Role of Second Generation Tyrosine Kinase Inhibitors in Newly Diagnosed CML

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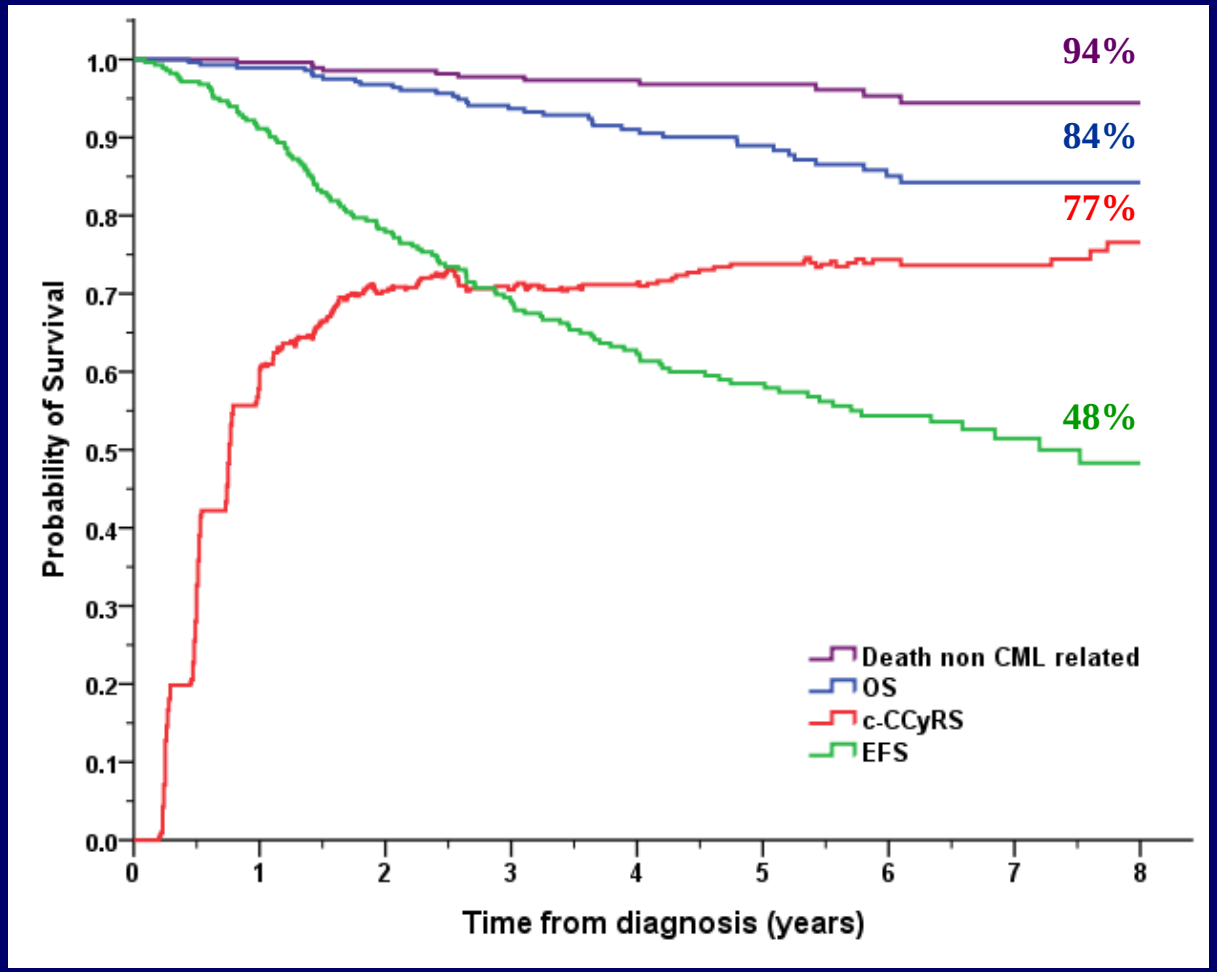
Outcome in 282 Patients Treated with Imatinib First Line in Hammersmith Hospital



6% death non CML

10% death from CML

7% alive but not in CCyR

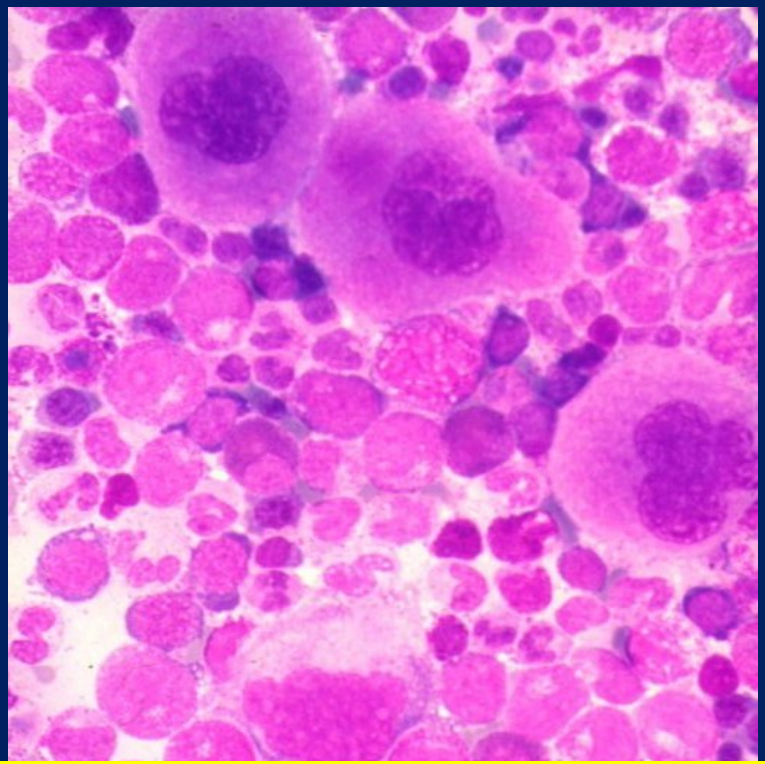
29% in CCyR w/o IM

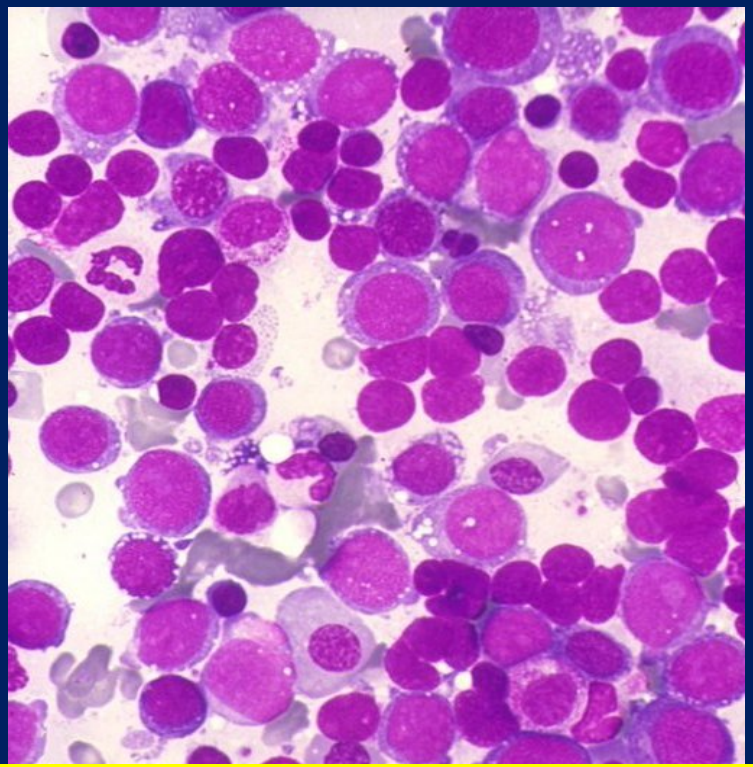
48% in CCyR on IM

De Lavalade et al. JCO 2008 Jul 10;26(20):3358-63.

