New drugs in first-line therapy

Gianantonio Rosti
Dept of Hematology and Oncology “Seràgnoli”, Bologna University (Italy)

GIMEMA
(Gruppo Italiano Malattie Ematologiche dell’ Adulto)
CML WORKING PARTY

IRIS Trial: 8 Year Follow-up on Imatinib

- Among pts randomized to imatinib, after 8 years:
  - 81% event-free survival
  - 85% overall survival
  - 86% had achieved MMR
  - 92% did not progress to AP/BC
- Rate of progression to AP/BC in yrs 4 to 8 was:
  - 0.9%, 0.5%, 0%, 0%, 0.4%.
- **No pt in MMR at 12m subsequently progressed**

Deininger M, et al. Blood. 2009;114(22):142. Abs # 1126 (Poster).

This does not add up to 100%!!

WE WANT “100%”!!!

Postulate 1 (Pessimistic Vision)

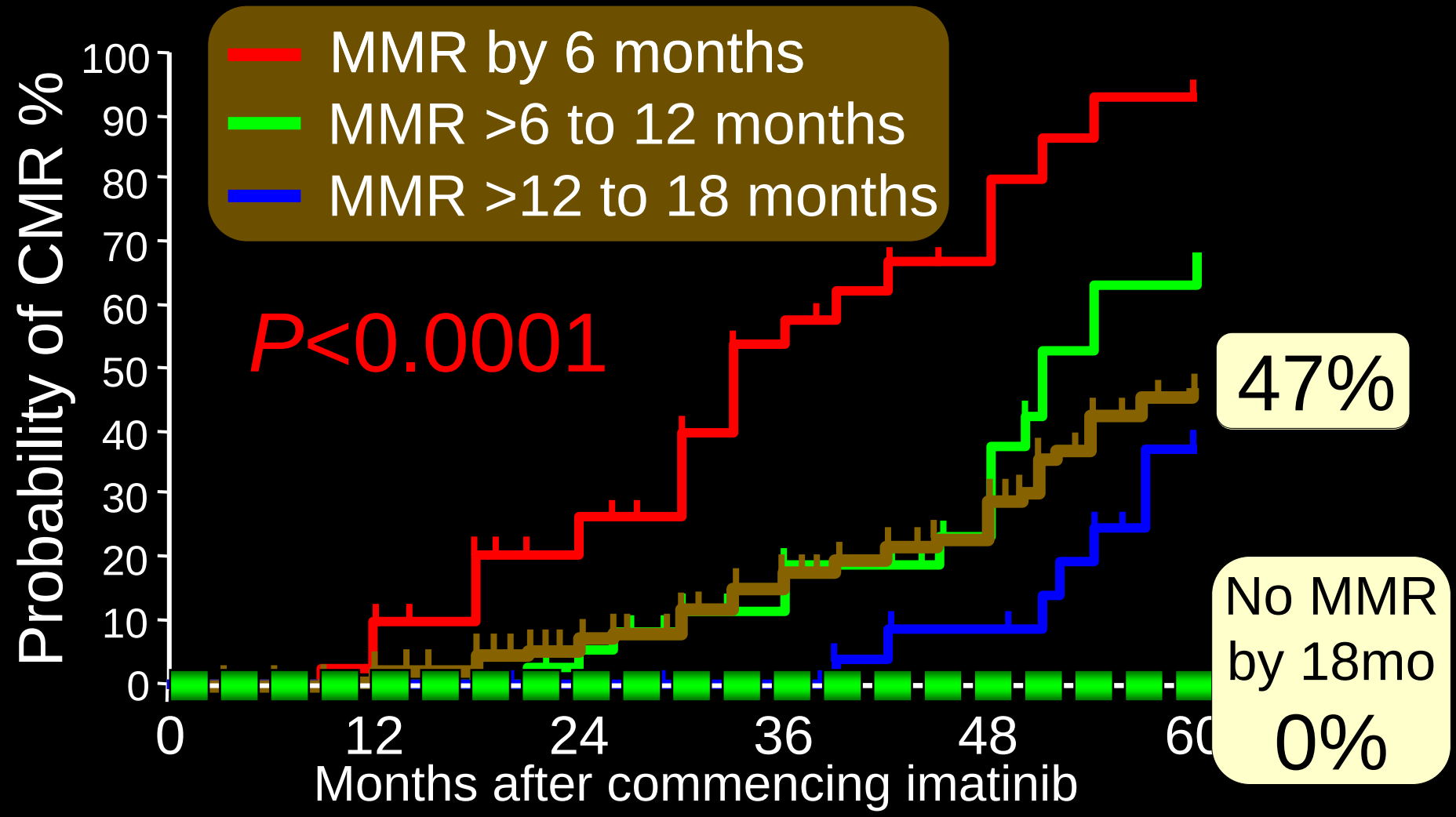
- Some Ph+ CML are intrinsically TKI resistant and it does not matter how fast the response is

