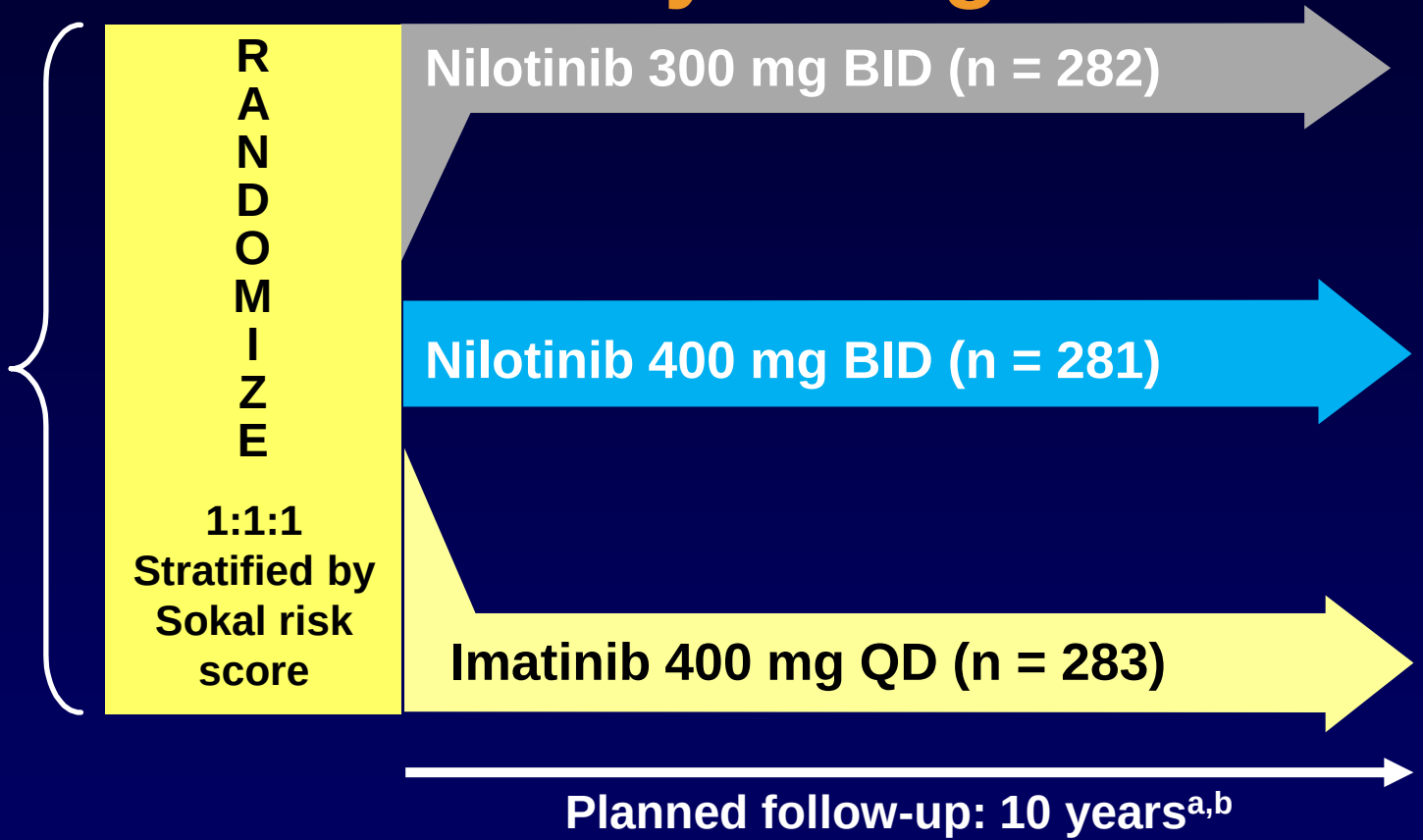
Efficacy and Safety of Nilotinib vs Imatinib in Patients With Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase: Long-Term Follow-Up of ENESTnd

Abstract 4541

Larson RA, Kim D-W, Issaragrisil S, le Coutre PD, Dorlhiac-Llacer PE, Etienne G, Clark RE, Flinn IW, Nakamae H, Hochhaus A, Saglio G, Kantarjian HM, Donohue B, Deng W, Menssen HD, Hughes TP

Methods
ENESTnd Study Design



[a] The ENESTnd study protocol originally called for 5 years of follow-up, which was later extended to 10 years.

[b] Patients randomized to nilotinib 300 mg BID or imatinib who experienced suboptimal response or treatment failure could discontinue core treatment and enter an extension study in which they received nilotinib 400 mg BID. Patients randomized to nilotinib 400 mg BID were initially permitted to enter the extension study and receive imatinib 400 mg QD; however, a protocol amendment after the 36-month data cutoff removed this option. Survival and progression outcomes during extension study follow-up were included in the "on study" analyses for the core study.

