ITK de 2da Generación como Tratamiento de Primera Línea para Pacientes con LMC-FC de Reciente Diagnóstico

JORNADA CHILENA DE HEMATOLOGÍA Y MEDICINA TRANSFUSIONAL

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DE LA PLATA

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Clinical Spotlight In Chronic Myeloid Leukemia

Dasatinib Continues to Show Enhanced Efficacy Compared to Imatinib: 24-Month Update of the DASISION Trial

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Dasatinib or Imatinib in Newly Diagnosed Chronic Myeloid Leukemia In Chronic Phase (CML-CP): Two-Year Follow-Up From DASISION

Kantarjian H, Shah N, Cortes J, Baccarani M, Bradley-Garelik MB, Zhu C, Hochhaus A

Background

- Dasatinib, a BCR-ABL inhibitor 325-fold more potent than imatinib *in vitro*,[1] is an established second-line treatment for patients with CML-CP post imatinib failure[2]
- Dasatinib 100 mg once daily (QD) has been approved as first-line treatment for CML-CP based on the phase III DASISION (Dasatinib versus Imatinib Study In Treatment-Naïve CML) trial[3]
  - DASISION compares dasatinib 100 mg QD with imatinib 400 mg QD as first-line treatment in patients with newly diagnosed CML-CP
- 1-year data from DASISION (presented at ASCO 2010) demonstrated
  - Superior efficacy of dasatinib over imatinib, including a significantly higher rate of complete confirmed cytogenetic response (cCCyR) by 12 months (77% vs 66%, *P* = .007; primary endpoint)
  - An acceptable safety profile of dasatinib[4,5]
- 2-year data are presented here

Median follow-up of 28.1 months (range 0.1–40.1 months)

1. O'Hare T, et al. *Cancer Res.* 2005;65(11):4500-4505. 2. Shah NP, et al. *Haematologica* 2010;95(2):232-240. 3. SPRYCEL® [package insert]. Princeton, New Jersey: Bristol-Myers Squibb. 4. Kantarjian H, et al. *N Engl J Med.* 2010;362(24):2260-2270. 5. Kantarjian H, et al. *J Clin Oncol.* 2010;28(15S): Abstract 6500.

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

DASISION (CA180-056) Study Design

- Treatment-naïve CML-CP patients (N = 519)
- 108 centers
- 26 countries

Randomized*

Dasatinib 100 mg QD (N = 259)

Imatinib 400 mg QD (N = 260)

Follow-up 5 years

*Stratified by Hasford risk score

- **Primary endpoint** — Confirmed CCyR by 12 months
- **Other key endpoints** — Rates of CCyR and MMR, times to CCyR and MMR, time in CCyR (measure of duration), progression-free survival, overall survival

CCyR = complete cytogenetic response; MMR = major molecular response

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Eligibility Criteria

- Philadelphia chromosome–positive (Ph +) CML-CP within 3 months from diagnosis
- No prior therapy for CML excluding hydroxyurea or anagrelide

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Key Endpoint Definitions

- CCyR
  - No Ph+ metaphases by standard bone marrow cytogenetic assessments (FISH not allowed)
- cCCyR
  - No Ph+ metaphases in 2 consecutive bone marrow assessments
  - cCCyR by 12 months was the primary endpoint
- MMR
  - *BCR-ABL* transcript level in peripheral blood ≤0.1% on the International Scale (IS), ie, 3-log lower than standardized baseline
- Complete molecular response ($CMR^{4.5}$)
  - *BCR-ABL* transcript level in peripheral blood ≤0.0032% on the IS, ie, 4.5-log lower than standardized baseline
- Missing samples were counted as nonresponders
  - For MMR/CMR, atypical transcripts were also counted as nonresponders

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Statistical Considerations

- Cumulative response rates by various time points were based on intention-to-treat (ITT) population (all randomized patients)
- Safety was analyzed in all patients who received at least 1 dose of the study drug
- Times to CCyR and MMR were calculated using the Kaplan-Meier product-limit method
- *P*-values provided are descriptive and were not adjusted for multiple comparisons

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Results
Patient Disposition And Discontinuations

	Treated Patients, n (%)	
	Dasatinib 100 mg QD N = 258	Imatinib 400 mg QD N = 258
Still on treatment	199 (77)	194 (75)
Discontinued	59 (23)	64 (25)
Progression*	14 (5)	17 (7)
Treatment failure	8 (3)	11 (4)
Adverse event (AE)	18 (7)	12 (5)
Nonhematologic	12 (5)	8 (3)
Hematologic	6 (2)	4 (1)
Unrelated AE	5 (2)	1 (<1)
Death†	4 (2)	1 (<1)
Other‡	10 (4)	22 (8)

*Increasing WBC count; loss of CHR; loss of major cytogenetic response (MCyR) including 30% rise in Ph+ metaphases and additional chromosomal abnormalities; or progression to AP/BP; represents a subset of total progression

†Discontinuation due to death, which represents a subset of total deaths; overall there have been 16 deaths in the dasatinib arm and 14 deaths in the imatinib arm

‡Includes consent withdrawal, loss to follow-up, pregnancy, patient request, and poor/non compliance

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Dose Interruption, Reduction, Escalation, and Intensity

	Dasatinib 100 mg QD N = 258	Imatinib 400 mg QD N = 258
Median treatment duration, months (range)	24.9 (0.03–36.96)	24.9 (0.26–44.09)
Duration >12 months	87%	88%
Duration >24 months	62%	60%
Dose interruption, n (%)	152 (59)	111 (43)
Dose reduction, n (%)	71 (28)	39 (15)
Dose escalation, n (%)*	19 (7)	52 (20)
Median dose intensity, mg/day	99.5	400.0

*Dose escalation to dasatinib 140 mg QD and to imatinib 600–800 mg QD was permitted for a suboptimal response (no complete hematologic response [CHR] by 3 months, no partial CyR by 6 months, no CCyR by 12 months, or no MMR by 18 months)

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Efficacy—CCyR

- 24-month response rates for dasatinib vs imatinib were
  - cCCyR: 80% vs 74%
  - CCyR: 86% vs 82% (Figure 2)

- Based on analysis of time to CCyR, the likelihood of achieving a CCyR at any time was 1.5-fold higher with dasatinib than with imatinib (stratified log-rank *P*<.0001; Hazard Ratio [HR] = 1.5)

- Median time to CCyR in all patients calculated by competing risks analysis was 3.2 months for dasatinib and 6.0 months for imatinib

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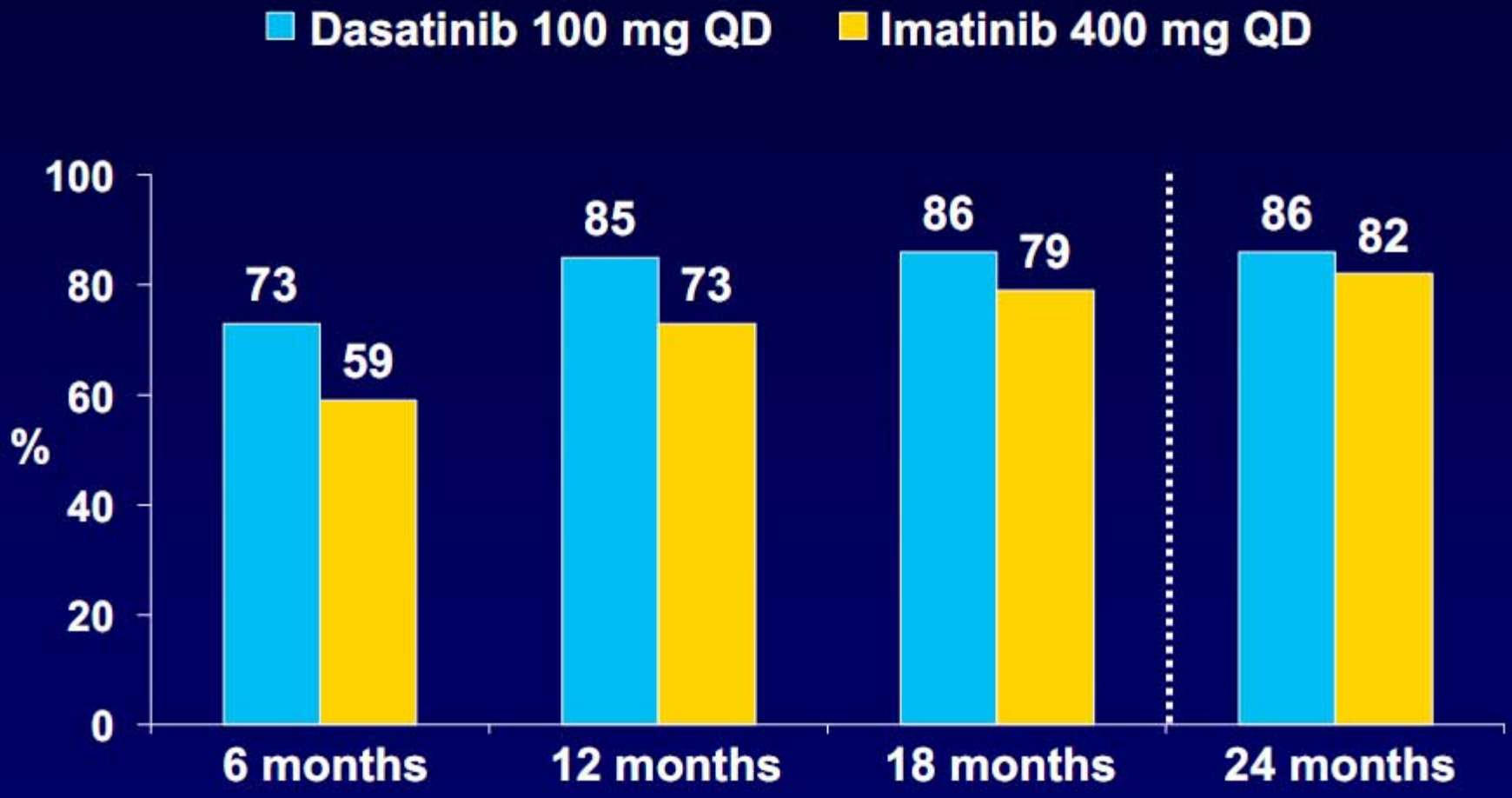
Cumulative CCyR Rates (ITT) By Month Of Treatment



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Efficacy—MMR

- MMR rate by 24 months was higher for dasatinib compared with imatinib (64% vs 46%; *P*<.0001)
- Based on analysis of time to MMR, likelihood of achieving a MMR was 1.7-fold higher with dasatinib vs imatinib (stratified log-rank *P*<.0001; HR = 1.69)
- Median time to MMR in all patients calculated by competing risks analysis was 15 months for dasatinib and 36 months for imatinib
- In all Hasford risk groups, rates of MMR at any time were higher among dasatinib-treated patients