Postulate 2 (Optimistic, Realistic? Vision)

- Most patients are sensitive to TKIs at the onset and an early response reduces the risk of upfront resistance and late progression

Probability of CMR by 60 months

181 de-novo patients 400/600 mg imatinib (Adelaide)



Branford et al. Blood. 2008:112. Abstract 2113.

Less Targeted Strategy

Nilotinib targets DFG-out ABL & is BCR-ABL selective
Dasatinib binds DFG-in & is unselective

Imatinib	DDR-1/-2	>	PDGFR	>	KIT	>	BCR-ABL	> SRC
(IC_{50} nM)	43 / 141		72		97		221	>1000 nM
Nilotinib	DDR-1/-2	>	BCR-ABL	>	PDGFR	>	KIT	> SRC
(IC_{50} nM)	4 / 5		20 nM		71 nM		207 nM	>1000 nM
Dasatinib	SRC	>	DDR-1/-2	>	BCR-ABL	>	PDGFR	> KIT
(IC_{50} nM)	0.1 nM		1.3 / 5.2		1.8 nM		2.9 nM	18 nM

Manley *et al*. Biochim Biophys Acta 2010;1804:445; Fabian *et al*. Nature Biotech. 2005;23:329;
Karaman *et al*. ibid 2008;26:127

Patients Achieving MMR on 2nd-Generation TKIs used in First-Line Therapy

% of Patients Achieving MMR		
	6 months	12 months
Nilotinib (GIMEMA)[1]	66%	85%
Nilotinib (MDACC)[2]	75%	81%
Dasatinib (MDACC)[3]	64%	74%