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Results
Patient Disposition

Patient Status, n (%)	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
Still on study[a]	231 (81.9)	238 (84.7)	224 (79.2)
Still on core treatment	151 (53.5)	155 (55.2)	127 (44.9)
Discontinued core treatment and entered extension study	24 (8.5)	3 (1.1)	45 (15.9)
Discontinued core treatment without entering extension study	107 (37.9)	123 (43.8)	111 (39.2)
Adverse event/laboratory abnormalities	39 (13.8)	64 (22.8)	39 (13.8)
Withdrawal of consent	19 (6.7)	22 (7.8)	22 (7.8)
Suboptimal response/treatment failure[b]	11 (3.9)	10 (3.6)	19 (6.7)
Death	7 (2.5)	2 (0.7)	2 (0.7)
Disease progression	2 (0.7)	4 (1.4)	10 (3.5)
Other reason[c]	29 (10.3)	21 (7.5)	19 (6.7)

[a] On core or extension treatment or in posttreatment follow-up.
[b] Per the 2009 European LeukemiaNet criteria [Baccarani M, et al. *J Clin Oncol*. 2009;27(35):6041-6051] or investigator assessment.
[c] Included abnormal test procedure results (n = 0 [nilotinib 300 mg BID], 1 [nilotinib 400 mg BID], and 1 [imatinib]), condition no longer required study drug (n = 1, 0, and 0, respectively), lost to follow-up (n = 4, 2, and 3, respectively), administrative problems (n = 7, 6, and 7, respectively), treatment duration completed per protocol (n = 3, 1, and 2, respectively), and protocol deviation (n = 14, 11, and 6, respectively).

- More patients in the nilotinib arms than in the imatinib arm remained on core treatment at the data cutoff

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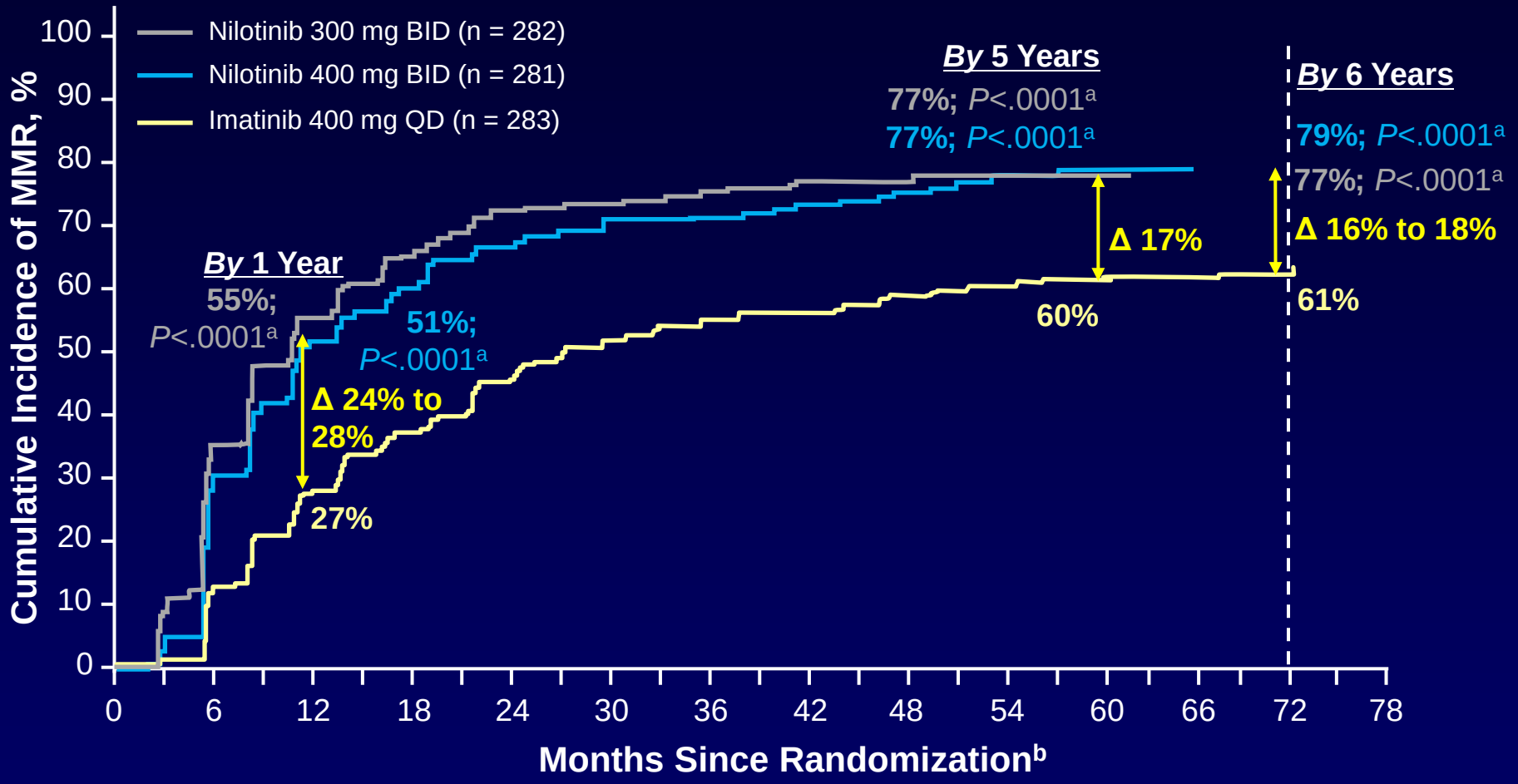
Cumulative Incidence of MMR