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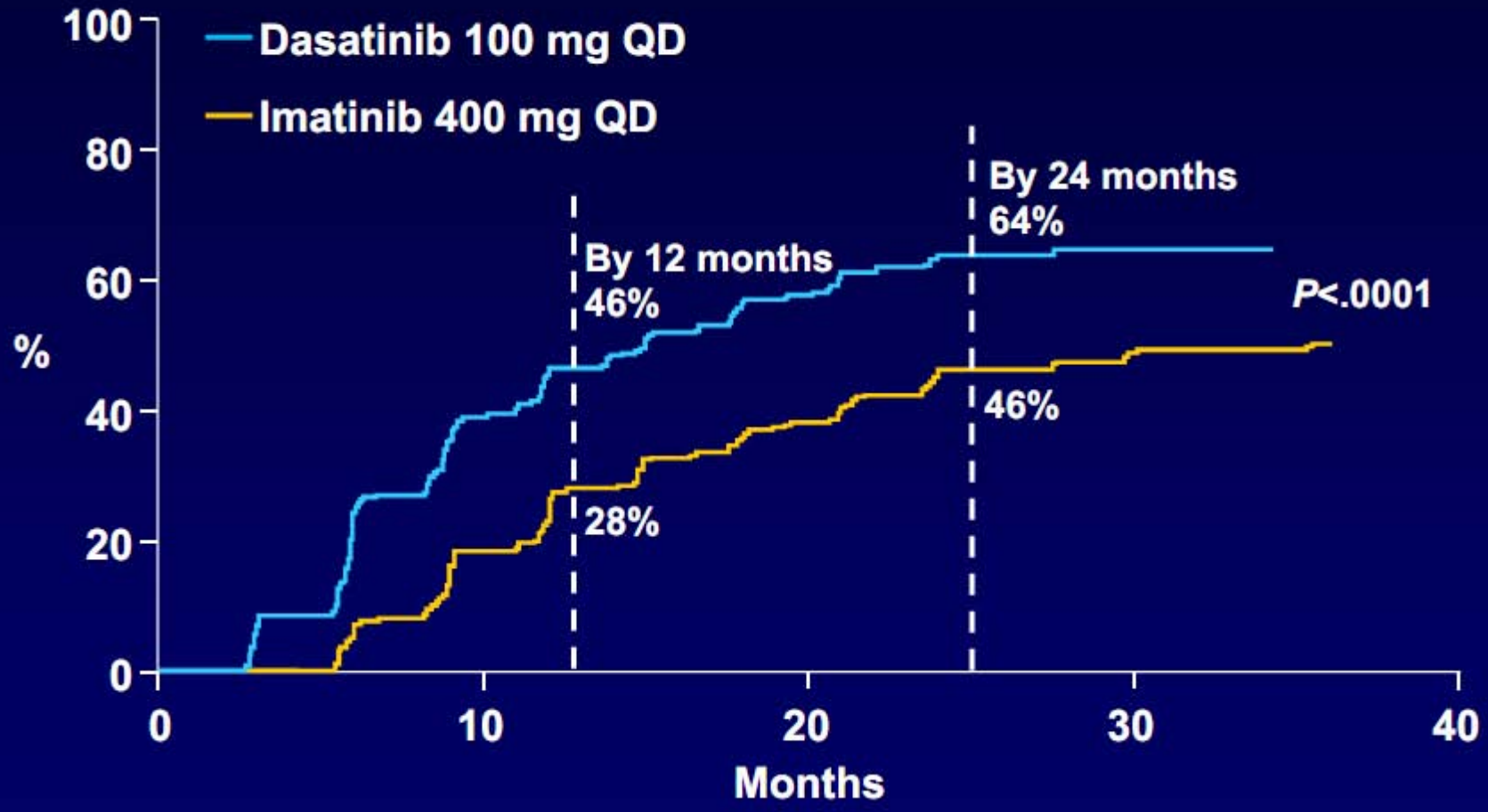
Cumulative Incidence Of MMR



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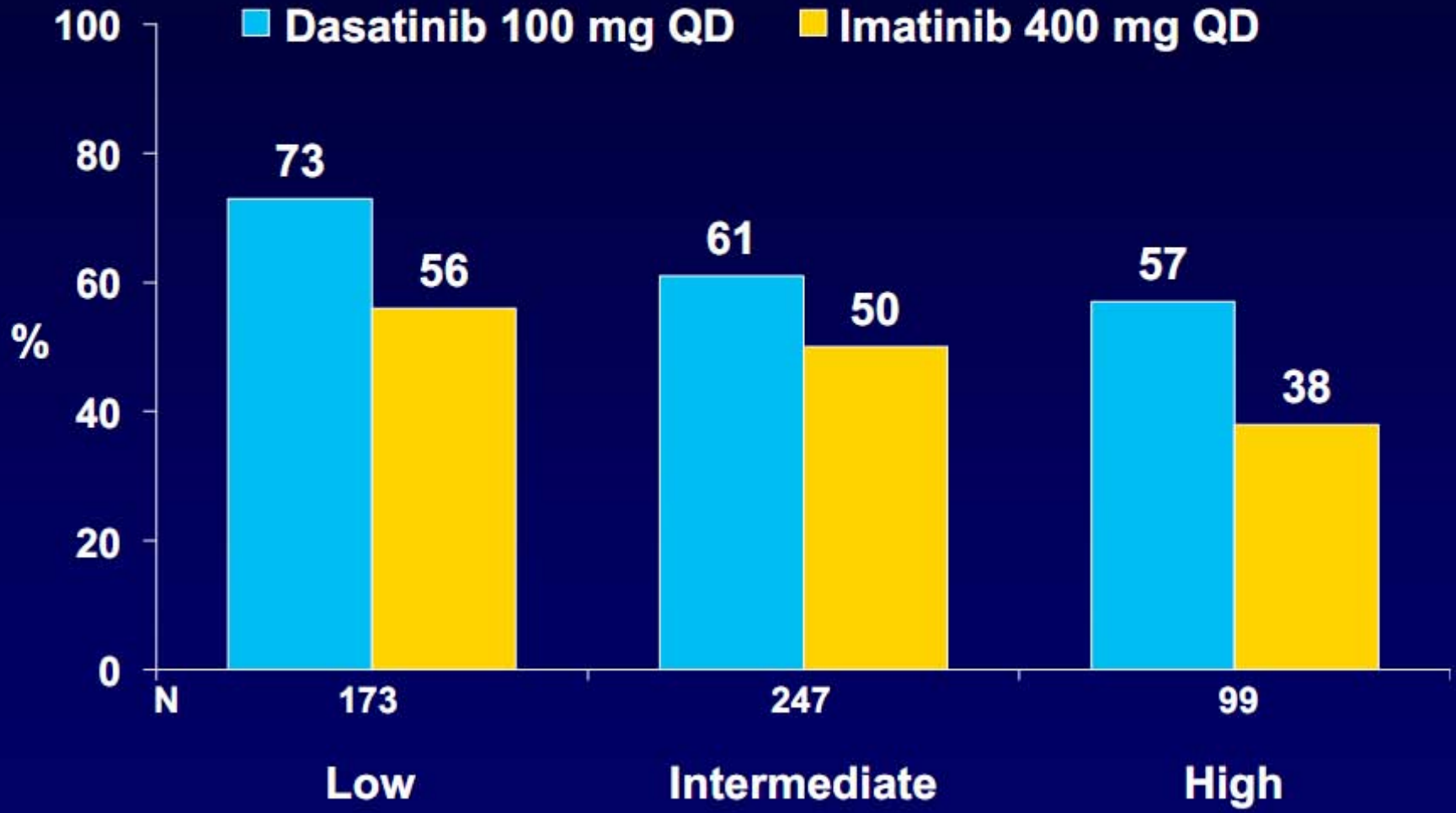
Cumulative MMR Rates at Any Time by Euro/Hasford Risk Group



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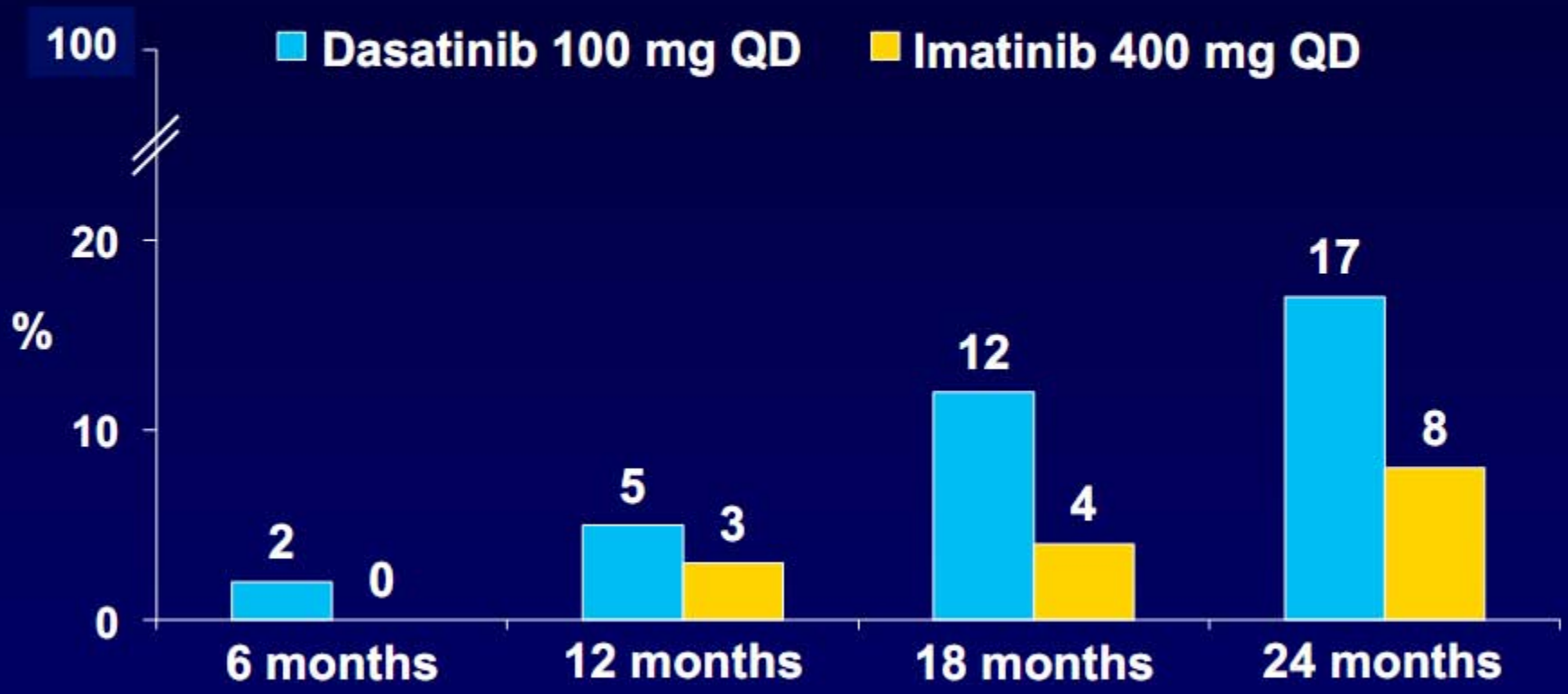
Cumulative CMR[4.5] Rates (ITT) by Month of Treatment



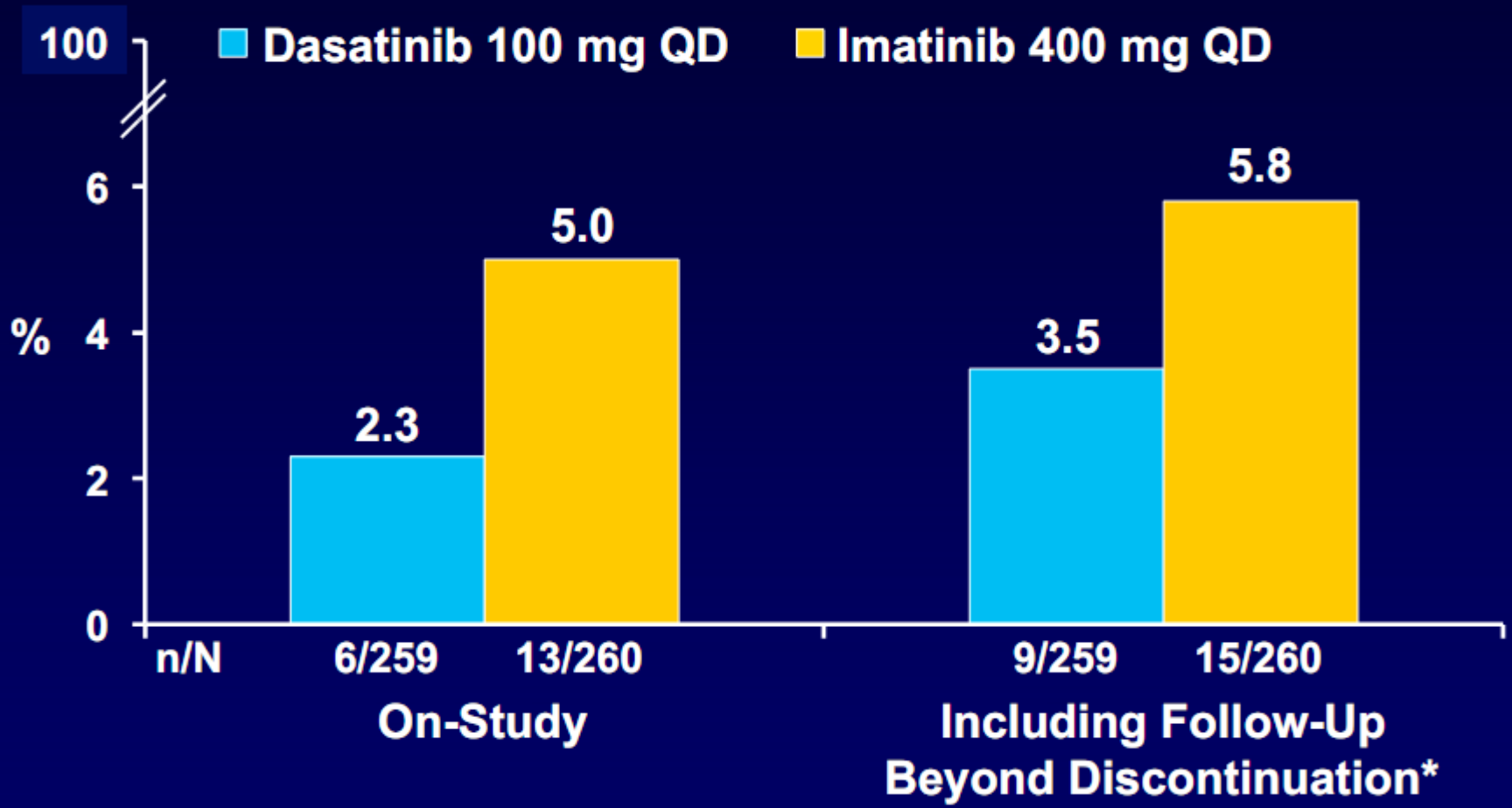
Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Efficacy—Transformation