CML: Progression

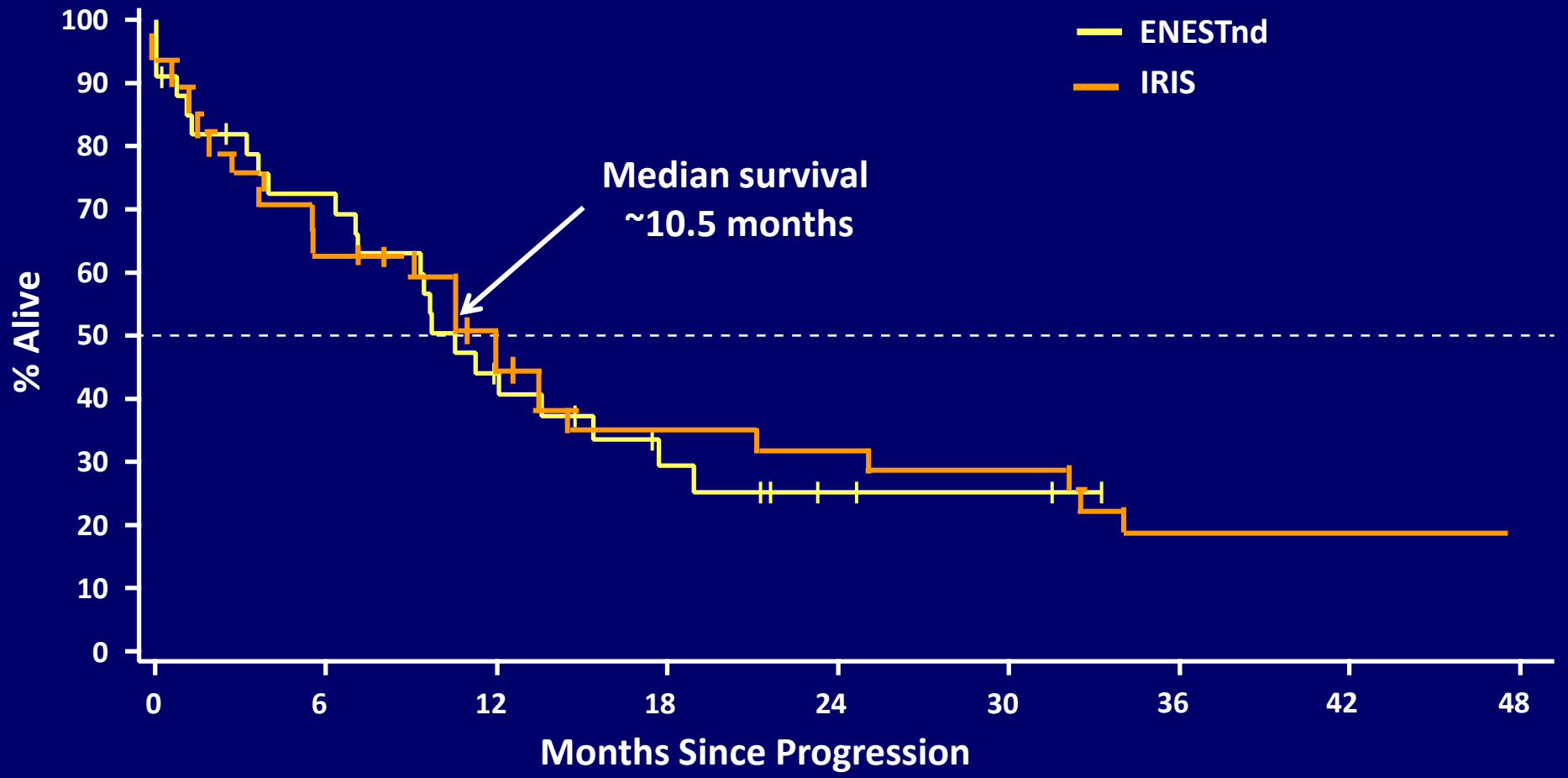
Chronic Phase → Acc./Blastic Phase



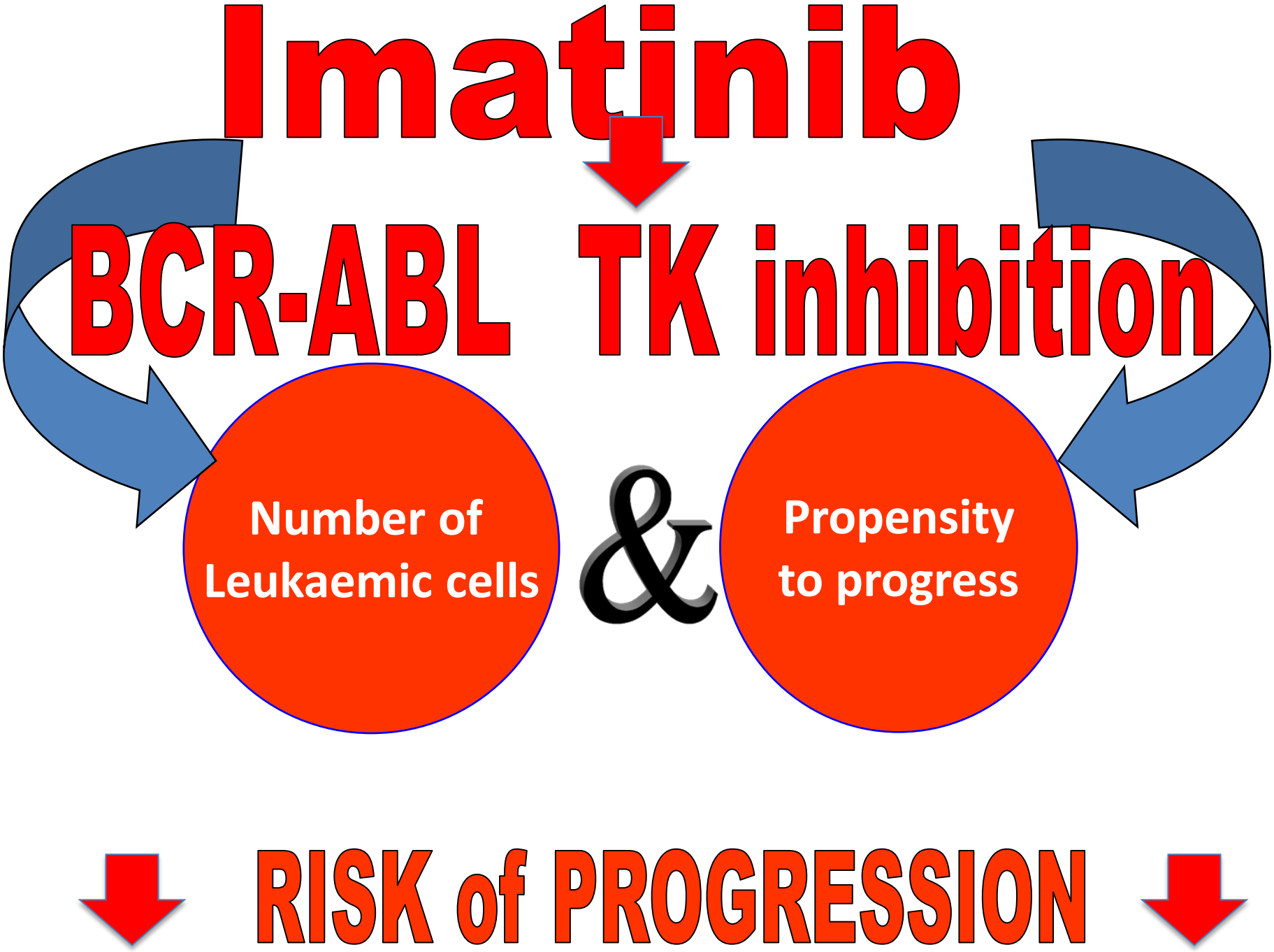


In the natural history of the disease, progression would occur in almost 100% of the cases in rather short median time (3-4 years)

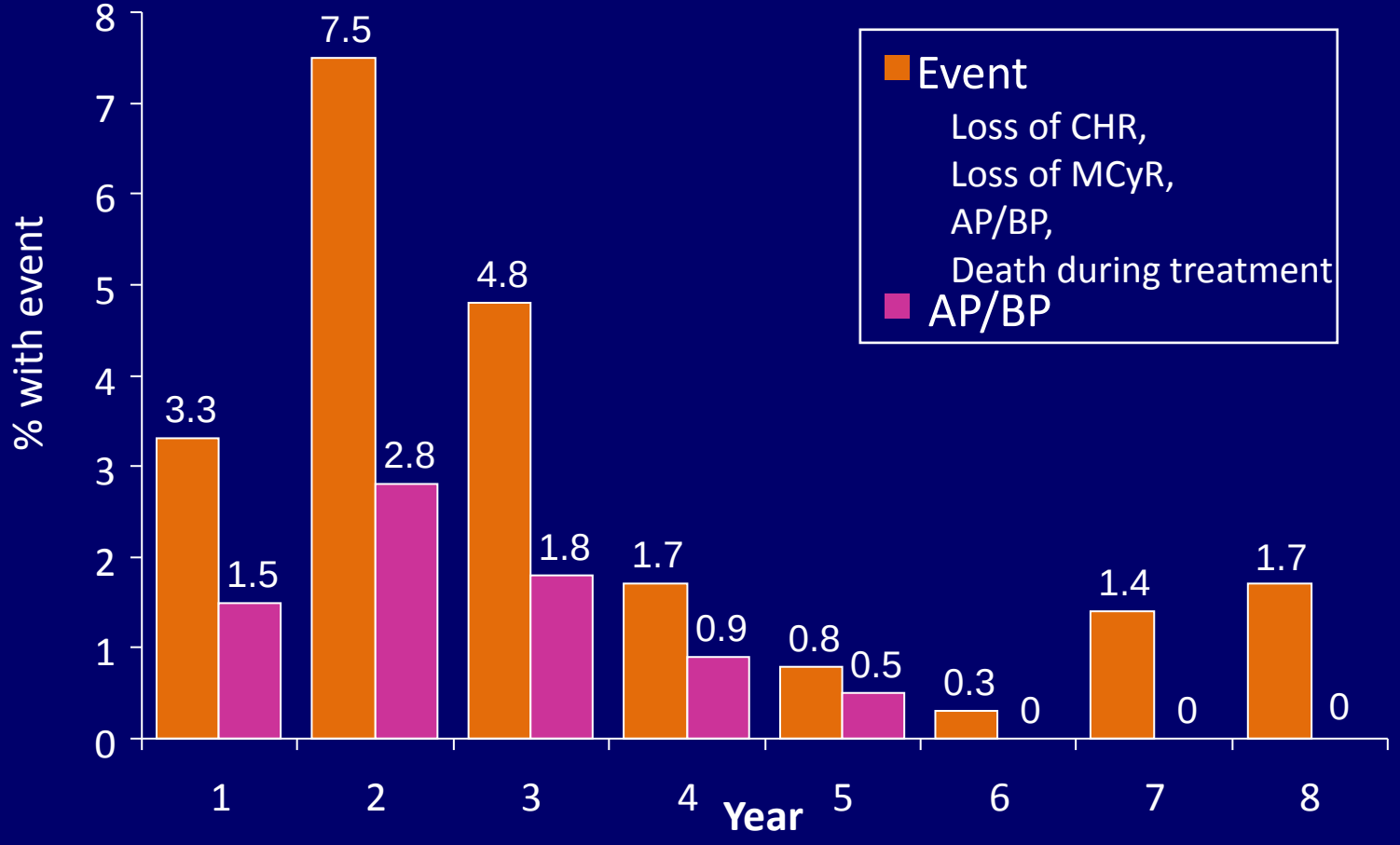
Survival of Patients after Progression Is Still Very Poor. Prevention of Progression Is the Goal of Therapy



Saglio et al. *Blood*. 2011;118(21):208-209 [abstract 452].


Imatinib
BCR-ABL TK inhibition
Number of Leukaemic cells
&
Propensity to progress
RISK of PROGRESSION

IRIS 8-Year Update: Majority of Events Occur Early



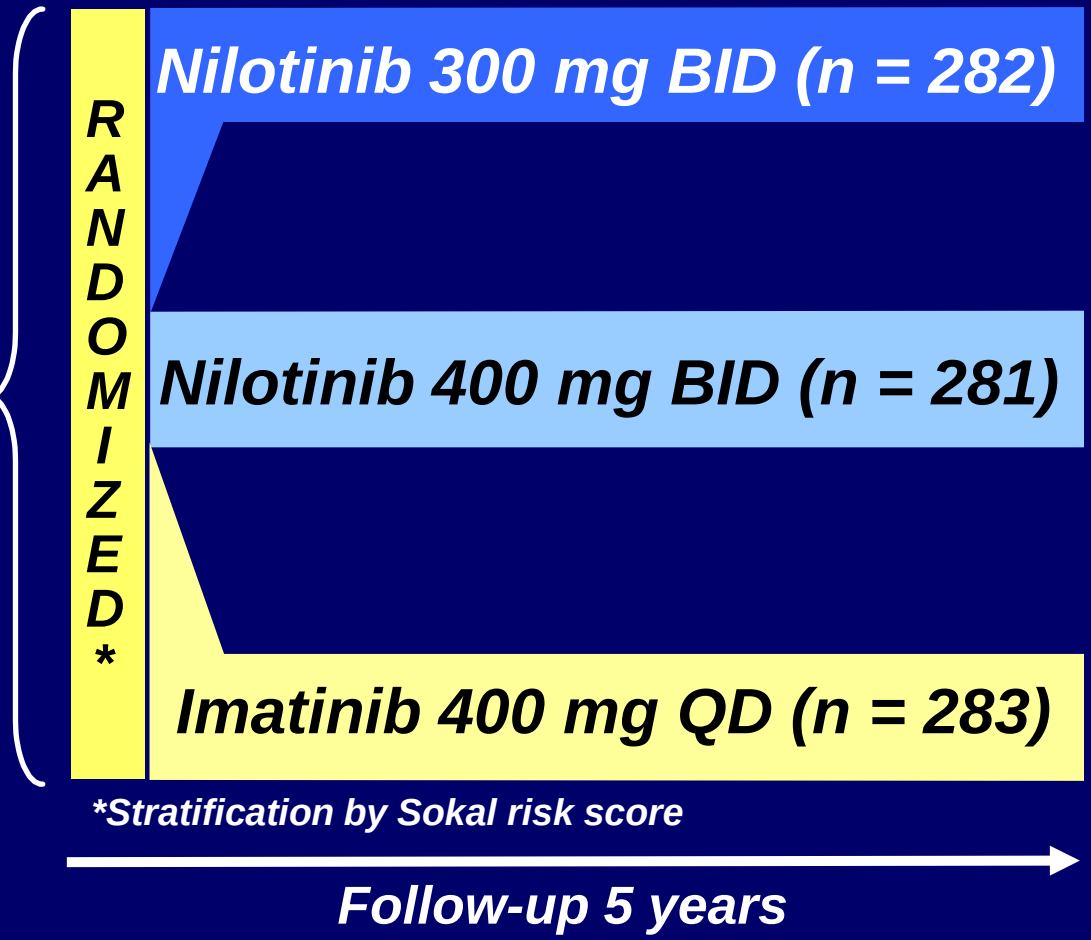
Hughes et al; Blood 2010 116:3758-3765.
Deininger M, et al. ASH 2009; 114: Poster #1126.