- Rates of MMR by 6 years remained higher in the nilotinib arms than in the imatinib arm
- Nearly all pts still on core treatment at the data cutoff had achieved MMR; in each arm, 4 pts 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%)

[a] *P* values are nominal. [b] For each arm, the curve stops at the latest timepoint at which a patient first achieved MMR.

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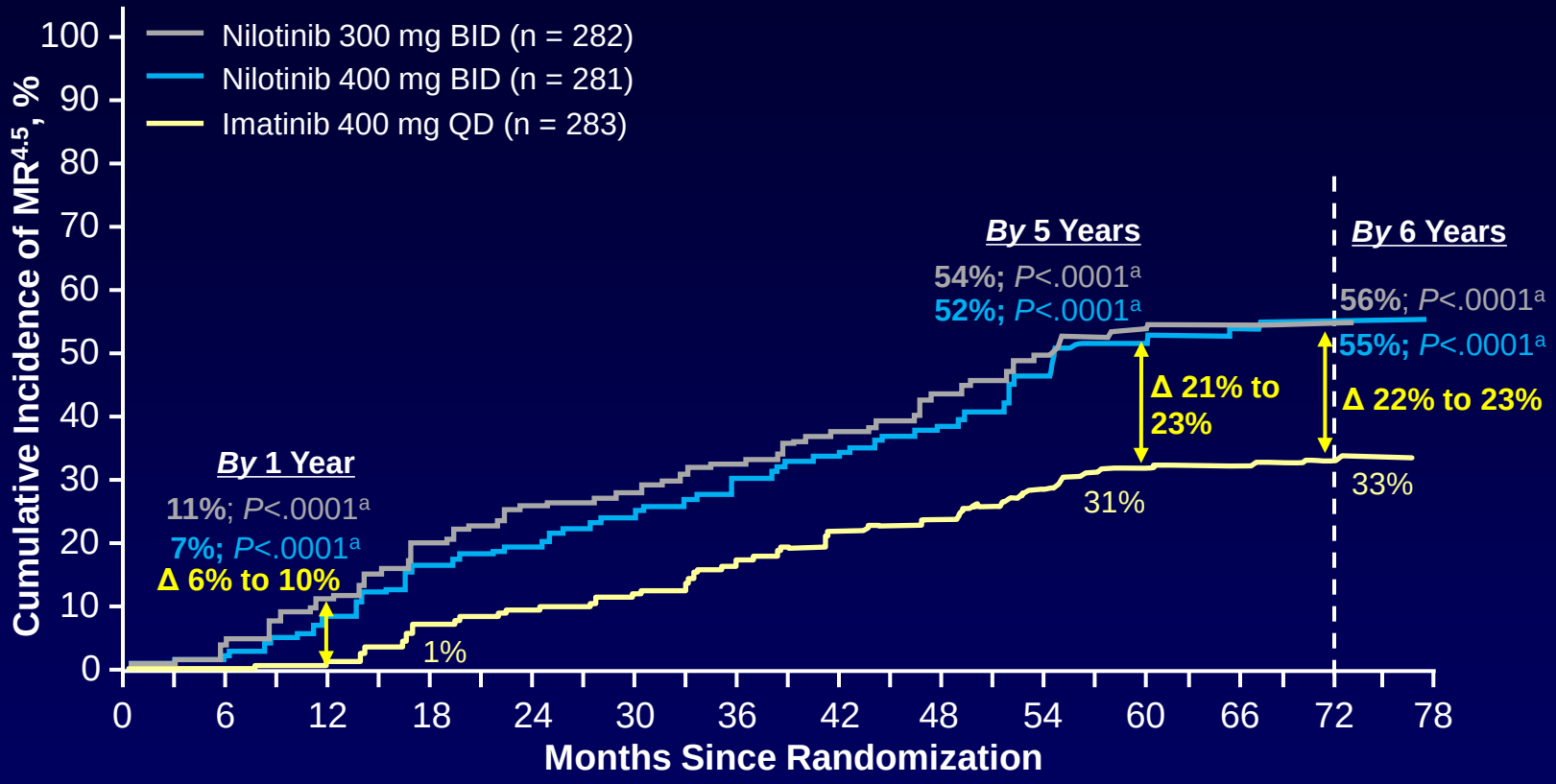
Cumulative Incidence of MR$^{4.5}$



