standard
  - Imatinib
  - 2nd TKIs (dasatinib, nilotinib, bosutinib?) better
  - Sequential therapy?
- Early response matters (3-6 months)
- No need to change if responding to imatinib
- Mutation analysis when clinical failure
- Rx discontinuation: not recommended
- Ponatinib: the new super TKI?

Leukemia Questions?

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