Registered TKIs in first-line CML treatment

- ✓Imatinib 400 mg
- ✓Nilotinib 300 mg BID
- ✓Dasatinib 100 mg QD

ENESTnd: Study Design

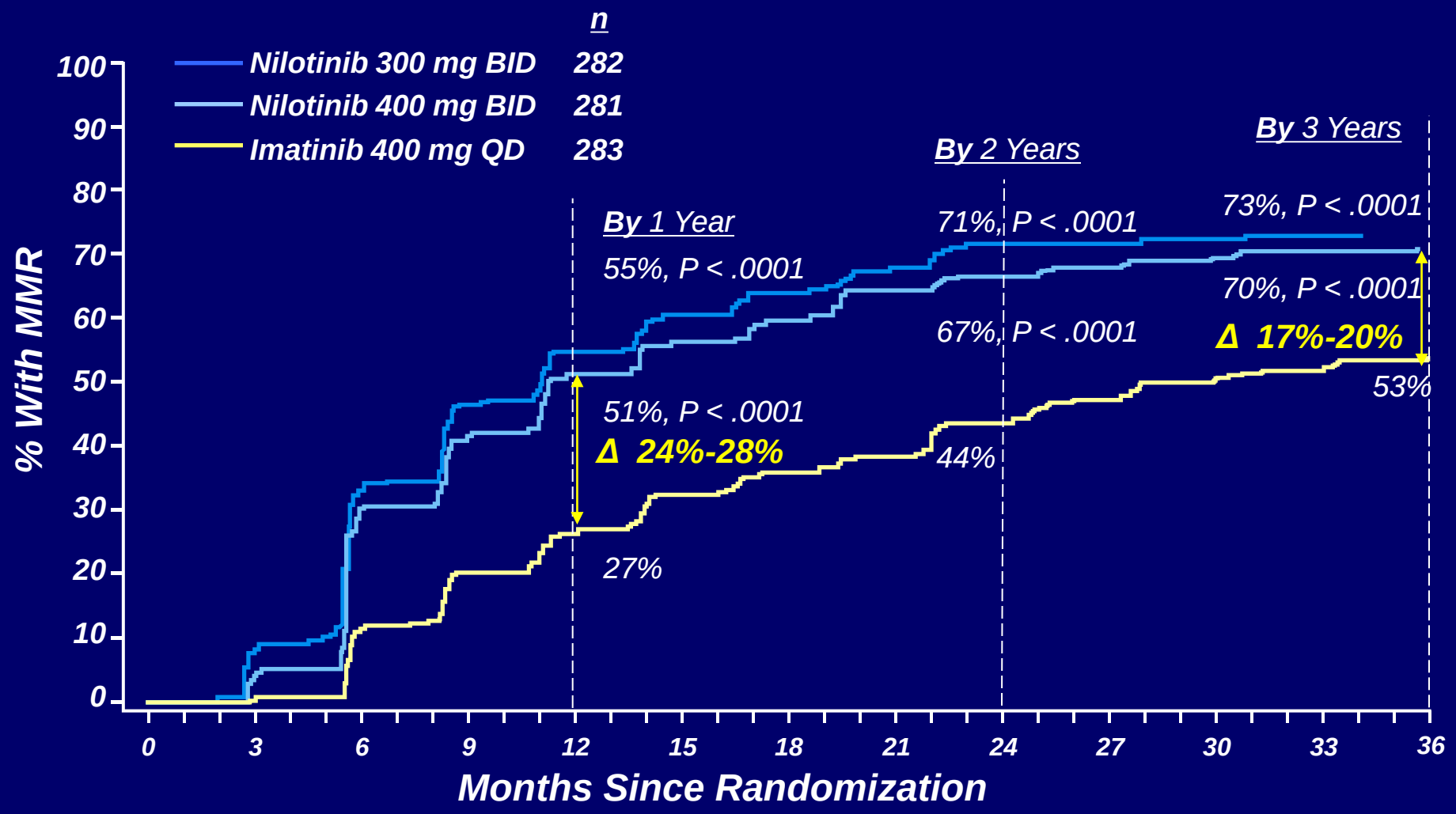
- *N = 846*
- *217 centers*
- *35 countries*



3 years follow-up report at ASH 2011

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

ENESTnd: Cumulative Incidence of MMR

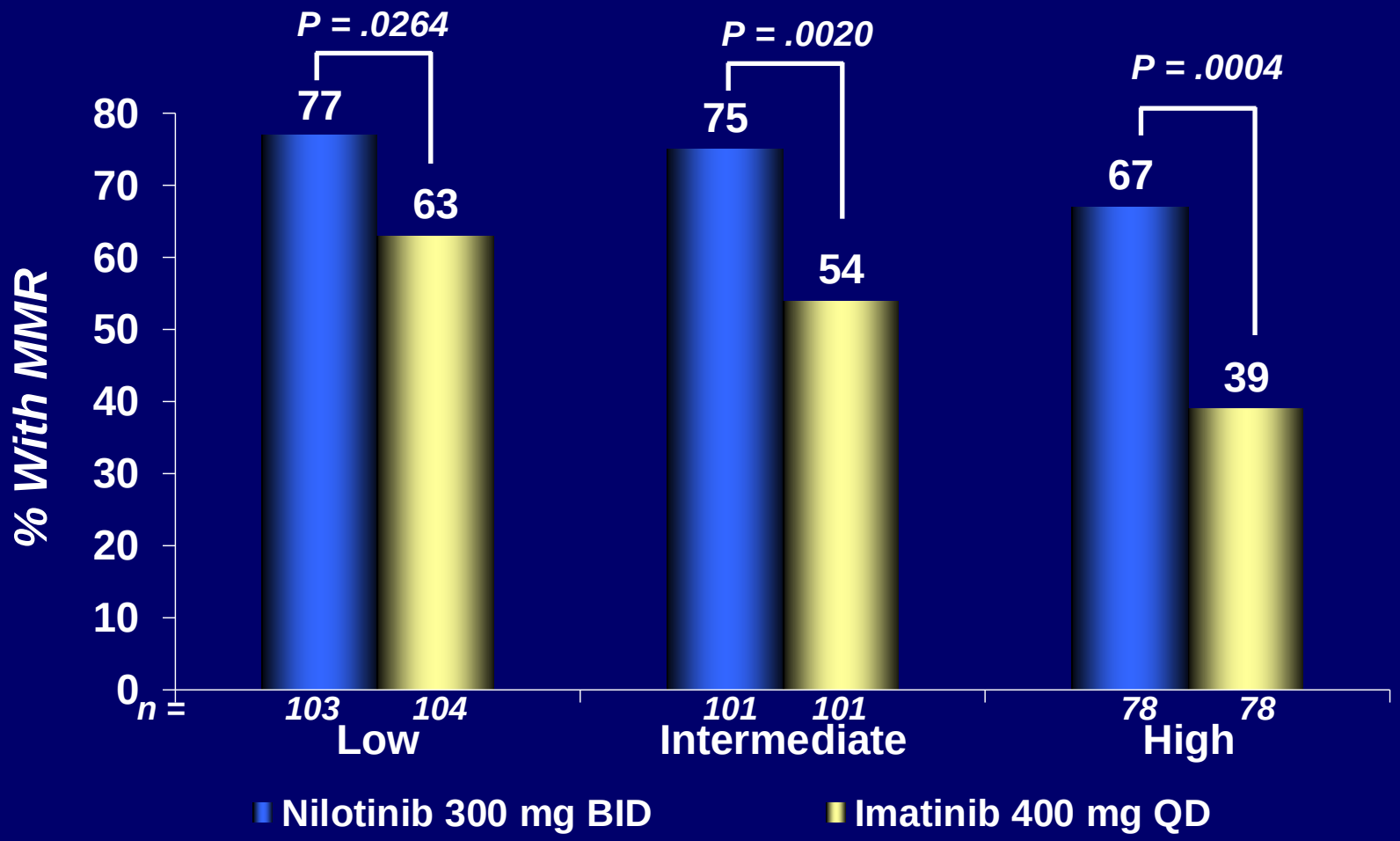


3-5% of patients across treatment arms lost MMR
All nilotinib pts who remained on study after loss of MMR regained MMR

Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

ENESTnd: MMR by 3 Years According to Sokal Risk

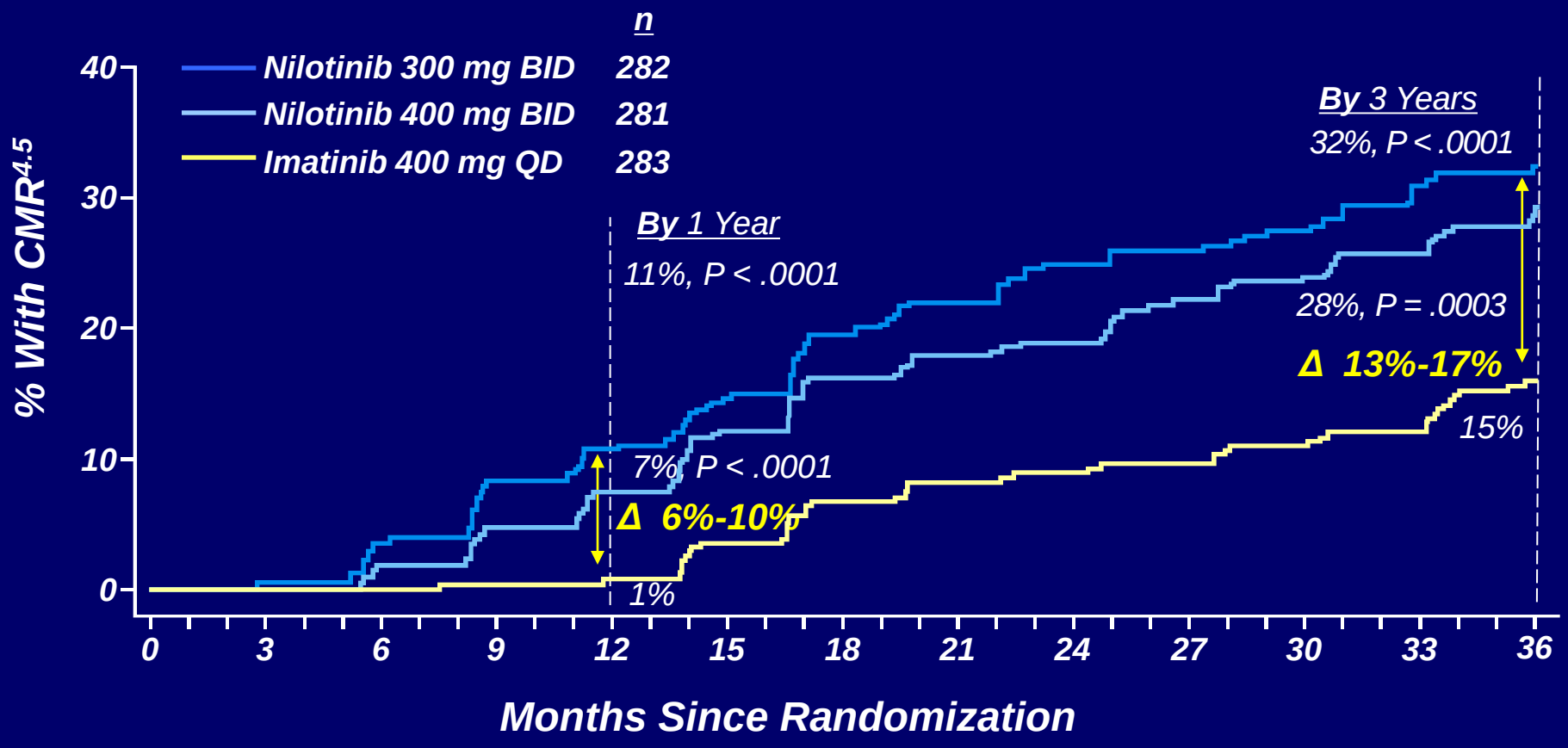


- *Rates of MMR were consistently higher in patients treated with nilotinib vs imatinib across Low, Intermediate, or High Sokal risk scores*

Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

ENESTnd: Cumulative Incidence of MR$^{4.5}$*

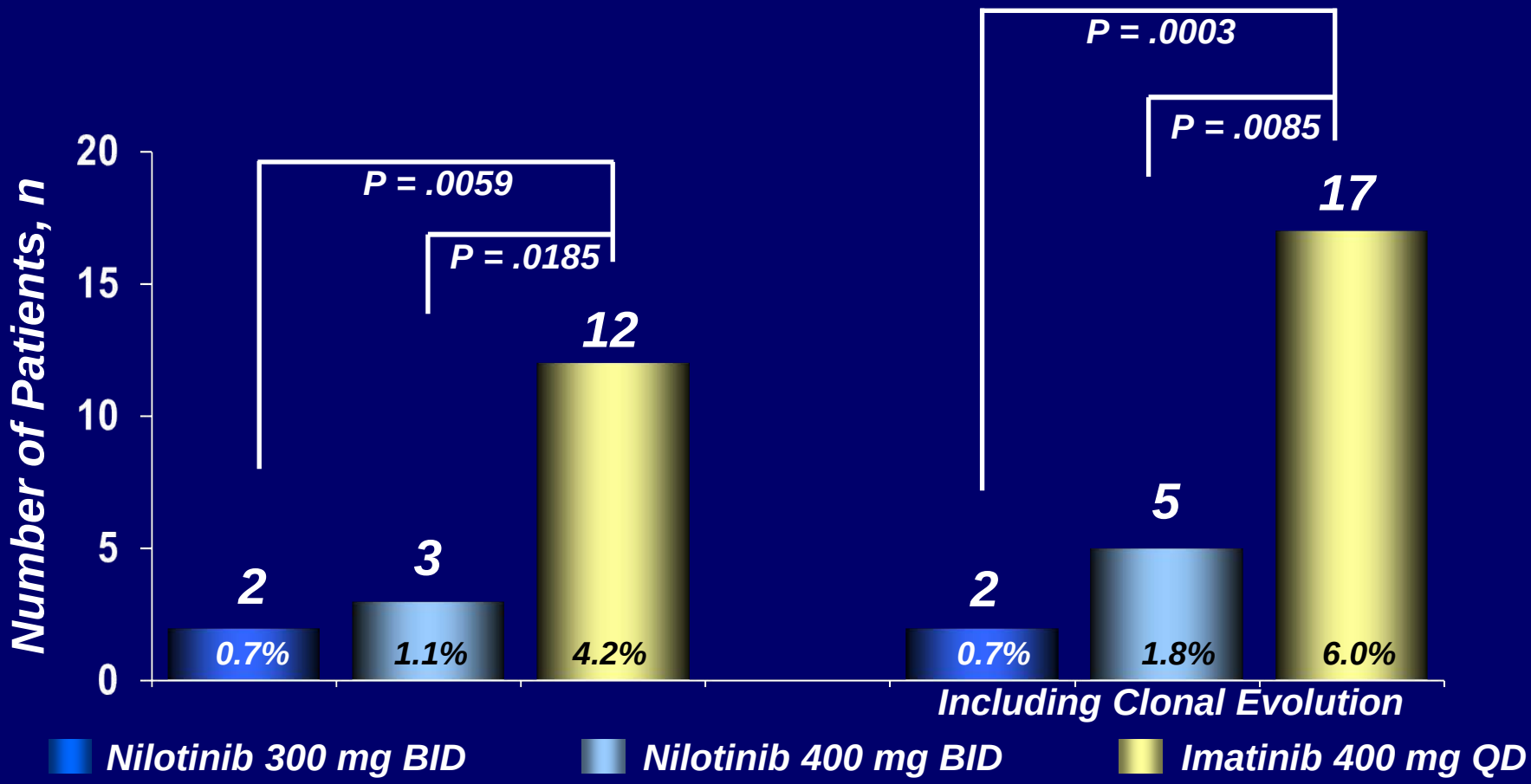


* Equivalent to BCR-ABL transcript levels of ≤ 0.0032% (IS).

Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

ENESTnd 3 Year Update: Progression to AP/BC* on Core Treatment



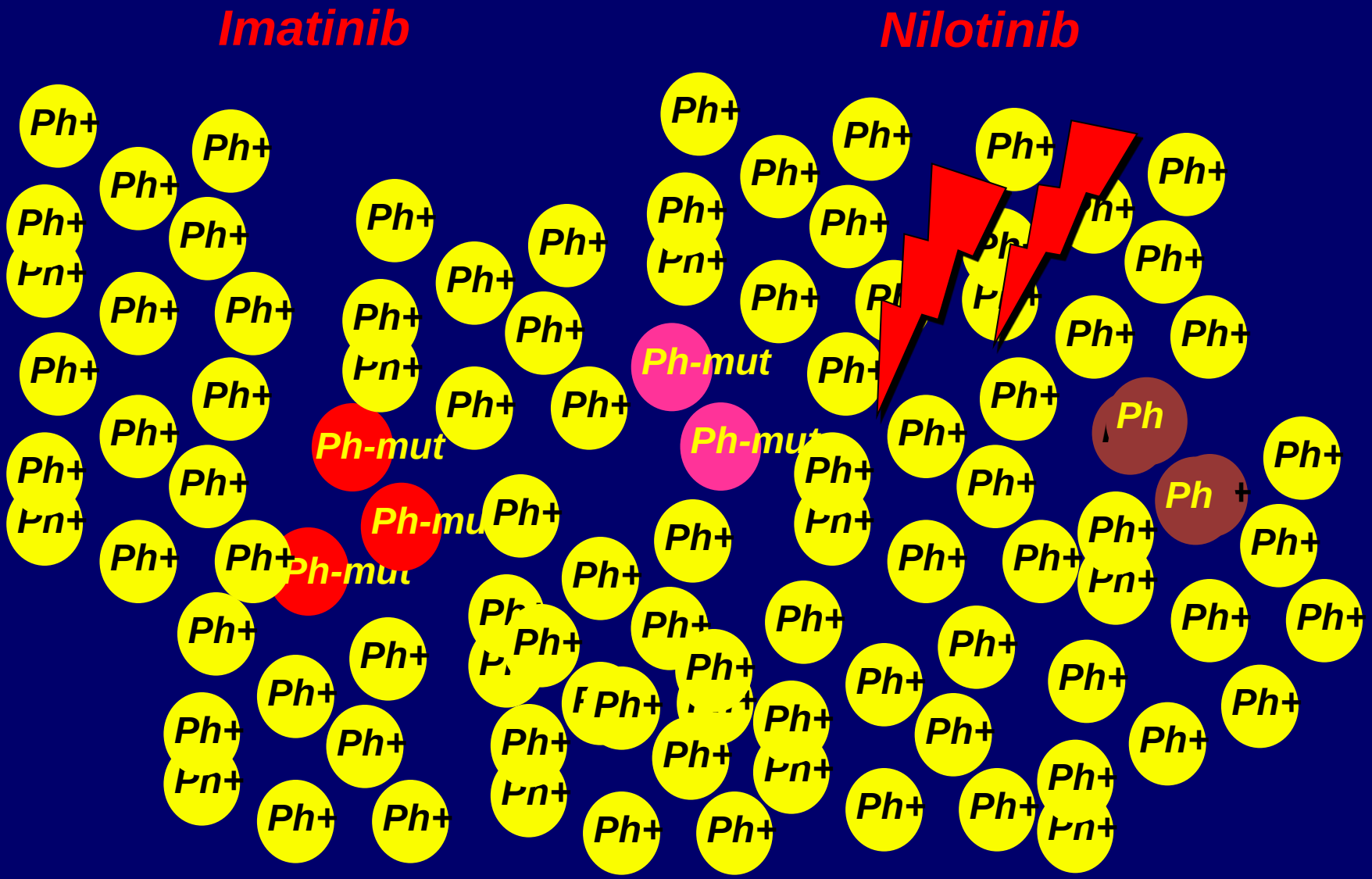
- *No new progressions occurred on core treatment since the 2-year analysis*

** Progression to AP/BC or death following progression.*

Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

What Is the Nature of the Residual Population? Different with Different TKIs?



Progression to AP/BC According to Sokal Risk

	Total	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib n = 283
Progression to AP/BC, n	17	2	3	12
By Sokal Risk, n				
Low	1	0	1	0
Intermediate	10	1	1	8
High	6	1	1	4

- Regardless of treatment, the majority of progressions occurred in patients with intermediate or high Sokal risk scores

Hughes TP, et al. Blood. 2011;118(21):1184-1185 [abstract 2755].

Data cut-off: 27Jul2011.

Emergent Mutations According to Sokal Risk

	Total	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib n = 283
Patients with mutation(s), n	43	11	11	21
By Sokal Risk, n				
Low	4	1	2	1
Intermediate	16	5	3	8
High	23	5	6	12

- Regardless of treatment, the majority of emergent mutations were identified in patients with intermediate or high Sokal risk scores

Hughes TP, et al. Blood. 2011;118(21):1184-1185 [abstract 2755].