- More patients achieved MR$^{4.5}$ in each nilotinib arm than in the imatinib arm (**Figure 3**)
- Among pts still on core treatment at the data cutoff, 30 (nilotinib 300 mg BID), 42 (nilotinib 400 mg BID), and 47 (imatinib) pts had not achieved MR$^{4.5}$
- KM-estimated median times to first MR$^{4.5}$ were
  - Nilotinib 300 mg BID: 45.5 months (hazard ratio [HR] vs imatinib, 2.0387 [95% CI, 1.5807-2.6295]; nominal *P*<.0001)
  - Nilotinib 400 mg BID: 49.8 months (HR vs imatinib, 1.7770 [95% CI,1.3780-2.2915]; nominal *P*<.0001)
  - Imatinib 400 mg QD: 61.1 months

[a] *P* values are nominal.

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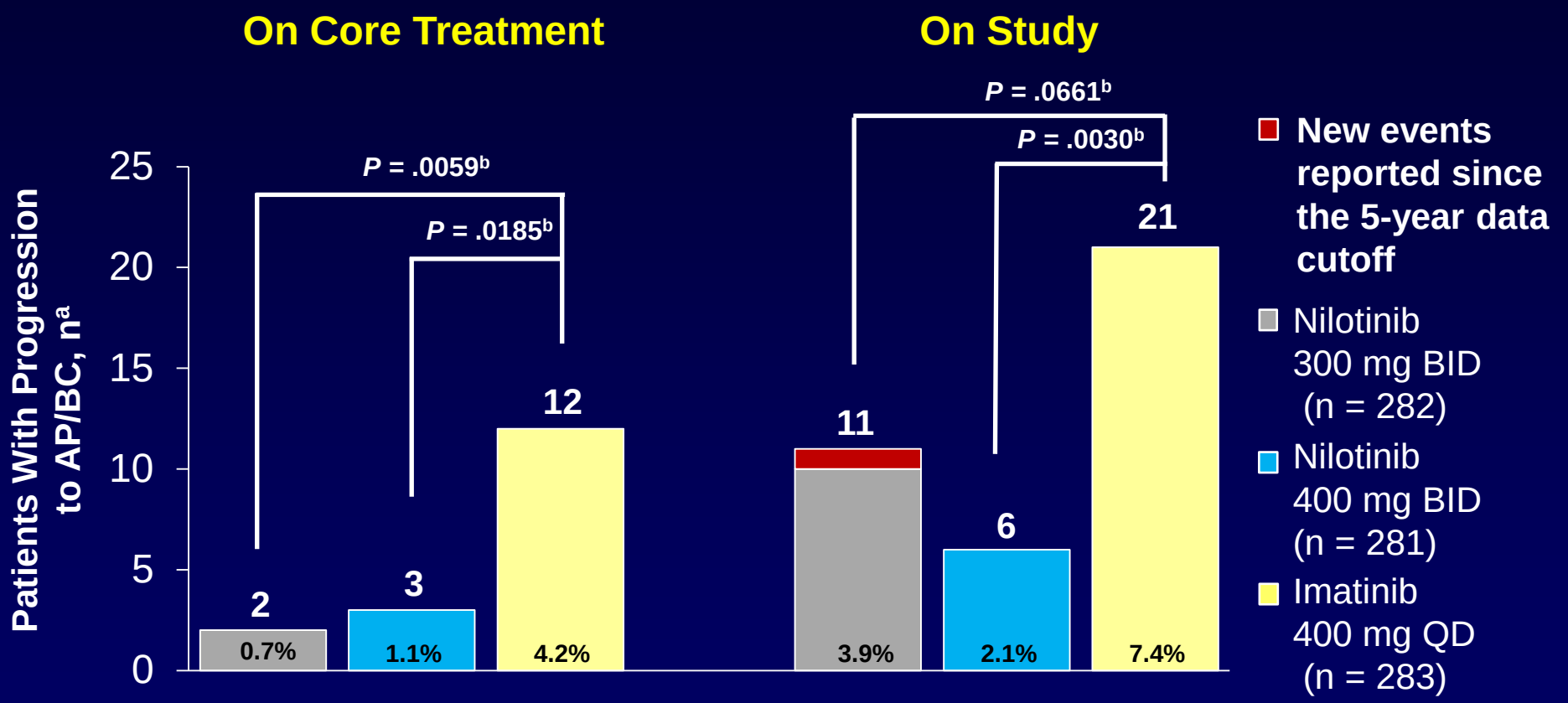
Progression to AP/BC