- Transformation to accelerated/blast phase (AP/BP) with dasatinib vs imatinib occurred in
  - 6 (2.3%) vs 13 (5.0%) patients on study
  - 9 (3.5%) vs 15 (5.8%) patients including follow-up beyond discontinuation of initial treatment (Figure 6)
  - Clonal evolution was not counted as transformation
- 9 patients who achieved a CCyR transformed to AP/BP CML on study (3 with dasatinib, 6 with imatinib)
- No patient who achieved a MMR or CMR transformed to AP/BP CML by data cut-off

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Transformation To AP/BP CML (ITT)



*Yearly evaluations after discontinuation are currently stipulated by the protocol; additional information on patient status may be provided by investigators at other times

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Efficacy—Survival

- At 24 months for dasatinib vs imatinib based on Kaplan-Meier analysis
  - Progression-free survival rates (no transformation to AP/BP or loss of response) were 93.7% vs 92.1%
  - Failure-free survival rates (ELN 2006 criteria) were 91.2% vs 87.8%
  - Event-free survival rates (no progression, failure, or intolerance) were 84.8% vs 83.8%
  - Patients who discontinued for reasons other than the outcome measure were censored at last hematologic or cytogenetic evaluation
- 24-month overall survival rates for dasatinib vs imatinib were 95.3% vs 95.2%
  - Surviving patients were followed after discontinuation of therapy and were censored on the last date the patient was known to be alive
  - Survival data remain immature; all patients, including those who discontinue, will be followed for 5 years

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Deaths on Treatment or After Discontinuation

	Treated Patients, n (%)	
	Dasatinib 100 mg QD N = 258	Imatinib 400 mg QD N = 258
Total deaths	16 (6)	14 (5)
CML progression	8 (3)	10 (4)
Cardiovascular disease	2 (1)	1 (<1)
Infection*	5 (2)	1 (<1)
Bleeding	0	1 (<1)
Other neoplasm	1 (<1)	0
Clinical deterioration	0	1 (<1)
Death on treatment†	7 (3)	4 (2)
Death after discontinuation‡	9 (3)	10 (3)

*Deaths due to infection in the dasatinib arm were sepsis/infection (no organisms identified; n = 3), meningoencephalitis (klebsiella; n = 1), and pneumonia (n = 1); 2 patients died of infection more than 30 days after discontinuation from the trial

†Within 30 days of last dose

‡Yearly evaluations after discontinuation are currently stipulated by the protocol; additional information on patient status may be provided by investigators at other times

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

BCR-ABL Mutations Detected in Patients Who Discontinued Study Treatment

	Dasatinib 100 mg QD N = 259	Imatinib 400 mg QD N = 260
Discontinued, n (%)	59 (23)	64 (25)
Mutation assay performed, n	44	49
Mutation detected	10	10
No mutations*	28	38
No amplification†	6	1

Mutations were detected by direct sequencing
*Includes patients with polymorphisms only (T240T, K247R, F311V, and E499E)
†Insufficient BCR-ABL amplified for mutational assessment

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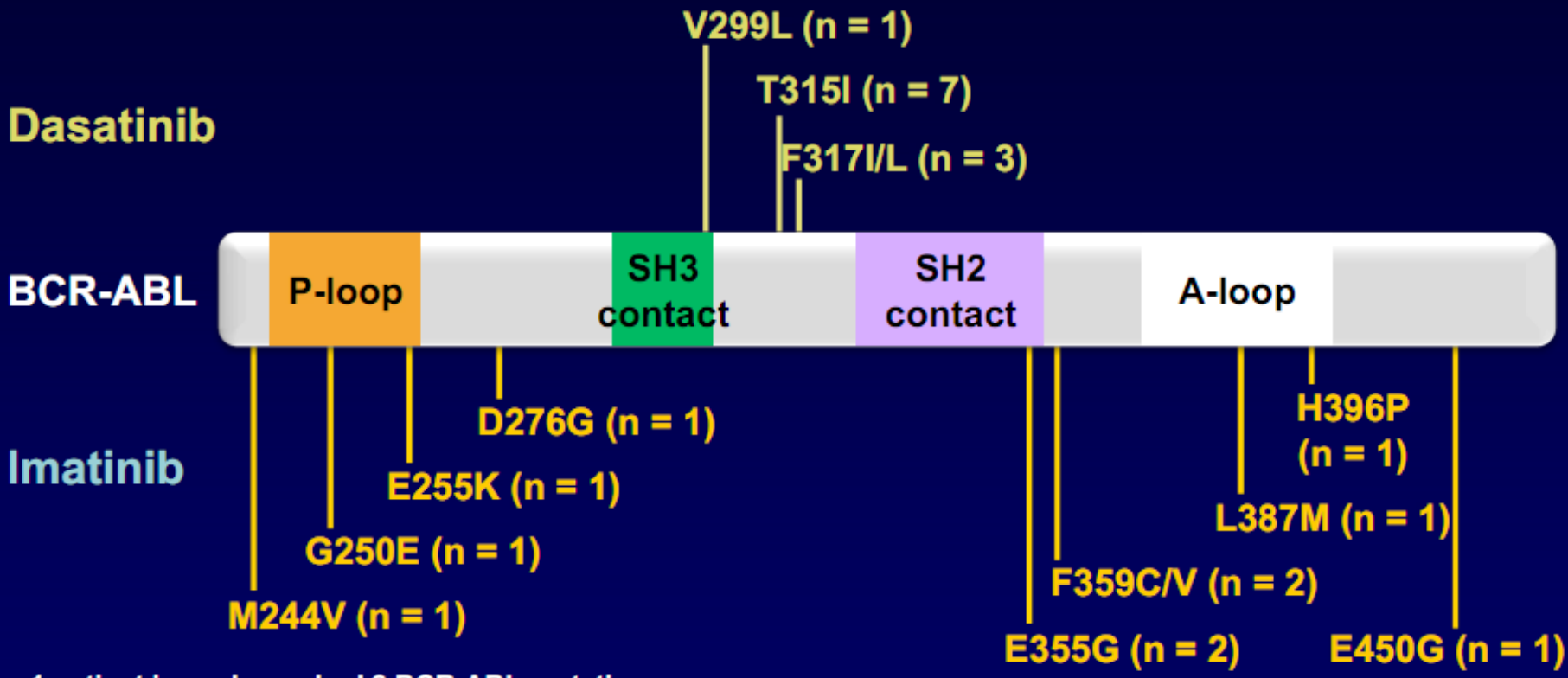
Map of BCR-ABL Mutations Detected After Discontinuation



1 patient in each arm had 2 BCR-ABL mutations.
3 and 9 different amino acid changes were detected in dasatinib-treated and imatinib-treated patients, respectively.
Of 10 patients in the dasatinib arm who had a mutation detected, reasons for discontinuation were protocol-defined disease progression in 8 patients (3 subsequently died), treatment failure in 1 patient, and loss of CCyR in 1 patient; of 10 patients in the imatinib arm who had a mutation detected, reasons for discontinuation were protocol-defined disease progression in 7 patients (3 subsequently died) and treatment failure in 3 patients.
Of patients with a mutation, 6/10 dasatinib-treated patients and 3/10 imatinib-treated patients were of Asian origin.

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Safety

- Rates of drug-related nonhematologic and hematologic AEs after 12 and 24 months of minimum follow-up were comparable (Figures 8 and 9)
- By 24 month follow-up, pleural effusion* occurred in 37 (14.3%) dasatinib patients: grade 1/2 in 35 (13.6%) and grade 3 in 2 (0.8%) patients
  - Pleural effusion was managed by dose interruption (n = 30), dose reduction (n = 19), diuretics (n = 17), corticosteroids (n = 15), and therapeutic thoracentesis (n = 4)
- For all types of nonhematologic AE, rates of grade 3/4 AEs were 0%-1% in both arms
- Grade 3/4 bleeding occurred in 1% of dasatinib-treated patients and 1% of imatinib-treated patients
- Discontinuations due to AEs occurred in 7% with dasatinib and 5% with imatinib

*A detailed analysis of patients who developed a pleural effusion is was presented by Laneuville et al at the 2011 Oncology Annual Meeting [Laneuville P,et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6605.]

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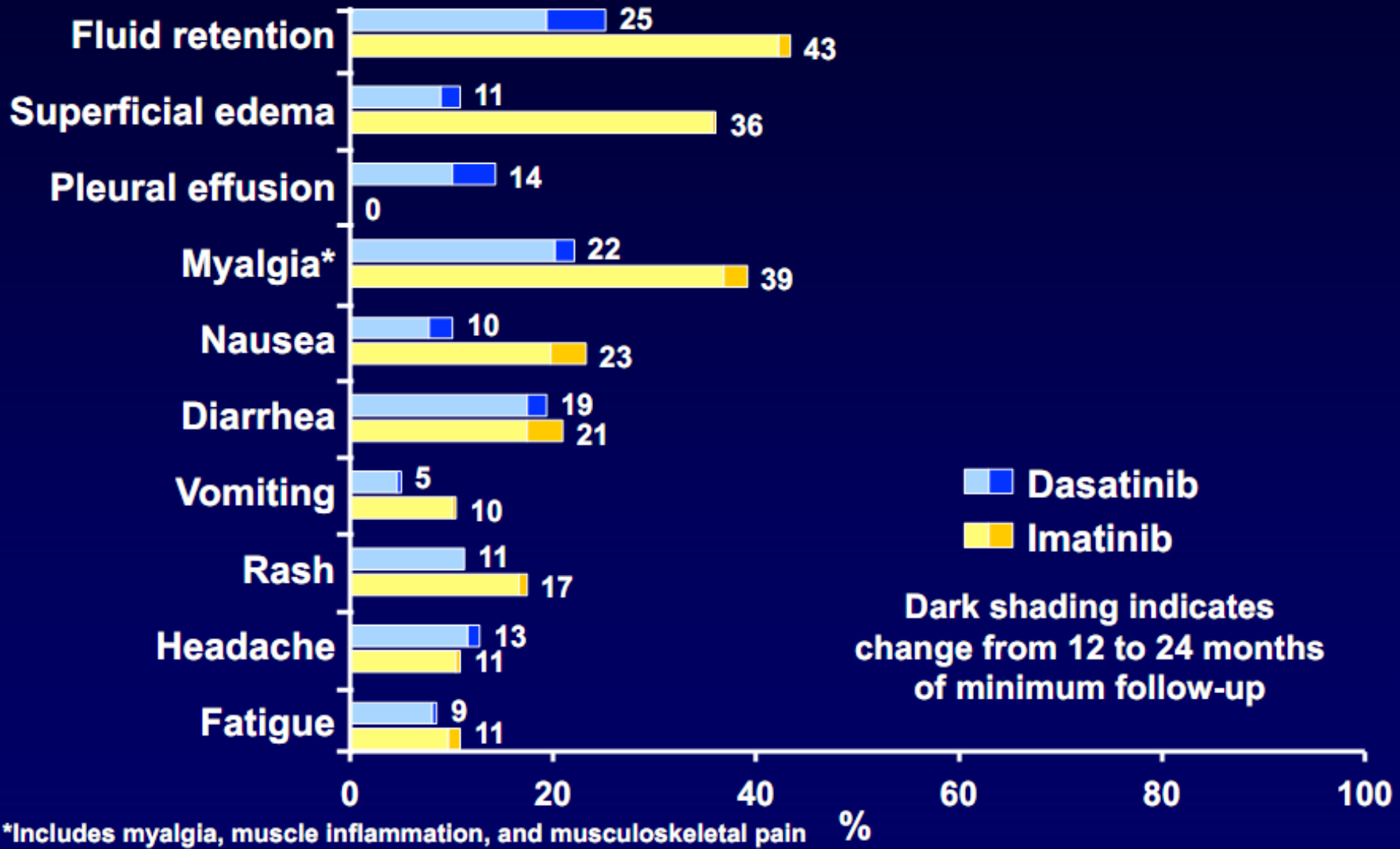
Rates of Nonhematologic Drug-Related AEs of Any Grade (≥10%)