Data cut-off: 27Jul2011.

ENESTnd: BCR-ABL Mutations Identified on Treatment

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Patients with mutation(s), n	11	11	21
Mutation category, n			
T315I	3	2	3
Less sensitive to nilotinib*	6	9	4
Other mutations†	2‡	0	14
Multiple mutations §	3	2	3

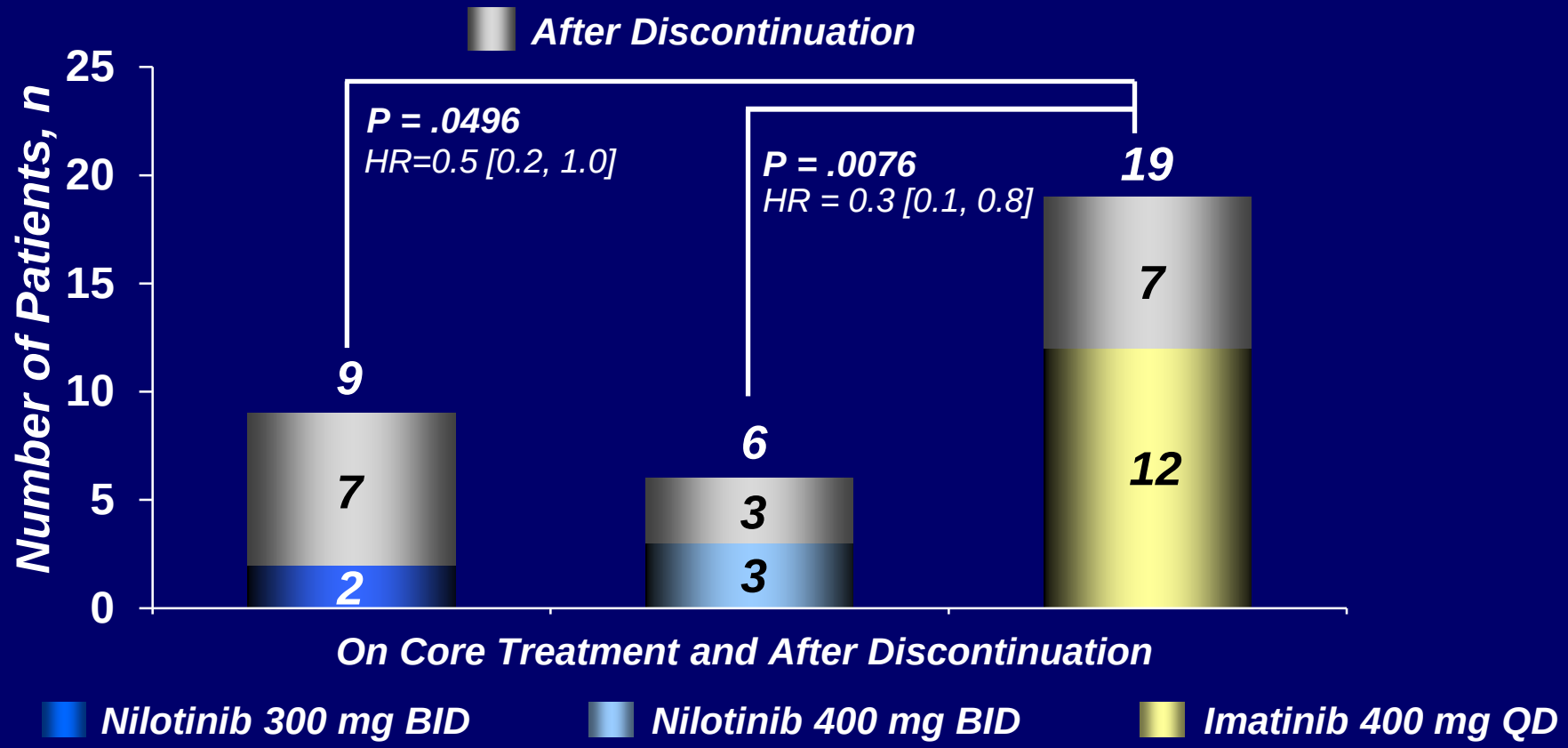
** Mutations less sensitive to nilotinib: E255K/V, Y253H, and F359C/V.*
† All mutations except E255K/V, Y253H, F359C/V and T315I.
‡ Of the 2 nilotinib-treated patients with other mutations, 1 had an E459K mutation and the other had a G250E mutation.
§ Multiple mutations were identified as follows for each arm. Nilotinib 300 mg BID: Y253H/F359V(1), E255K/T315I(1), T315I/F359V(1); Nilotinib 400 mg BID: Q252H/T315I(1), Y253H/T315I(1); Imatinib 400 mg QD: M244V/T315I(1), Y253H/F359I(1), H396R/M351T(1).
Individual mutation totals include patients > 1 mutation.

BID, twice daily; QD, once daily.

Data cut-off: 27Jul2011.

Hughes TP, et al. Blood. 2011;118(21):1184-1185 [abstract 2755].

ENESTnd: Progression to AP/BC: Including Events After Discontinuation (ITT)*



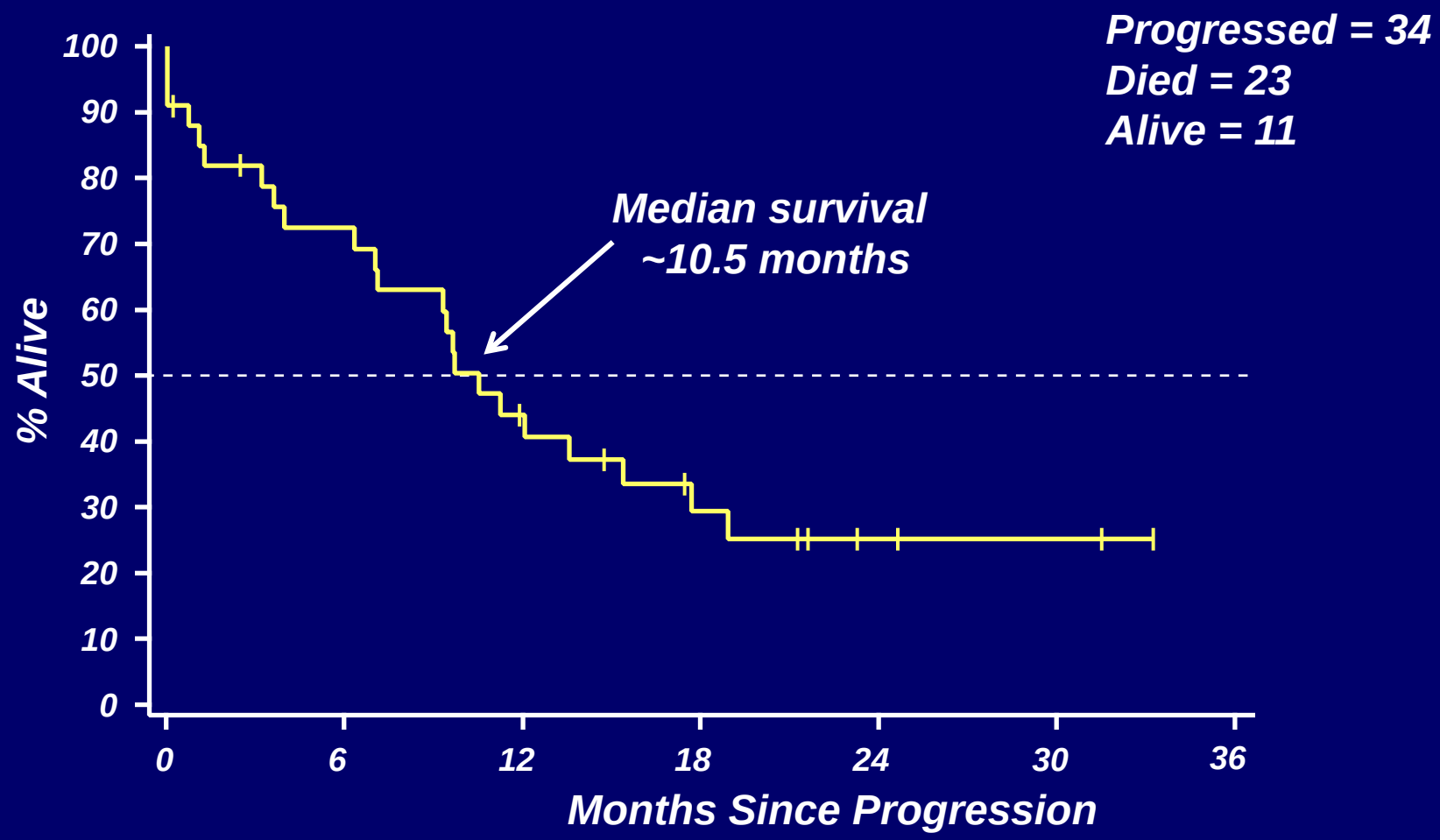
- *Off treatment progression information was prospectively collected for all patients every 3 months after discontinuation*

**Progression to AP/BC or CML-related death.*

Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

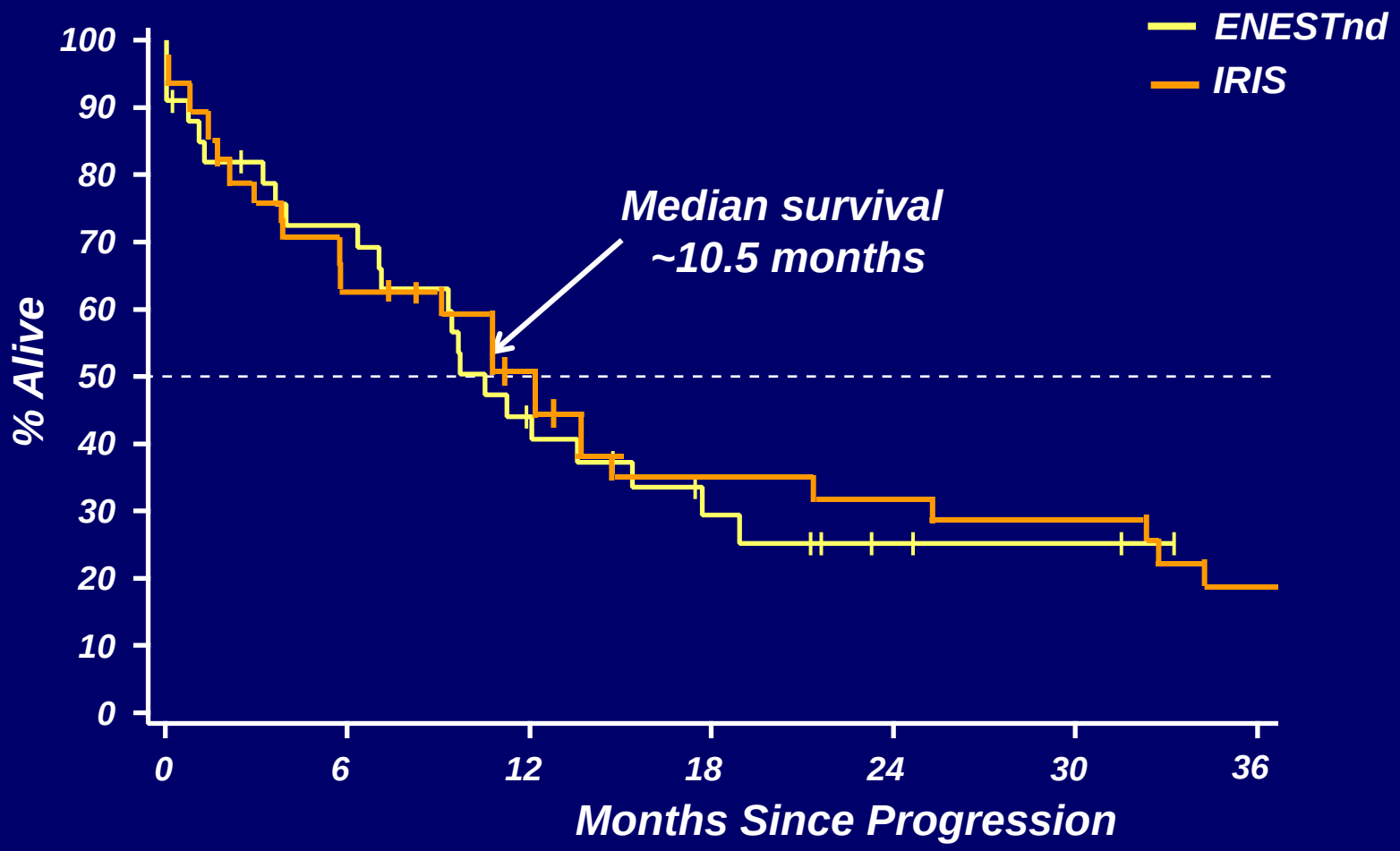
Survival After Progression to AP/BC (ENESTnd)



Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

Survival After Progression to AP/BC (ENESTnd and IRIS)

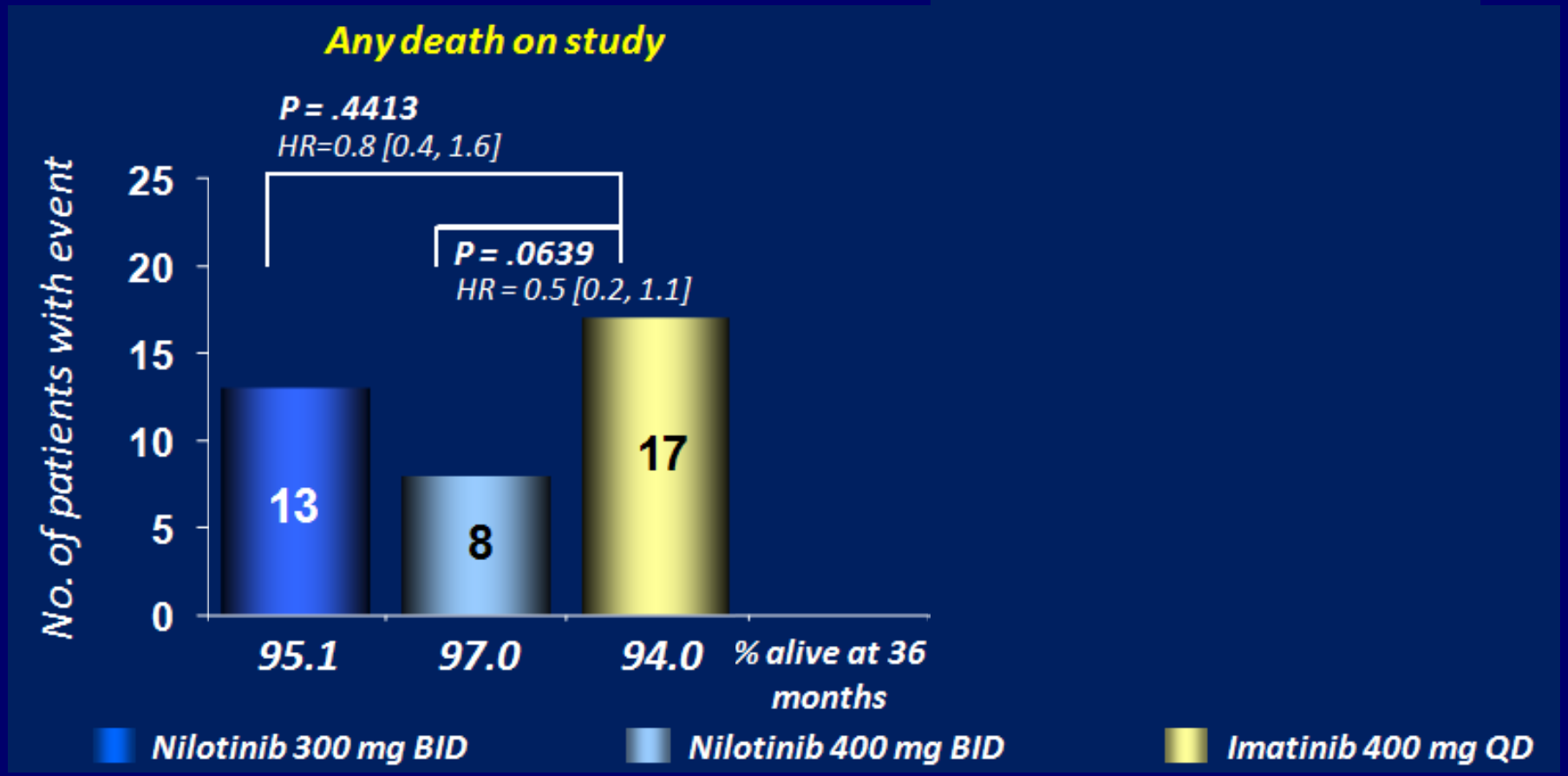


Data cut-off: 27Jul2011.

Clark RE, et al. Haematologica. 2012;97(s1):237 [abstract 0583].

ENESTnd: Overall Survival / CML-Related Deaths

- *Significantly fewer CML-related deaths on nilotinib than on imatinib, better overall survival*



Data cut-off: 27Jul2011.

Saglio et al. Blood. 2011;118(21):208-209 [abstract 452].

DASISION (CA180-056): Study Design

- Treatment-naïve CML-CP patients (N=519)
- 108 Centers
- 26 Countries

Randomized[a]

- Dasatinib 100 mg QD (N=259)
- Imatinib 400 mg QD (N=260)

Long-term follow-up

[a]Stratified by EURO (Hasford) risk score

- **Primary endpoint** Confirmed CCyR (cCCyR) by 1 year

Jabbour et al., EHA 2012

DASISION (CA180-056):NCT00481247;
CCyR = complete cytogenetic response

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

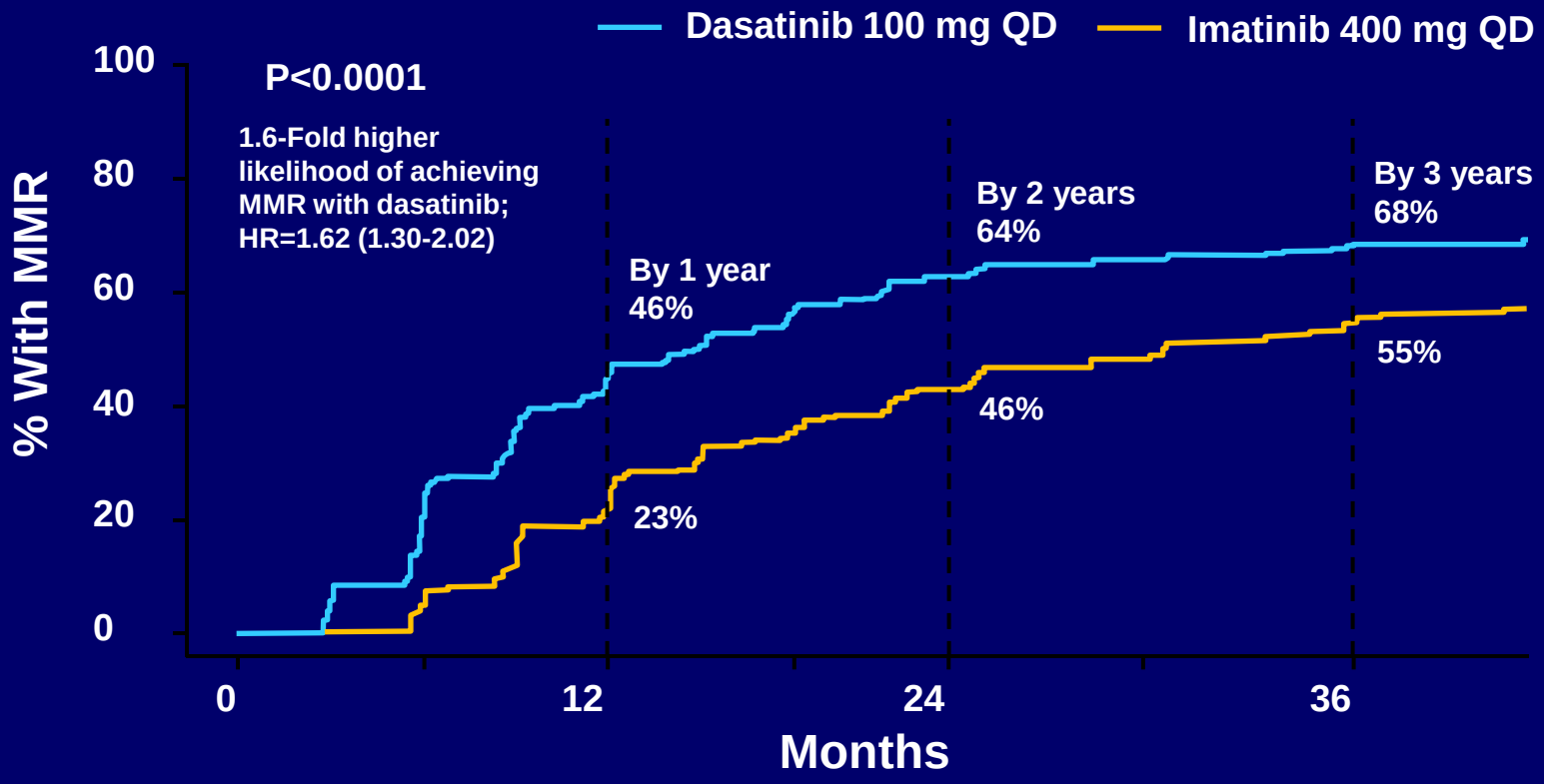
DASISON: Patient Disposition and Discontinuation

	Treated patients, n (%)	
	Dasatinib 100 mg QD N=258	Imatinib 400 mg QD N=258
Still on treatment	183 (71)	179 (70)
Discontinued	75 (30)	79 (31)
Progression[a]	17 (7)	18 (7)
Treatment failure	8 (3)	12 (5)
Adverse event (AE)	27 (11)	16 (6)
Nonhematologic	20 (8)	12 (5)
Hematologic	7 (3)	4 (2)
Unrelated AE	6 (2)	2 (<1)
Death[b]	4 (2)	1 (<1)
Poor/nonadherence	0 (0)	4 (2)
Other[c]	13 (5)	26 (10)