- Since the 5-year data cutoff, 1 new progression to AP/BC on study was reported in the nilotinib 300 mg BID arm (**Figure 4**); this patient had a low Sokal risk score at baseline, achieved *BCR-ABL*^{IS} ≤10% at 3 months, and discontinued core treatment due to neutropenia ≈5 years before progression to AP/BC was reported

[a] Defined as progression to AP/BC or death due to advanced CML. [b] *P* values are nominal.

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Estimated Rates of Freedom From Progression to AP/BC at 6 Years

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
Progression to AP/BC on core treatment, n	2	3	12
KM-estimated 6-year freedom from progression to AP/BC (95% CI), %	99.3 (98.2-100)	98.7 (97.2-100)	95.2 (92.6-97.9)
Hazard ratio vs imatinib (95% CI)	0.1599 (0.0358-0.7143)	0.2457 (0.0693-0.8713)	–
Nominal *P* value vs imatinib	.0059	.0185	–
Progression to AP/BC on study, n	11	6	21
KM-estimated 6-year freedom from progression to AP/BC (95% CI), %	95.8 (93.3-98.2)	97.8 (96.0-99.5)	92.2 (89.1-95.4)
Hazard ratio vs imatinib (95% CI)	0.5110 (0.2464-1.0600)	0.2773 (0.1119-0.6870)	–
Nominal *P* value vs imatinib	.0661	.0030	–

- **By 6 years, fewer progressions to AP/BC were reported in each nilotinib arm than in the imatinib arm, both on core treatment and on study**

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OS and Deaths Due to Advanced CML

	Nilotinib 300 mg BID (n = 282)	Nilotinib 400 mg BID (n = 281)	Imatinib 400 mg QD (n = 283)
Total deaths on study, n[a]	21	11	23
KM-estimated 6-year OS on study (95% CI), %	91.6 (88.0-95.1)	95.8 (93.4-98.2)	91.4 (88.0-94.7)
Hazard ratio vs imatinib (95% CI)	0.8934 (0.4944-1.6143)	0.4632 (0.2258-0.9503)	–
Nominal *P* value vs imatinib	.7085	.0314	–
Deaths due to advanced CML, n	6	4	16
KM-estimated 6-year freedom from death due to advanced CML (95% CI), %	97.7 (96.0-99.5)	98.5 (97.1-100)	93.9 (91.0-96.8)
Hazard ratio vs imatinib (95% CI)	0.3694 (0.1445-0.9440)	0.2433 (0.0813-0.7279)	–
Nominal *P* value vs imatinib	.0302	.0061	–

[a] Death from any cause at any time (during study treatment or during posttreatment follow-up).

- **By 6 years, fewer deaths were reported in the nilotinib 400 mg BID arm than in the imatinib arm; fewer deaths due to advanced CML were reported in either nilotinib arm than in the imatinib arm**