*Includes myalgia, muscle inflammation, and musculoskeletal pain

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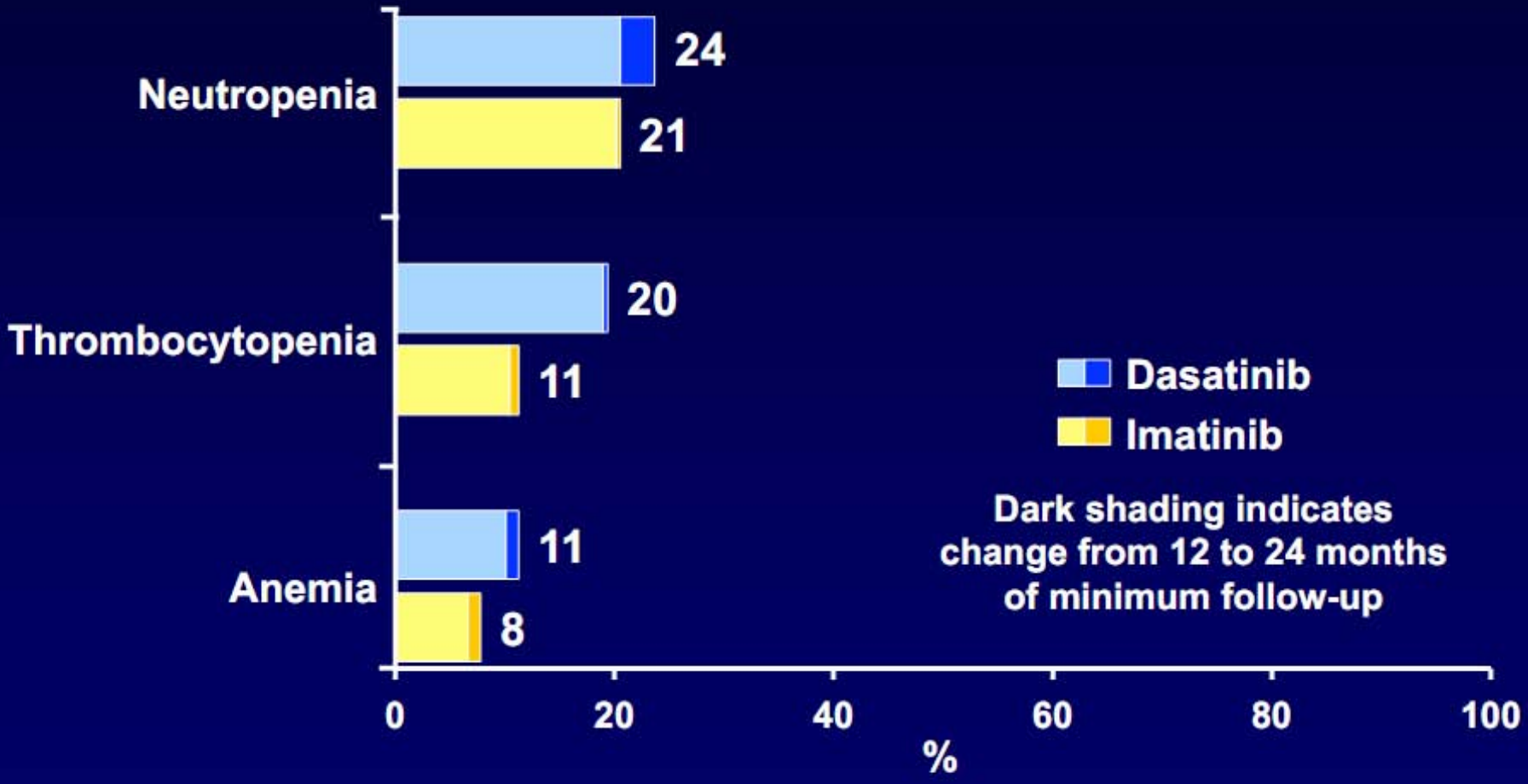
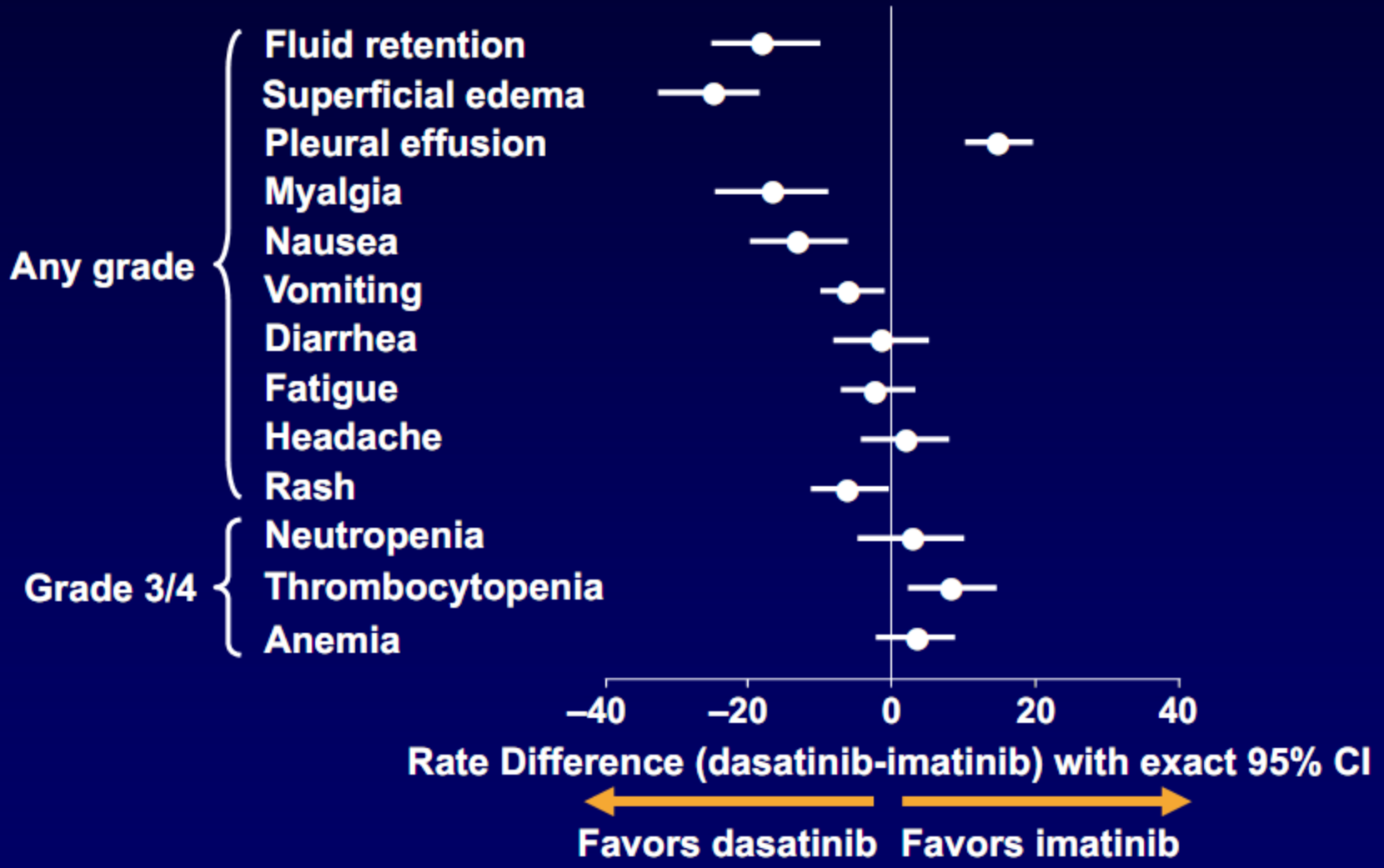
Rates of Grade 3/4 Cytopenias



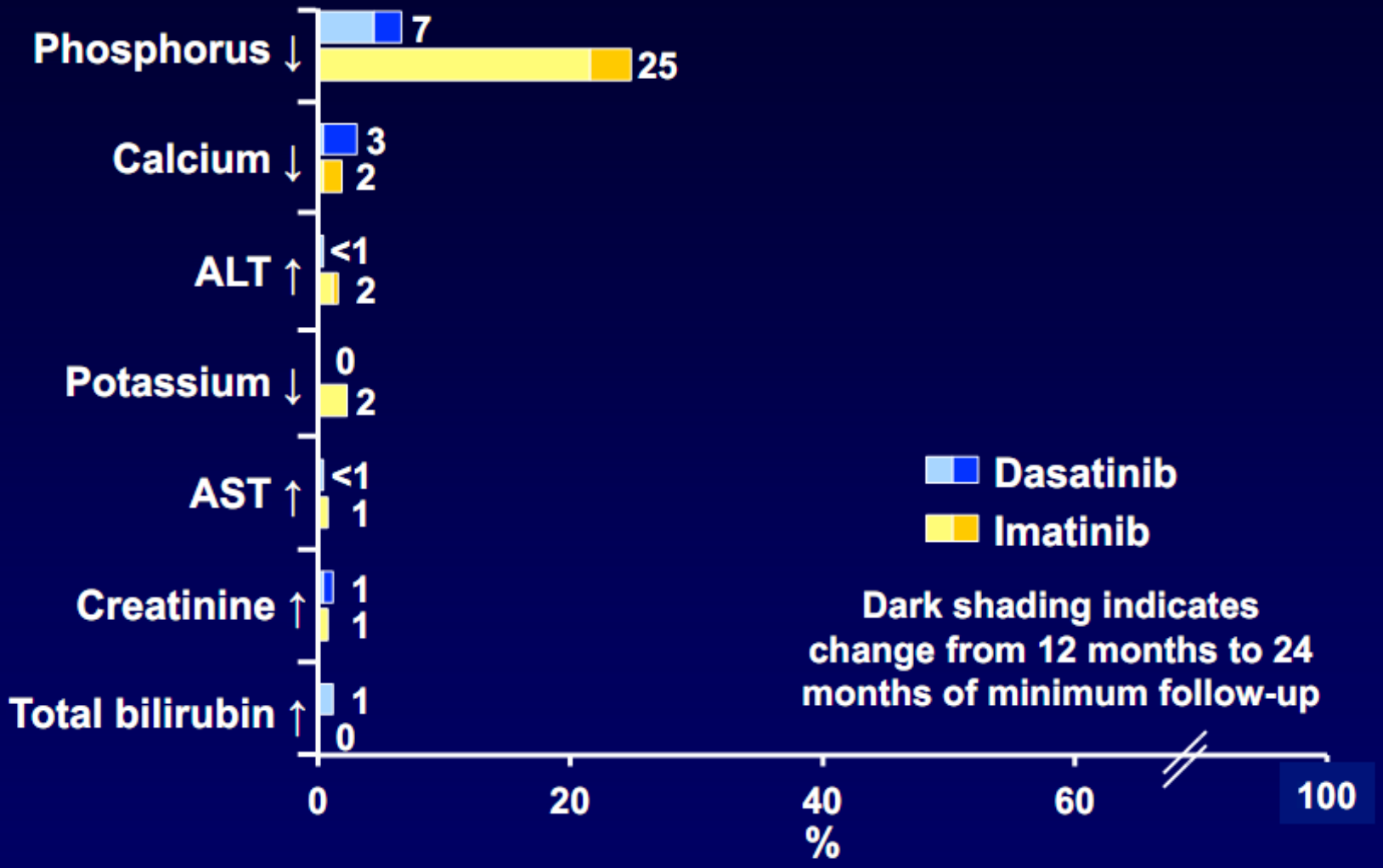
Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Forest Plot Comparing Differences in AE Rates for Dasatinib and Imatinib



Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

Rates of Grade 3/4 Lab Abnormalities



No patient in either arm had a grade 3/4 elevation in serum lipase, amylase, or glucose
5 patients discontinued treatment due to lab abnormalities (1 with dasatinib, 4 with imatinib)
ALT = alanine transaminase; AST = aspartate aminotransferase