[a]Increasing WBC count; loss of CHR; loss of MCyR, including 30% rise in Ph+ metaphases and additional chromosomal abnormalities; or progression to AP/BP
[b]nDiscontinuation due to death, which represents a subset of total deaths: 17 deaths overall in dasatinib arm, 20 deaths in imatinib arm
[C]Includes consent withdrawal, loss to follow-up, pregnancy, patient request, and poor/nonadherence

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

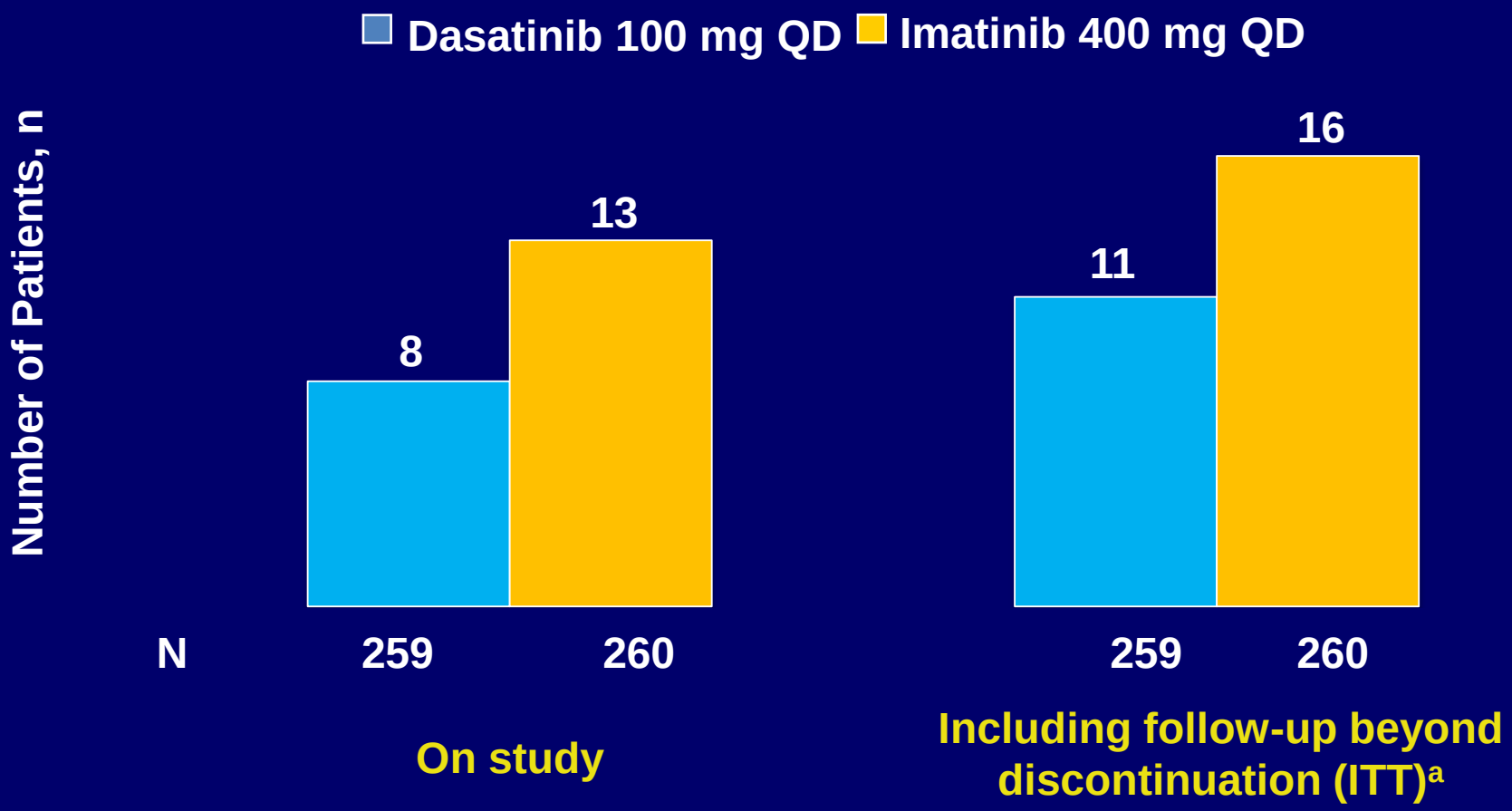
DASISION: Cumulative Incidence of MMR (BCR-ABL ≤0.1%)



MMR 3-y cumulative rates	Hasford Risk Score		
	Low	Intermediate	High
Dasatinib	83%	65%	61%
Imatinib	65%	57%	43%

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

DASISION: Transformation To AP/BP CML by 3 Years



[a]Yearly evaluations after discontinuation are currently stipulated per protocol; additional information on patient status may be provided by investigators at other times

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

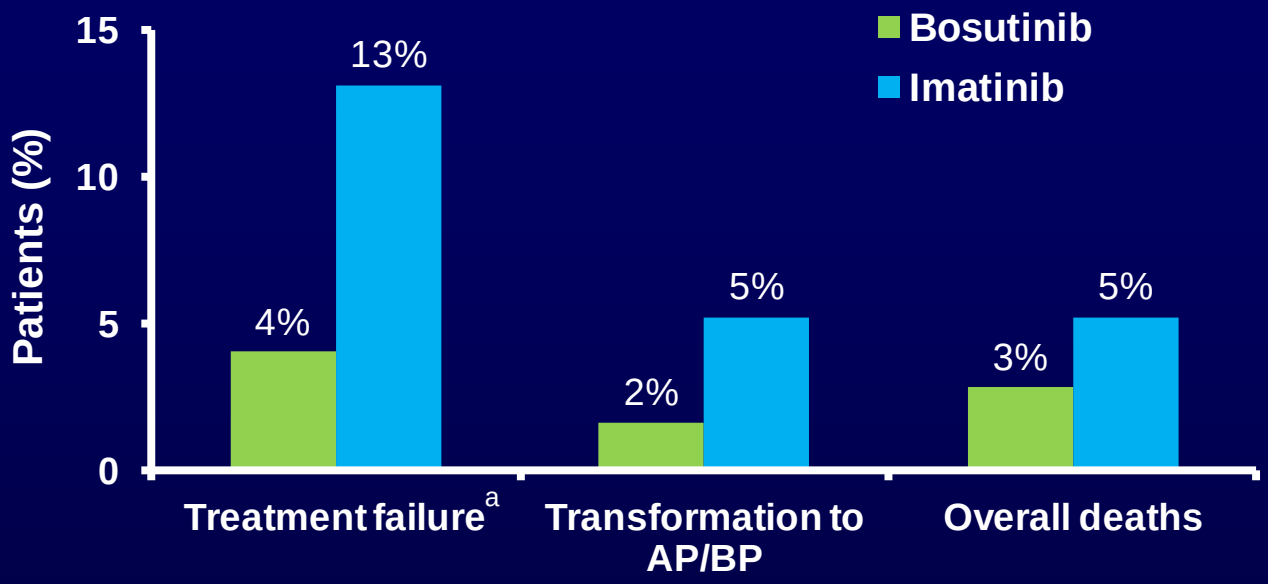
DASISION: Overall Survival (OS) and Progression Free Survival (PFS)

	Dasatinib 100 mg QD N=259	Imatinib 400 mg QD N=260	Hazard ratio
Total number of deaths,[a] n	17	20	-
Estimated 3-year OS, %	93.7 (90.6-96.7)	93.2 (90.1-96.4)	HR=0.86 (0.45-1.65)
Estimated 3-year PFS, %	91.0 (87.4-94.7)	90.9 (87.1-94.6)	HR=1.00 (0.55-1.80)

[a]On study treatment and in follow-up after discontinuation of randomized treatment

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

BELA – Rates of Treatment Failure: ITT Population

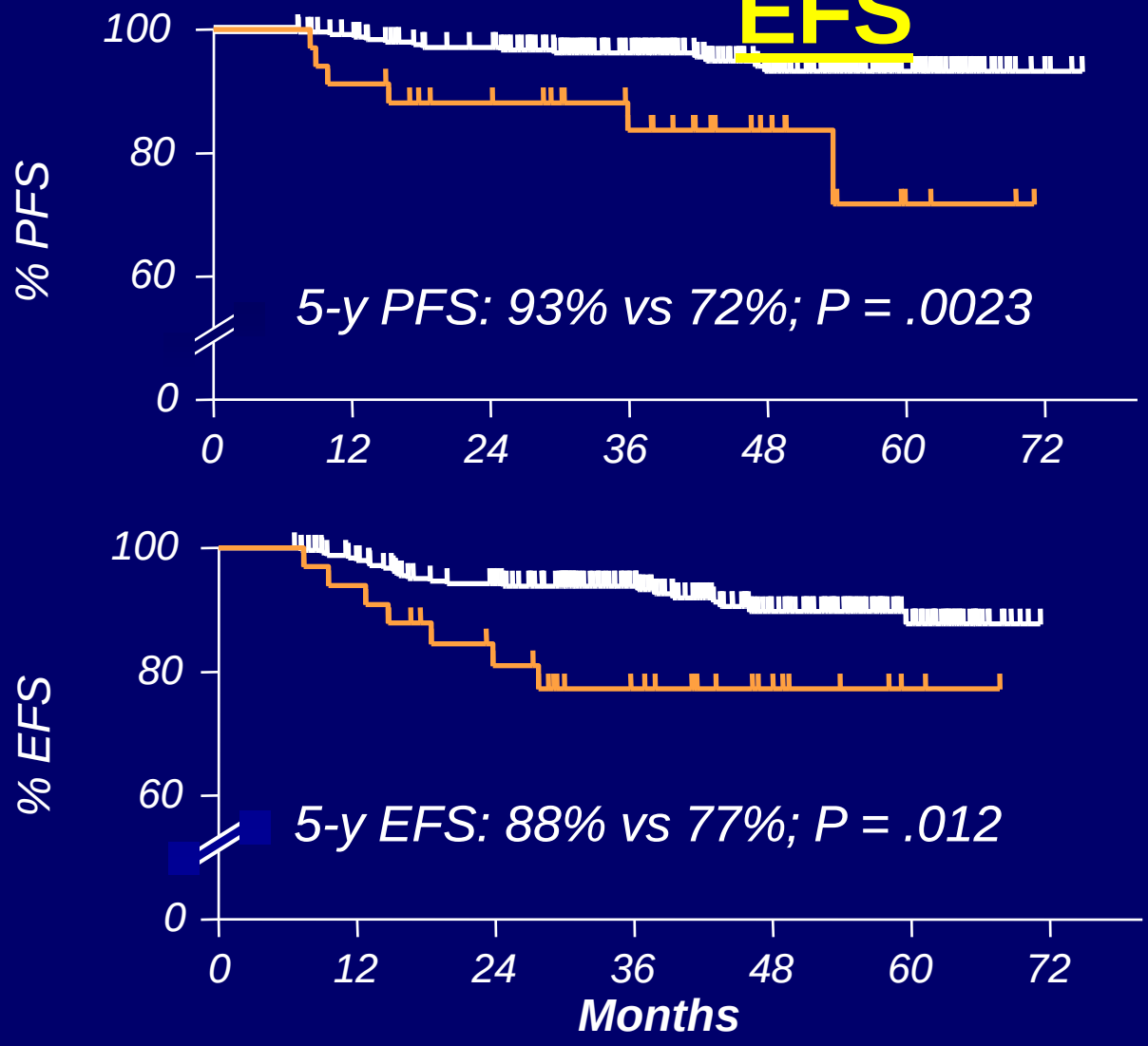


AP, accelerated phase; BP blast phase.
[a]Treatment failure/disease progression includes both on-treatment transformation to AP/BP and lack of efficacy.
Patients were followed for up to 8 years from randomization (treatment plus long-term follow-up phases).