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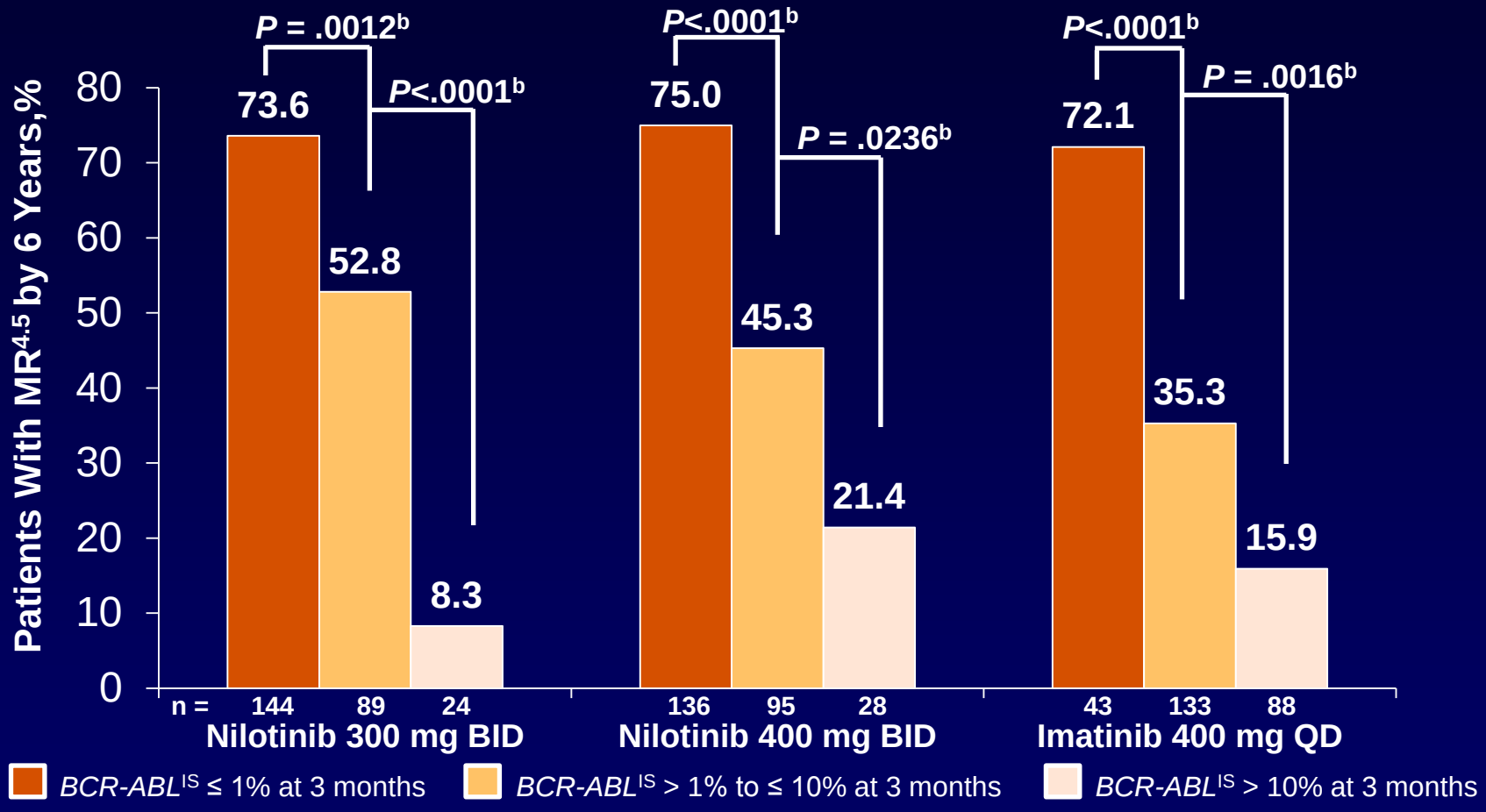
Rate of MR$^{4.5}$ by 6 Years According to 3-Month *BCR-ABL*^{IS} Levels[a]



- **In each arm, rates of MR$^{4.5}$ by 6 years were highest among patients with *BCR-ABL*^{IS} ≤ 1% at 3 months and lowest among patients with *BCR-ABL*^{IS} > 10% at 3 months**
  - **The majority of evaluable patients in each nilotinib arm (nilotinib 300 mg BID, n = 145; nilotinib 400 mg BID, n = 137), but not in the imatinib arm (n = 43), achieved *BCR-ABL*^{IS} ≤1% at 3 months**

[a] Among patients with evaluable 3-month assessments and without MR$^{4.5}$ by 3 months. One patient in each nilotinib arm achieved MR$^{4.5}$ by 3 months and was excluded from this analysis. [b] *P* values are nominal.

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PFS and OS According to 3-Month *BCR-ABL*^{IS} Levels[a]

	Nilotinib 300 mg BID		Nilotinib 400 mg BID		Imatinib 400 mg QD	
***BCR-ABL*^{IS} at 3 months**	**≤10% (n = 234)**	**>10% (n = 24)**	**≤10% (n = 232)**	**>10% (n = 28)**	**≤10% (n = 176)**	**>10% (n = 88)**
KM-estimated 6-year PFS on study (95% CI), %[b]	**92.3 (88.3-96.2)**	**73.7 (55.6-91.9)**	**95.8 (93.1-98.5)**	**89.0 (77.3-100)**	**97.1 (94.5-99.6)**	**79.9 (71.3-88.5)**
Hazard ratio (95% CI)	0.2140 (0.0829-0.5521)		0.3327 (0.0900-1.2305)		0.1293 (0.0477-0.3506)	
Nominal *P* value	.0004		.0830		< .0001	
KM-estimated 6-year OS on study (95% CI), %	**94.5 (91.2-97.7)**	**77.1 (59.3-94.8)**	**95.9 (93.3-98.5)**	**92.7 (83.0-100)**	**97.6 (95.3-99.9)**	**79.5 (70.8-88.3)**
Hazard ratio (95% CI)	0.1859 (0.0645-0.5355)		0.5118 (0.1105-2.3705)		0.1013 (0.0341-0.3014)	
Nominal *P* value	.0005		.3829		< .0001	

[a] Among patients with evaluable 3-month assessments and without the evaluated outcome (PFS or OS events) by 3 months. [b] PFS events included death from any cause and progression to AP/BC.