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

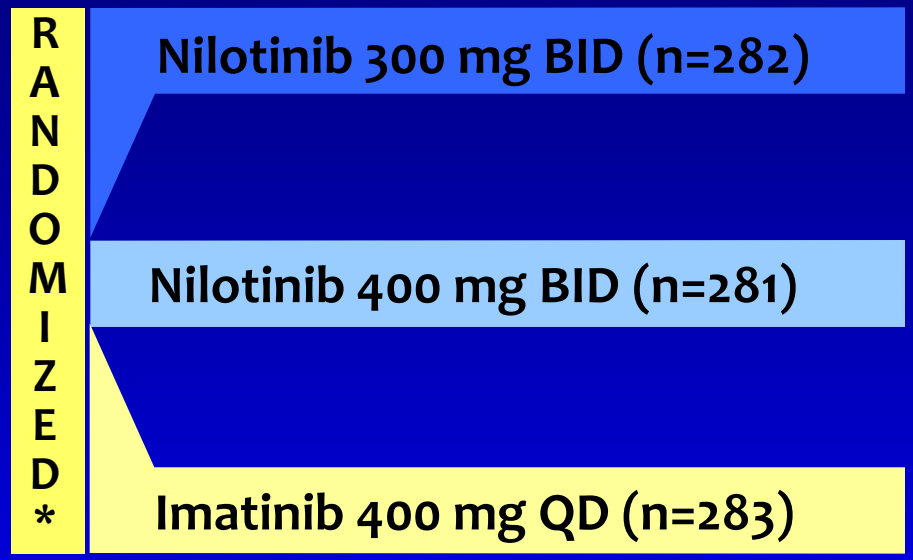
Conclusions

- 24-month follow-up of patients with newly diagnosed CML-CP in the DASISION trial continues to demonstrate:
  - High rate of CCyR with dasatinib
  - Higher and faster rate of MMR with dasatinib over imatinib
- Few patients transformed to AP/BP CML
  - 6 on dasatinib, 13 on imatinib
- Dasatinib treatment was associated with few discontinuations due to toxicity
  - Frequency of many of the most common nonhematologic AEs was comparable to or lower than imatinib
  - Most cytopenias occurred within the first year
- Longer follow-up continues to support the use of dasatinib 100 mg once daily as first-line treatment for newly diagnosed CML-CP

Kantarjian H, et al. *J Clin Oncol.* 2011;29(suppl): Abstract 6510.

ENESTnd: Diseño del estudio

* N = 846
* 217 centros
* 35 países



- **Objetivo Primario:** RMolM a 12 meses
- **Objetivo Secundario:** RCyC en 12 meses
- **Otros objetivos:** tiempo a y duración de RMolM y RCyC, SLE, SLP, tiempo a FA/CB, SG

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Datos demográficos, tratamiento previo y exposición a Nilotinib.

	Nilotinib 300 mg BID N = 282	Nilotinib 400 mg BID N = 281	Imatinib 400 mg QD N = 283
Edad, mediana (rango)	47 (18–85)	47 (18–81)	46 (18–80)
Tiempo desde Dx, mediana (días)	31	31	28
Sokal risk, % - Bajo - Intermedio - Alto	 37 36 28	 37 36 28	 37 36 28
Tratamiento previo, % - Hydroxyurea - Anagrelide - Imatinib (≤ 2 semanas)	 77 2 13	 75 0 9	 71 1 11
Duración del tratamiento, mediana (meses)	13.8	13.8	13.8
Intensidad de dosis – mediana (mg/d)	592	779	400

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Nilotinib en LMC-FC de reciente Diagnóstico (ENESTnd)

Distribución de los pacientes

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Todavia en tratamiento (%)	80	81	75
Discontinuaron (%)	20	19	25
Progresaron *	< 1	< 1	4
Subop/fallo al trat*,#	6	2	8
Eventos adversos	5	10	8
Lab anormales	2	2	1
muertes	1	0	0
violación Protocolo	2	2	1
Otras razones	4	3	3

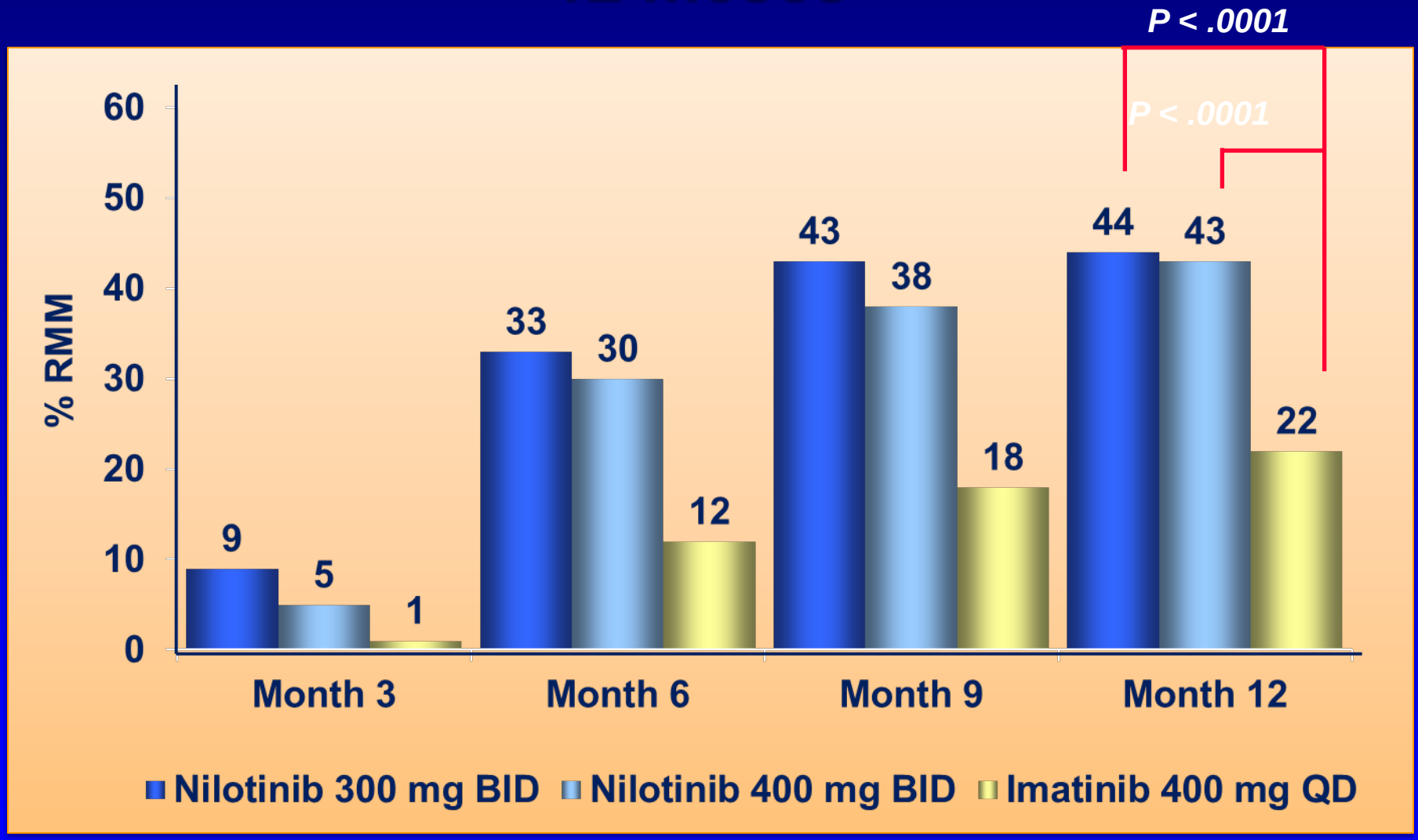
*Investigator assessment of criteria

#Patients were required to discontinue nilotinib 300 mg BID for suboptimal response but could remain on nilotinib 400 mg BID

Larson RA, et al. *J Clin Oncol*. 2010;28(7s): Abstract 6501.