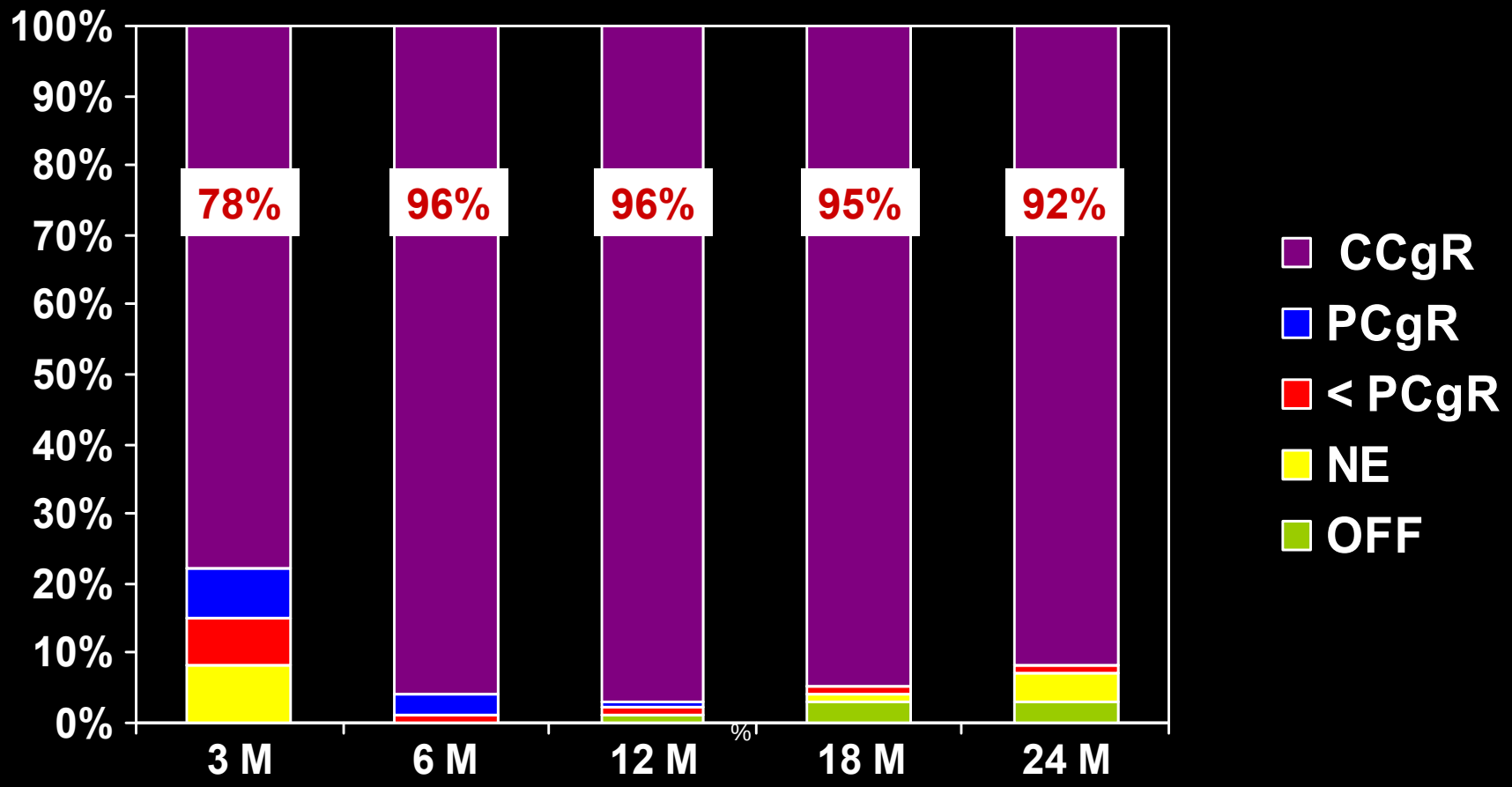
1. Rosti G, et al. Haematologica. 2009;94(s2):440 [abstract 1090] (oral).
2. Cortes J, et al. Blood. 2009;114(22):144-145 [abstract 341] (oral).
3. Cortes J, et al. Blood. 2009;114(22):144-145 [abstract 338] (oral).

Patients

(18 Centres enrolled ≥ 1 pt between Jun 2007 and Feb 2008)

	N = 73	
Age, years; median (range)	51 (18-83)	
65 years or older	20 (27%)	
Males	37 (51%)	
Relative Risk	**Sokal**	**Hasford**
• Low	33 (45%)	29 (40%)
• Intermediate	30 (41%)	43 (59%)
• High	10 (14%)	1 (1%)
Variant Translocations	10 (14%)	
CCA Ph+	3 (4%)	
Der(9) deletions	7 (10%)	
Prior Hydroxyurea	53 (73%)	
Follow-up, months; median (range)	27 (24-33)	