- **In each arm, patients who achieved *BCR-ABL*^{IS} ≤10% at 3 months had higher rates of estimated PFS and OS at 6 years vs patients with *BCR-ABL*^{IS} >10% at 3 months**

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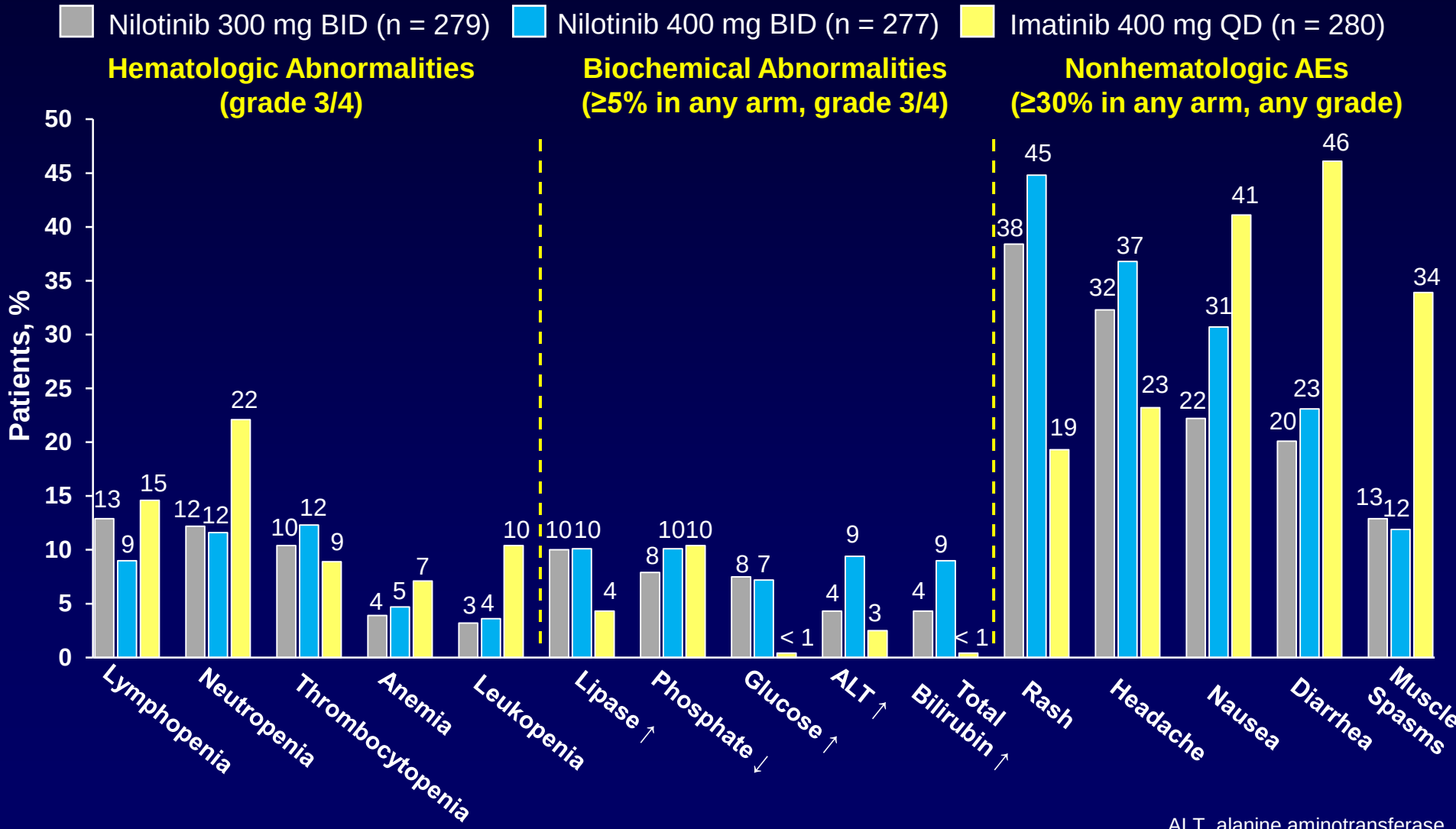
Frequently Reported Newly Occurring or Worsening Laboratory Abnormalities and Nonhematologic AEs



ALT, alanine aminotransferase

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AEs of Interest (All Cause, All Grade)