- No new on-treatment transformations to AP/BP CML have occurred on bosutinib since the 12-month primary analysis, compared with 3 new events on imatinib
- The majority of deaths (bosutinib, n = 5/7; imatinib, n = 9/13) occurred more than 28 days after treatment discontinuation
  - Deaths due to CML progression occurred in 6/7 patients receiving bosutinib and 10/13 patients receiving imatinib

Cortes JE, et al. Blood. 2011;118(17):4567-4576

Degree of Molecular Response at Early Timepoints Predicts PFS and EFS



BCR-ABL% (IS) at 3 months

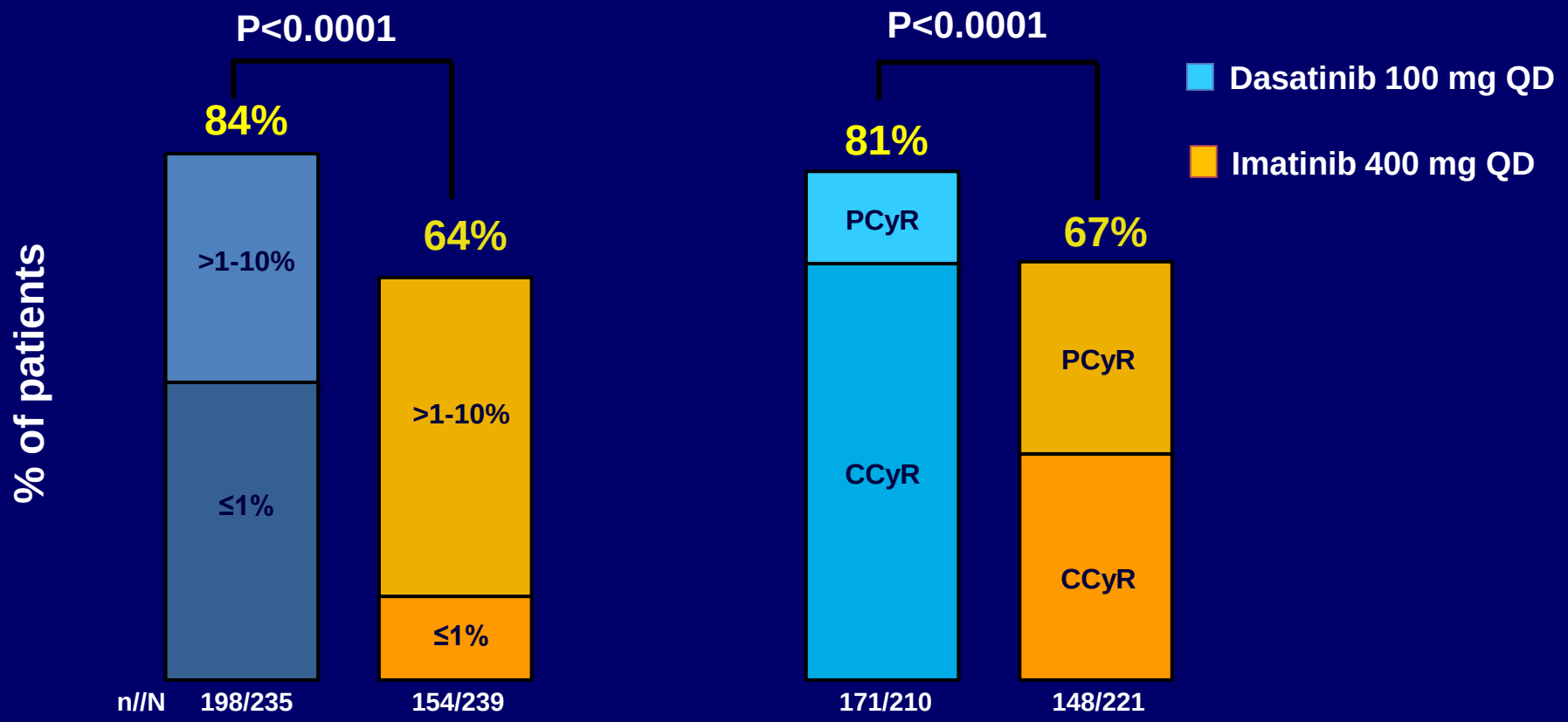
< 10%

>10%

Patients randomized to imatinib-based therapies in the German CML Study IV

Hanfstein B et al. EHA 2011

DASISION: Molecular and Cytogenetic Response at 3 Months[a]



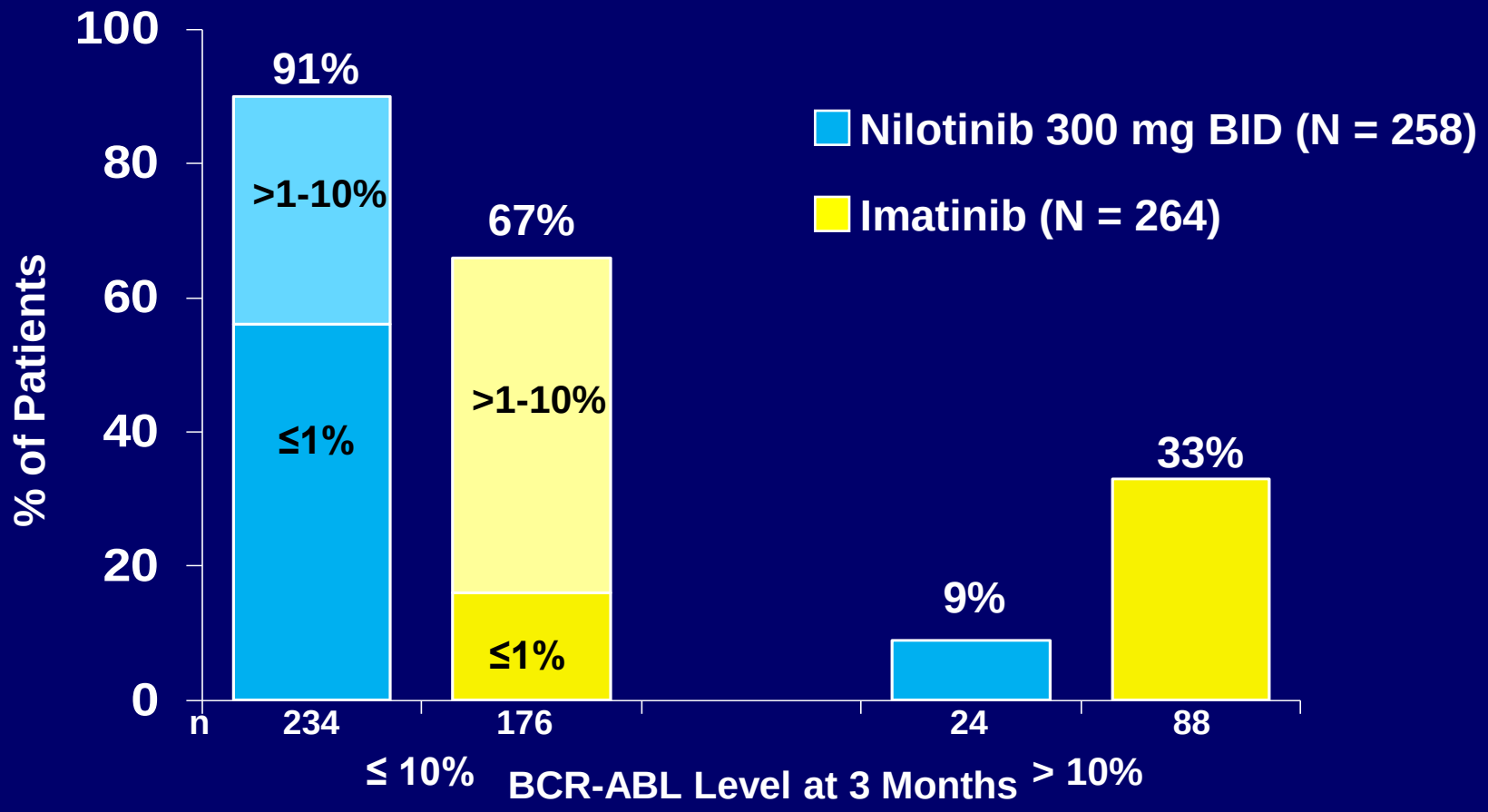
≤10% BCR-ABL at 3 Months **PCyR/CCyR at 3 Months**

- BCR-ABL of <10% and ≤1% are not fully concordant with ≥PCyR and CCyR, respectively
  - 96% and 83% of dasatinib and imatinib pts with ≥PCyR had <10% BCR-ABL, respectively
  - 68% and 26% of dasatinib and imatinib pts with CCyR had ≤1% BCR-ABL, respectively

[a] Calculated from total number of evaluable patients with PCR assessments at 3 months; restricted to subjects with B2A2 and B3A2 transcripts

Jabbour J, et al. *Haematologica*. 2012;97(s1) [abstract 1106].

ENESTnd: BCR-ABL Categories at 3 Months*



- Reasons for unevaluable samples:
  - Atypical transcripts: 5 patients on nilotinib, 2 patients on imatinib
  - Missing samples: 4 patients on nilotinib, 5 patients on imatinib
  - Discontinued: 15 patients (incl.1 progression) on nilotinib, 12 patients (incl.1 progression) on imatinib
- PFS/OS events prior to 3 months: 1 PFS event in each arm, no deaths

Hochhaus A, et al. Haematologica. 2012;97(s1):237 [abstract 0584].

Advantages of Second Generation TKIs With Respect to Imatinib

- ✓ Faster and deeper responses
- ✓ Less progression events
- ✓ Earlier identification of patients with inferior outcome
- – Higher and faster possibilities of treatment discontinuation?

Potential Options for CML First-line Therapy

- Imatinib or 2nd generation TKIs as first-line therapy?
- 2nd generation TKIs only for specific groups of patients like patients at a higher risk of progression, younger patients, etc…… ?
- Still imatinib 400mg as initial therapy for most patients and than early switch to 2nd-gen TKIs in case of non-optimal response?

? ELN 2013 ?

Non optimal response to Imatinib → 2nd gen. TKIs

Clinical benefit?

Non optimal response to 2nd gen. TKIs → ???

3rd generation TKIs (like ponatinib)?
AlloSCT for specific patients?
Combination therapies?

Thank you!