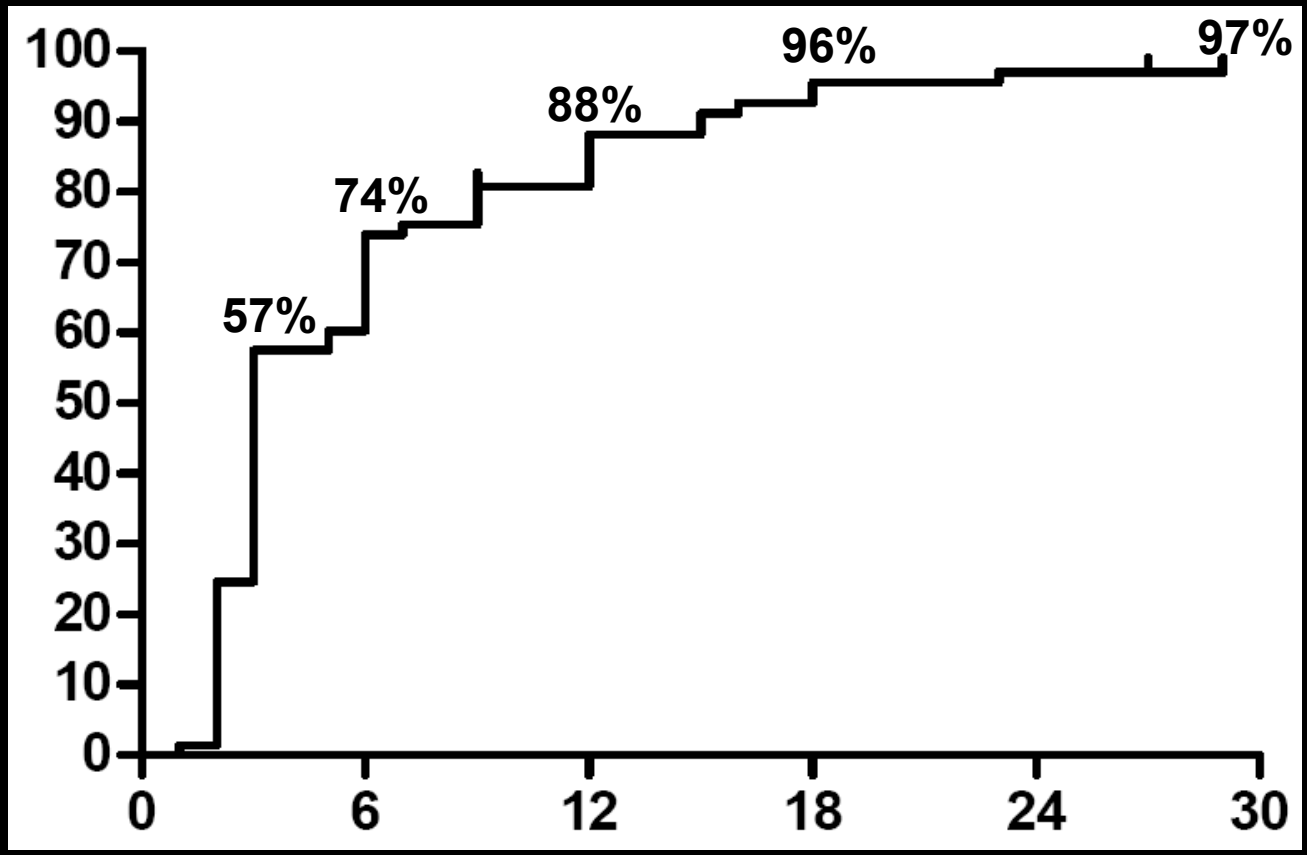
Complete Cytogenetic Response (ITT)