	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
Peripheral edema	28 (10.0)	40 (14.4)	56 (20.0)
Pleural effusion	5 (1.8)	3 (1.1)	3 (1.1)
Pericardial effusion	2 (0.7)	2 (0.7)	3 (1.1)
Pulmonary edema	1 (0.4)	0	0
Fluid retention	0	2 (0.7)	7 (2.5)
Hepatotoxicity[a]	5 (1.8)	15 (5.4)	7 (2.5)
Pancreatitis[a]	5 (1.8)	9 (3.2)	2 (0.7)
Significant bleeding[a]	10 (3.6)	16 (5.8)	5 (1.8)
CNS hemorrhage[a]	2 (0.7)	2 (0.7)	1 (0.4)
Gastrointestinal hemorrhage[a]	8 (2.9)	15 (5.4)	4 (1.4)
Symptomatic QT prolongation[a]	5 (1.8)	7 (2.5)	8 (2.9)
Hypertension	33 (11.8)	28 (10.1)	12 (4.3)
Pulmonary hypertension	0	2 (0.7)	1 (0.4)
Retinal vein occlusion	1 (0.4)	0	0
Thrombophlebitis	1 (0.4)	3 (1.1)	0
Superficial thrombophlebitis	0	1 (0.4)	0
Deep venous thrombosis	1 (0.4)	1 (0.4)	1 (0.4)
Cardiovascular event[a]	28 (10.0)	44 (15.9)	7 (2.5)
Ischemic heart disease[a]	14 (5.0)	28 (10.1)	6 (2.1)
Ischemic cerebrovascular event[a]	4 (1.4)	9 (3.2)	1 (0.4)
Peripheral artery disease[a]	12 (4.3)	9 (3.2)	0
Other[a,b]	4 (1.4)	3 (1.1)	0

CNS, central nervous system. [a] Includes predefined groupings of Medical Dictionary for Regulatory Activities (MedDRA) preferred terms or standardized MedDRA queries. Patients with multiple events for a given AE term or category were counted only once for the AE term or category. [b] Includes arteriosclerosis (nilotinib 300 mg BID, n = 4; nilotinib 400 mg BID, n = 2), arterial occlusive disease (nilotinib 300 mg BID, n = 1), and arterial stenosis (nilotinib 400 mg BID, n = 1); 5 of these patients (nilotinib 300 mg BID, n = 4; nilotinib 400 mg BID, n = 1) also had ischemic heart disease, ischemic cerebrovascular, and/or peripheral artery disease events.

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Cardiovascular Events by Year of Treatment

First Cardiovascular Event by Year, n (%)[a]	Nilotinib 300 mg BID (n = 279)	Nilotinib 400 mg BID (n = 277)	Imatinib 400 mg QD (n = 280)
<1 y	4 (1.4)	10 (3.6)	2 (0.7)
≥1 y to <2 y	4 (1.4)	6 (2.2)	0
≥2 y to <3 y	7 (2.5)	6 (2.2)	1 (0.4)
≥3 y to <4 y	4 (1.4)	4 (1.4)	1 (0.4)
≥4 y to <5 y	1 (0.4)	6 (2.2)	1 (0.4)
≥5 y to <6 y	5 (1.8)	9 (3.2)	1 (0.4)
≥6 y to <7 y	3 (1.1)	2 (0.7)	1 (0.4)
≥7 y to <8 y	0	1 (0.4)	0

[a] Year of first cardiovascular event was assigned based on the start date of the first cardiovascular event reported in each patient. Patients with multiple events were counted only once, under the year during which their first cardiovascular event was reported.

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Conclusions

- Nilotinib continued to show improved efficacy vs imatinib for the treatment of patients with CML-CP, including higher rates of molecular response, fewer progressions to AP/BC, and fewer deaths due to advanced CML
- In each arm, patients with *BCR-ABL*^{IS} ≤10% at 3 months (a milestone achieved by more patients in each nilotinib arm vs the imatinib arm) had higher 6-year rates of MR$^{4.5}$, PFS, and OS compared with patients with *BCR-ABL*^{IS} >10% at 3 months
- The safety profile of nilotinib remained consistent with previous reports
  - Cardiovascular events were more common with nilotinib vs imatinib; however, few deaths in any arm occurred within 3 months of a cardiovascular event
  - Pleural effusion, pericardial effusion, pulmonary edema, pulmonary hypertension, retinal vein occlusion, thrombophlebitis, superficial thrombophlebitis, and deep venous thrombosis were infrequent (<2% of patients in any arm)
- With 6 years of follow-up, results from ENESTnd continue to support use of front-line nilotinib 300 mg BID as a standard of care for patients with newly diagnosed Ph+ CML-CP

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