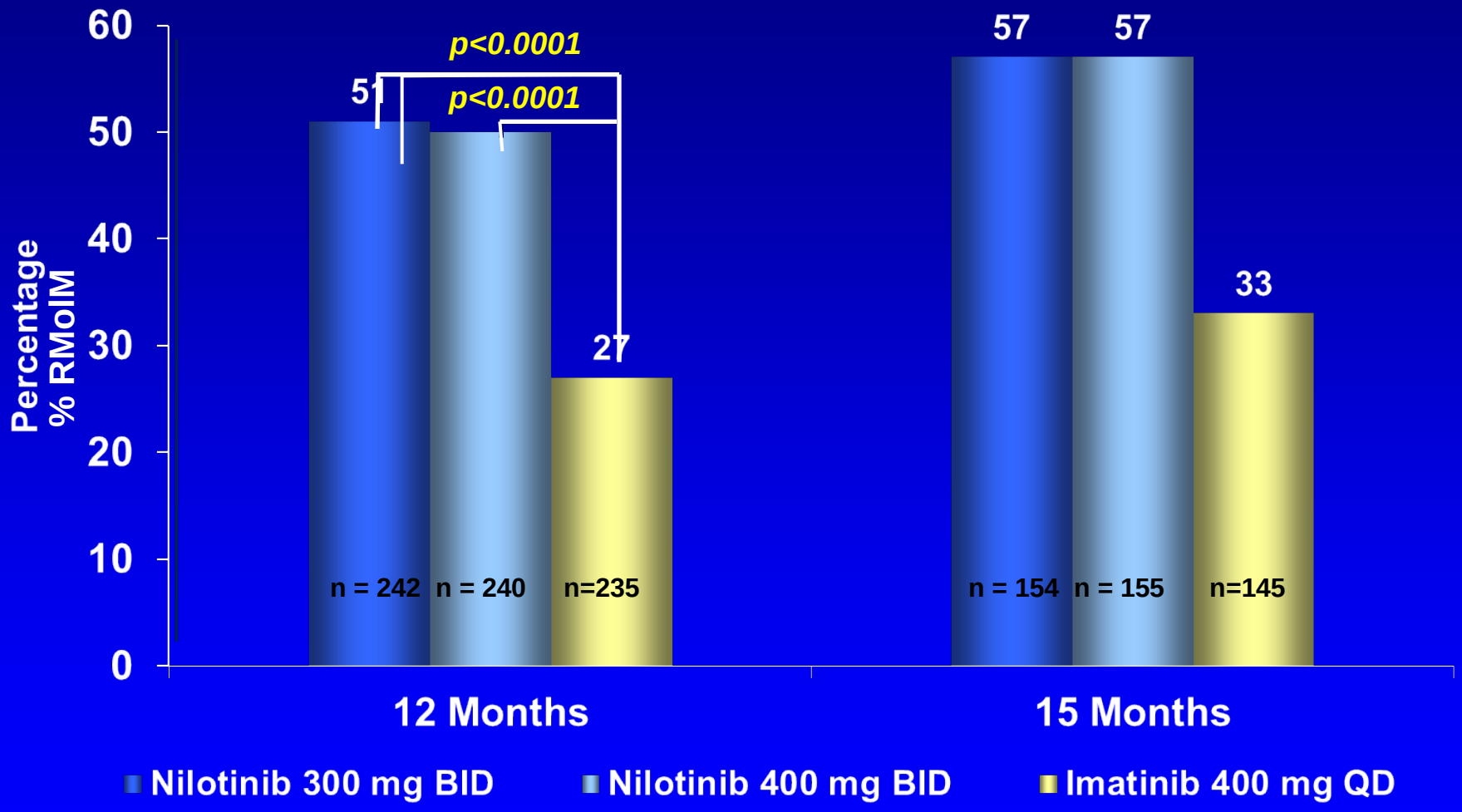
Data cut-off: 2Jan2010

Tasas de RMolM en el tiempo (ITT)
12 meses

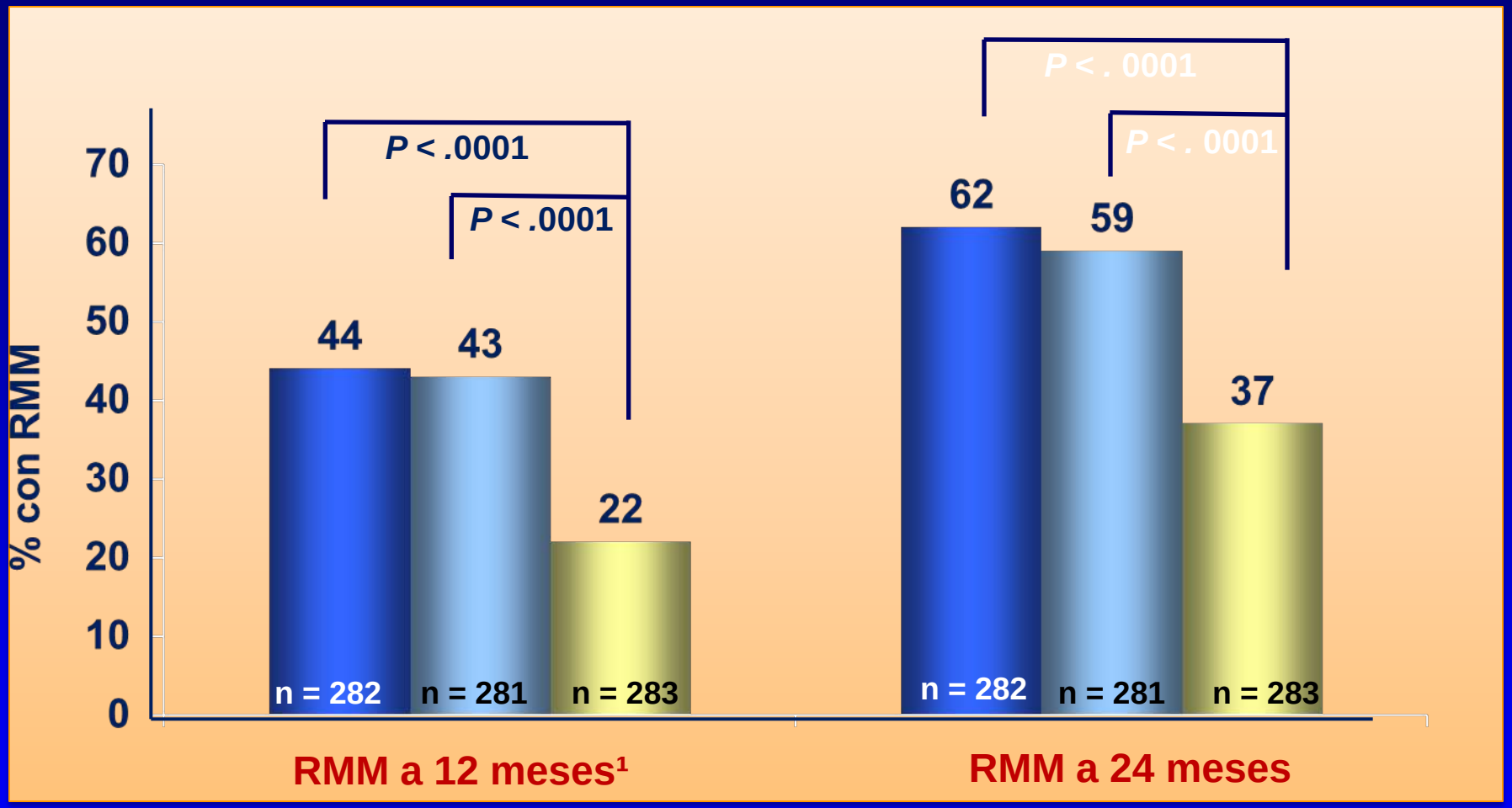


Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

RMolM a 12 y 15 Meses (Evaluables)



RMM *al* mes 12 y 24*



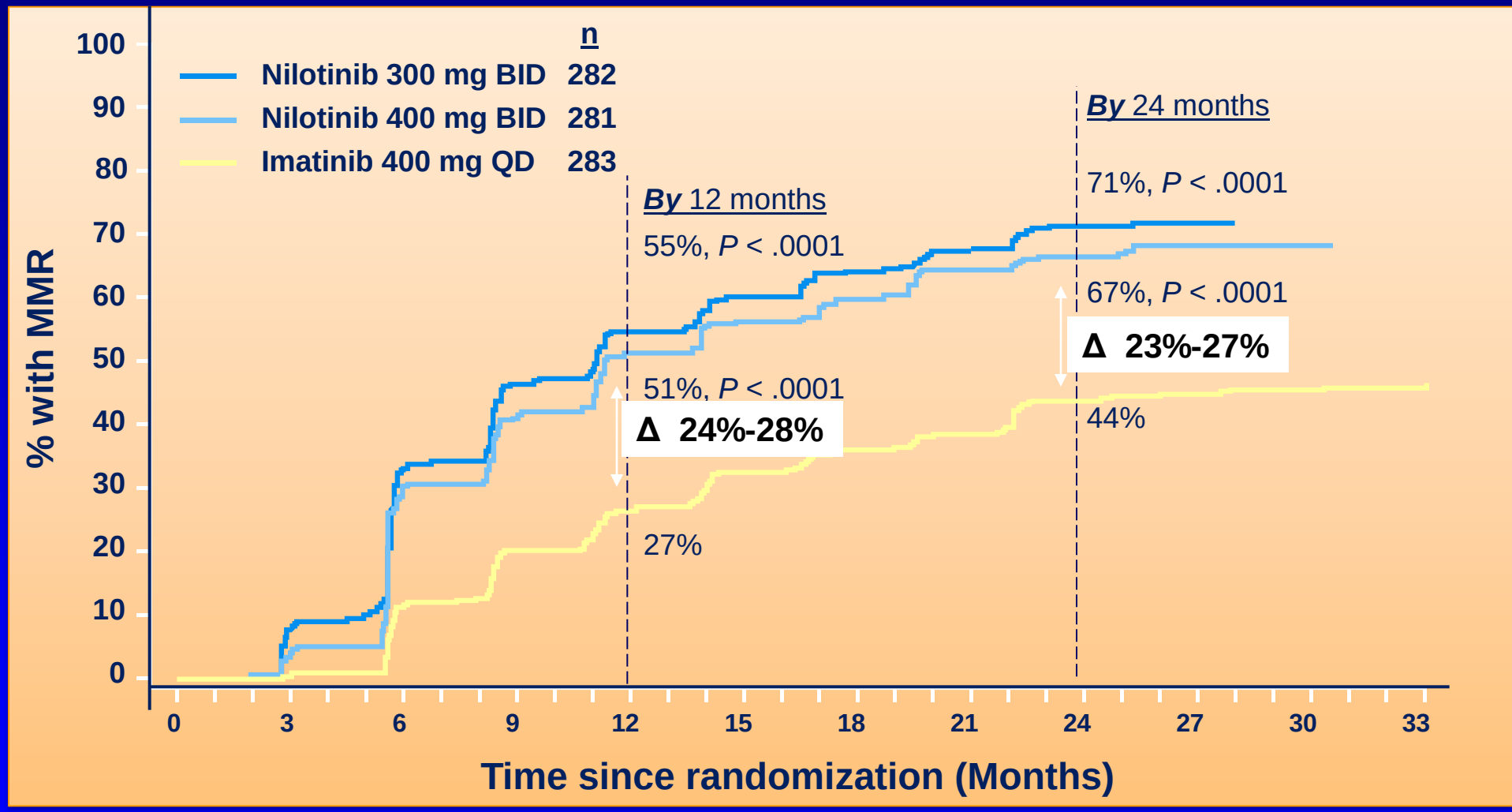
RMM *al* mes 24: menos del 2% de los ptes en cada rama perdieron la RMM entre el mes 12 y 24

*ITT population

1. Saglio G, et al. *NEJM*. 2010;362:2251-2259.

Data cut-off: 20Aug2010

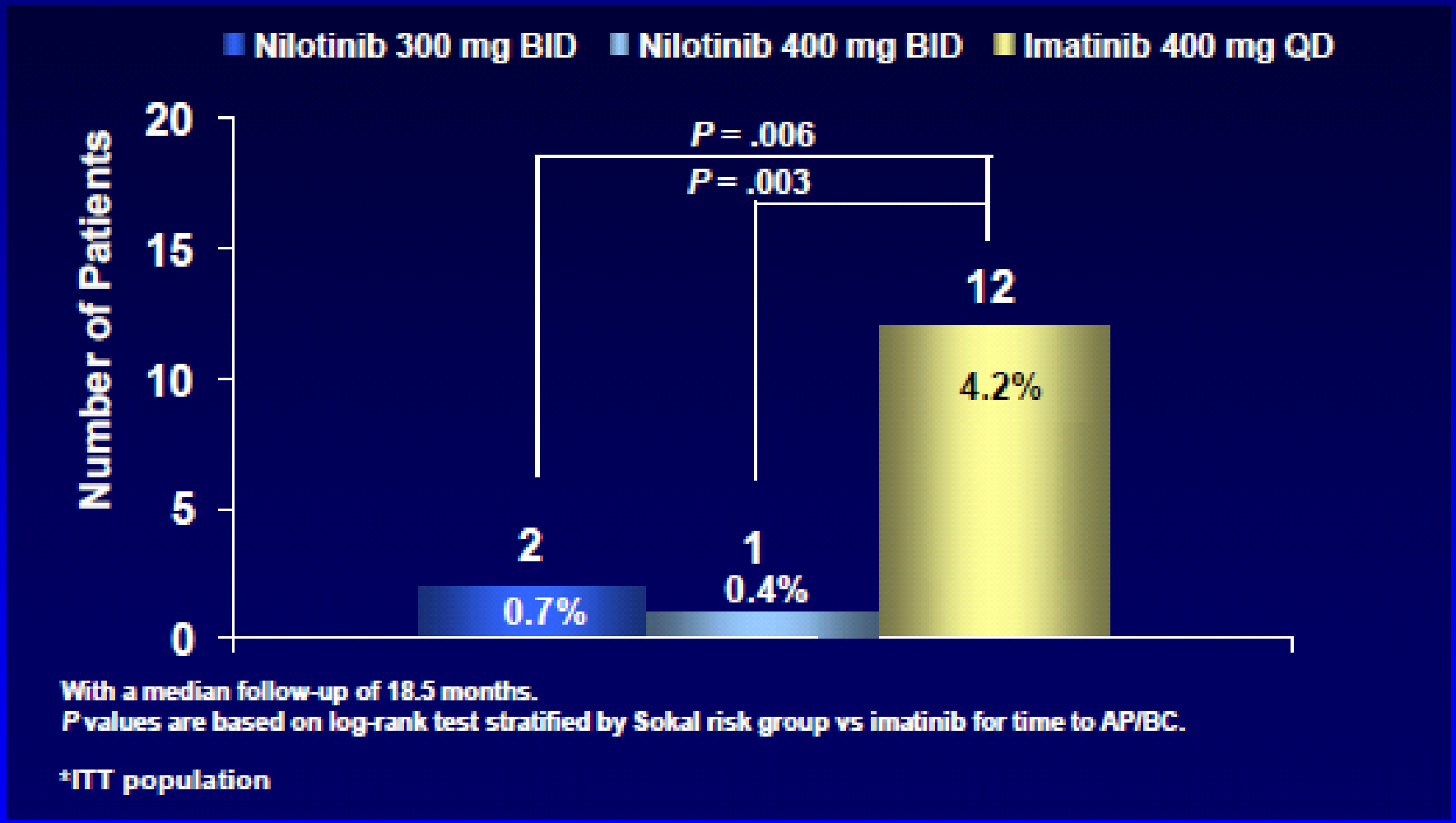
Incidencia acumulada de RMM*



*ITT population

Data cut-off: 20Aug2010

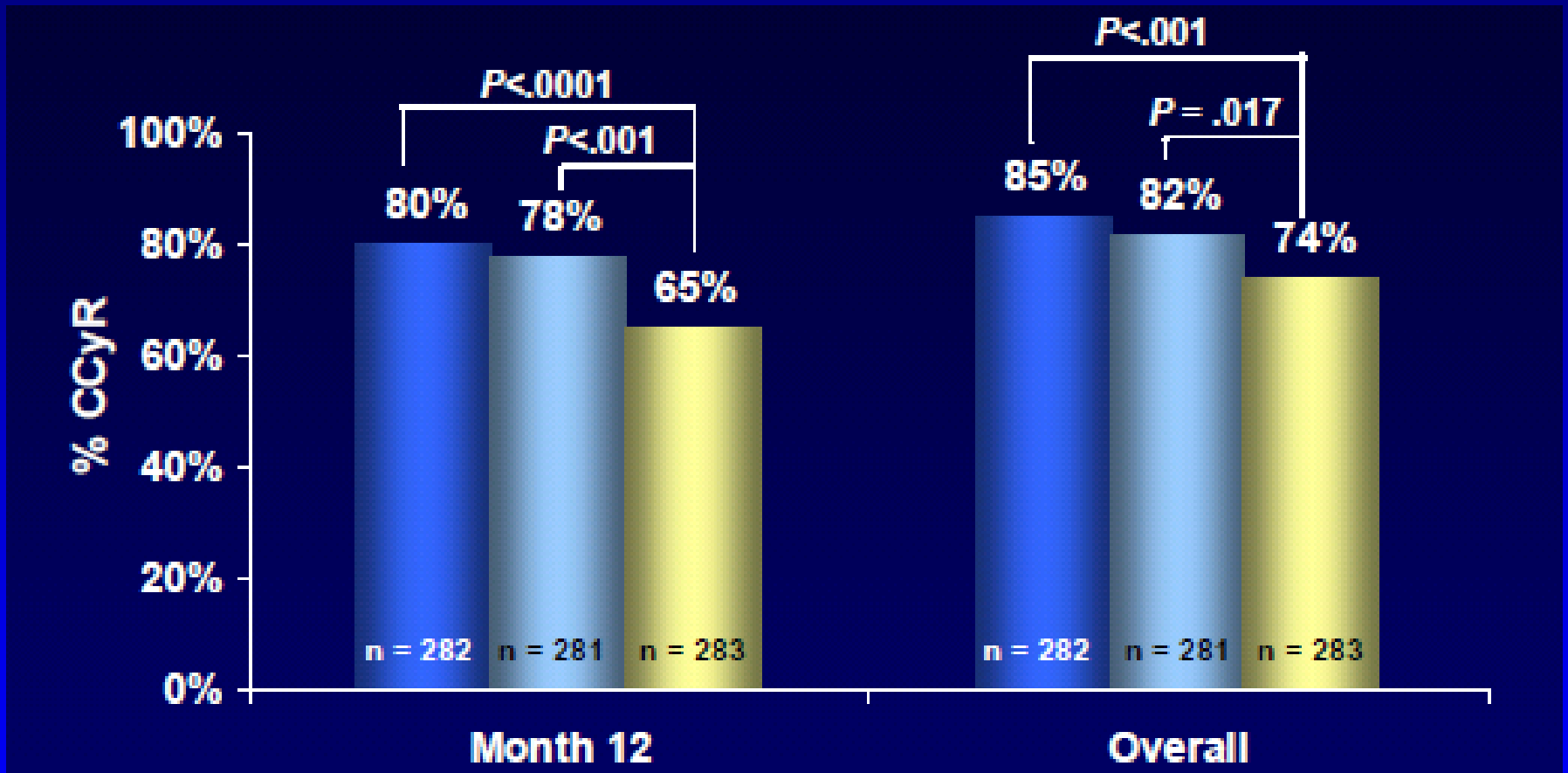
Progresión a FA/CB (ITT)



- Ningún paciente que logró RMM progresó a FA/CB
- 3 pacientes que lograron RCC en imatinib progresaron a FA/CB

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

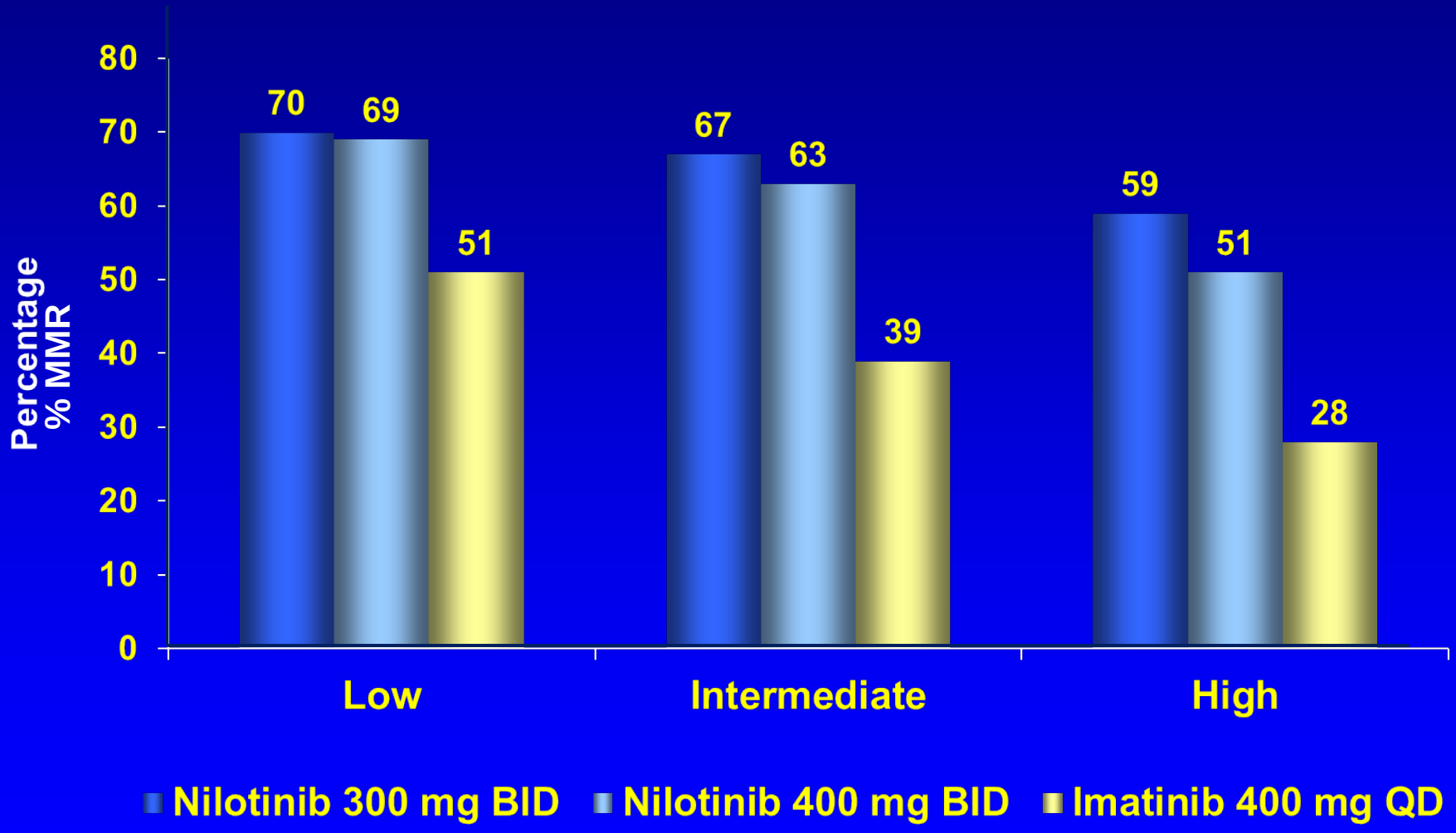
Tasa de RCC (ITT)



- Among patients who had a cytogenetic assessment at 18 months (n = 442/846), the rates of CCyR were:
  - 99%, 99%, and 89% for nilotinib 300 mg BID, 400 mg BID, and imatinib

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Tasas de RMolM Global según Sokal



*ITT population

Data cut-off: 2Jan2010

Resumen de los Pacientes con progresión a FA/CB durante el tratamiento*

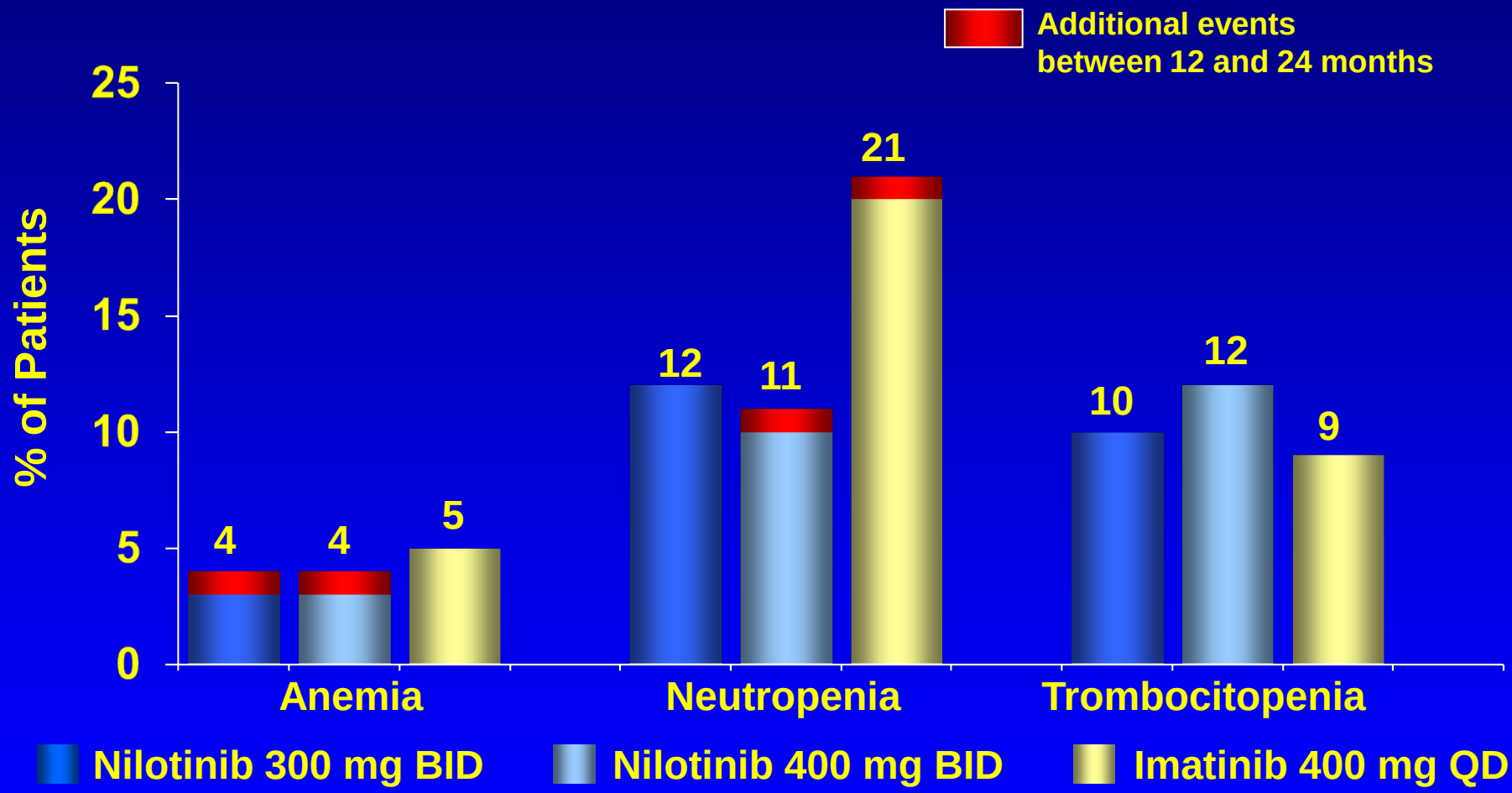
	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Progresión a FA/CB	2	1	12
Progresión a FA	1	1	3
Progresión a CB	1	0	9
Sokal, Riesgo Intermedio	1	1	8
Sokal, Riesgo Alto	1	0	4
Progresión dentro de los 12 m	2	1	9

Data cut-off: 2Jan2010

* ITT Population.

Hochhaus A, et al. *Haematologica*. 2010;95(s2):459 [abstract 1113] (oral).

Mielosupresión grado 3/4



Data cut-off: 20Aug2010

Eventos adversos relacionados a la droga en estudio (≥10% en cualquier grupo)

%de pacientes tratados	Nilotinib 300 mg BID N = 279		Nilotinib 400 mg BID N = 277		Imatinib 400 mg QD N = 280	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
Nausea	12	<1	20	1	31	0
Dolores musculares	7	0	6	<1	24	<1
Diarrea	8	<1	7	0	21	1
Vómitos	5	0	9	1	14	0
Rash	31	<1	36	3	11	1
Mialgia	10	<1	10	0	10	0
Dolor de cabeza	14	1	21	1	8	0
Fatiga	11	0	9	<1	8	<1
Prurito	15	<1	13	<1	5	0
Alopecia	8	0	13	0	4	0

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Retención de líquidos relacionados a la droga en estudio (todos los grados)

% de pacientes tratados	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277	Imatinib 400 mg QD N = 280
Edema periférico	5	5	14
Eyelid edema	<1	2	13
Edema Periorbital	<1	<1	12
Edema Facial	<1	2	8
Aumento peso	3	<1	6
Derrame Pericárdico	<1	0	<1
Derrame Pleural	<1	0	0

- EA grado 3/4 fueron raramente observados (<1%)

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Alteraciones de laboratorio (Grado 3/4)

% de pacientes tratados	Nilotinib 300 mg BID n = 279		Nilotinib 400 mg BID n = 277		Imatinib 400 mg QD n = 280	
	Todos los grados	Grado 3/4	Todos los grados	Grado 3/4	Todos los grados	Grado 3/4
Lipasa ↑	24	7	30	7	11	3
Amilasa ↑	16	< 1	20	1	13	1
ALT↑	67	4	74	9	23	3
AST ↑	41	1	49	3	25	1
Bilirrubina total ↑	54	4	63	8	11	< 1
Glucosa ↑	38	6	42	4	22	0
Albumina ↓	4	0	5	0	4	0
Colesterol ↑	22	0	22	< 1	3	0
Fósforo ↓	33	5	37	6	49	8
Fosfatasa alcalina ↑	21	0	27	0	33	< 1
Creatinina ↑	5	0	6	0	13	< 1
Calcio ↓	3	< 1	5	< 1	11	0

- Un paciente en la rama imatinib y uno en rama nilotinib 400 mg dos veces al día discontinuaron el estudio por pancreatitis aguda.

Data cut-off: 2Jan2010

Discontinuación por Eventos Adversos de Laboratorio

	Nilotinib 300 mg BID N = 279		Nilotinib 400 mg BID N = 277		Imatinib 400 mg QD N = 280	
Nº de pacientes	Todos los grados	Grado 3/4	Todos los grados	Grado 3/4	Todos los grados	Grado 3/4
Transaminasa y bilirrubina elevada	7	2	4	0	4	2
Aumento Lipasa	0	0	1	0	0	0
Hiperglucemia	0	0	0	0	0	0

Pancreatitis

No. de pacientes	Nilotinib 300 mg BID N = 279		Nilotinib 400 mg BID N = 277		Imatinib 400 mg QD N = 280	
	All Grade	Grade 3/4	All Grade	Grade 3/4	All Grade	Grade 3/4
Pancreatitis	2	0	4	0	1	0
Pancreatitis aguda	1	0	1	1	1	0

- 1 paciente en imatinib y 1 en nilotinib 400mg dos veces al día discontinuaron el estudio por pancreatitis aguda

Prolongación del QTc

% de pacientes tratados	Nilotinib 300 mg BID N = 279	Nilotinib 400 mg BID N = 277	Imatinib 400 mg QD N = 280
Absolute QTcF >480 ms	0	<1	0
Absolute QTcF >500 ms	0	0	0
QTcF increase >30 ms	26	26	18
QTcF increase >60 ms	<1	<1	0

- No hubo descenso del basal en la Fracción de eyección VI en ninguna de las tres ramas

glio G, Don-Wook K, et al. NEJM 2010, june 5.

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Muertes

- No se reportaron muerte súbita
- Un total de 16 muertes fueron reportaron
  - Imatinib 400mg/ día
    - 9 pts: 8 discontinuaron tratamiento por progresión y murieron durante el seguimiento por razones relacionadas a LMC 1 por enf renal.
  - Nilotinib 300mg dos veces al día : 5 ptes
    - 3 pts murieron en tratamiento (obstrucción intestinal, suicidio, arritmia cardíaca)
    - 2 pts progresaron, 1 murió post trasplante
  - Nilotinib 400mg dos veces al día:
    - 1 pt discontinuó por progresión y murió dentro de los 28 días de seguimiento
    - 1 pt discontinuó tratamiento y murió 6 semanas después por cáncer gástrico.

Conclusiones de ENSTnd 24 meses

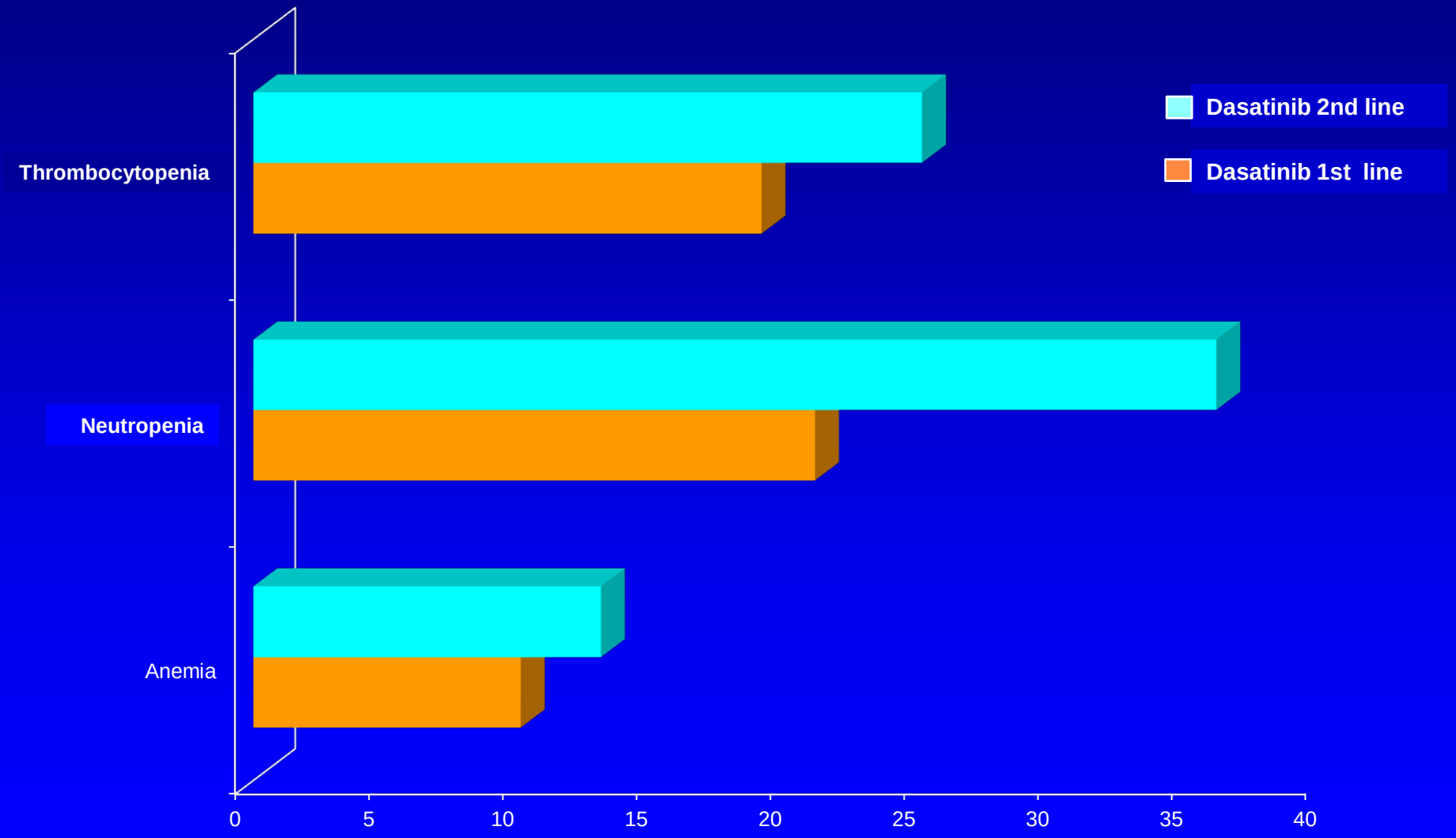
- Nilotinib demostró ser superior a imatinib, con una tasa significativamente mayor de RMolM y RCyC, con 300 o 400mg dos veces al día
- Muy pocos ptes con nilotinib progresaron comparados con imatinib
- Nilotinib demostró superioridad con respecto a imatinib en todos los grupos de Sokal
- La incidencia de EAs que llevaron a la interrupción del tratamiento fue menor entre los pacientes de nilotinib 300 mg BID
- Basados es estos resultados nilotinib fue aprobado por FDA y ANMAT para tratar pacientes con LMC en 1era línea.

Saglio G, et al. ASH 2009; abstract LBA-1 (oral).

Inhibidores de 2º en primera línea terapéutica.

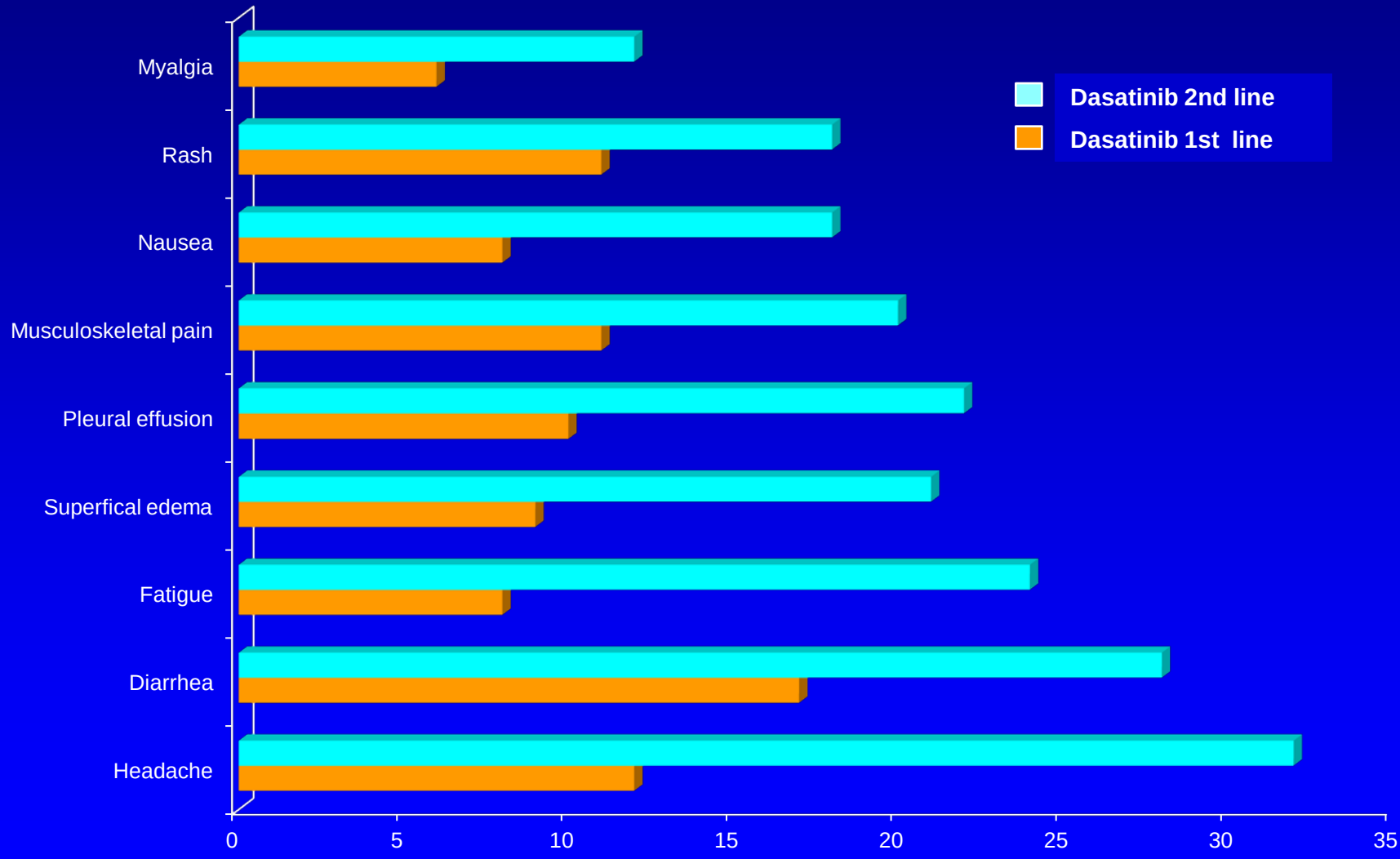
- Más efectivos
- Más tóxicos?

Toxicity: Second line dasatinib vs First line dasatinib



Shah N. JCO.Vol 28, No 18 suppl (June 20 Supplement), 2010
Kantarjian H. J Clin Oncol 28:15s, 2010 (suppl; abstr 6512)

Drug-related nonhematologic side effects in 2nd line vs 1st line dasatinib



Shah N. JCO.Vol 28, No 18 suppl (June 20 Supplement), 2010
Kantarjian H. J Clin Oncol 28:15s, 2010 (suppl; abstr 6512)

ITK de 2da Generación como Tratamiento de Primera Línea para Pacientes con LMC-FC de Reciente Diagnóstico

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