GIMEMA Protocol CML 0307

GIMEMA CML WP

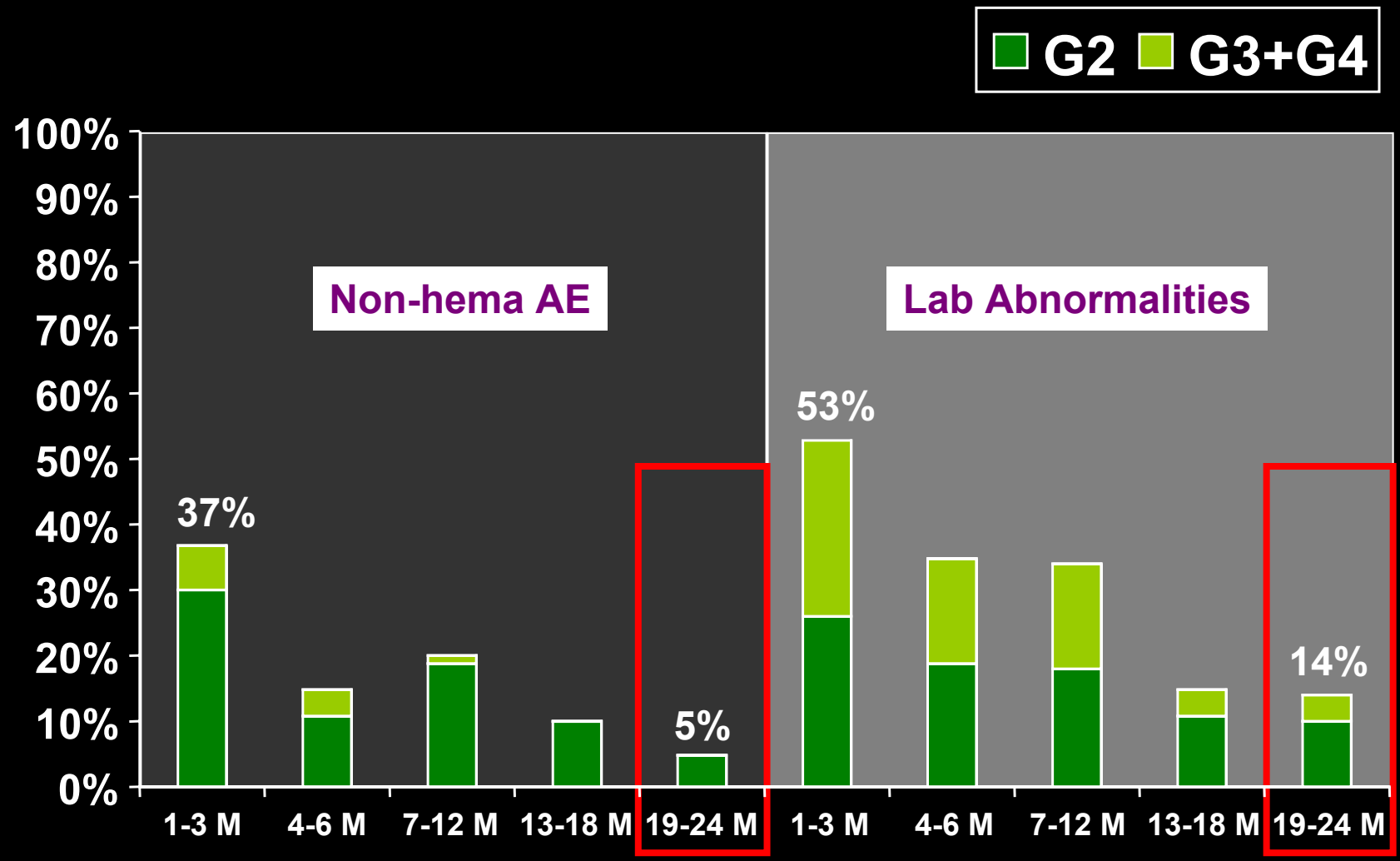
Time to MMR^{IS}



Patient Disposition (N = 73)

Median Follow-up 27 months (24-33 months)	N (%)
Ongoing treatment	68 (93)
Discontinued treatment	5 (7)
• Disease progression	1 (1)
• Lipase increase	3 (4)
• Atrial fibrillation	1 (1)
• On imatinib second line	3 (4)
• On dasatinib third line	1 (1)
• Death	1 (1)

Non-Hematologic Toxicity by Period
Incidence - Maximum Grade (N=73)

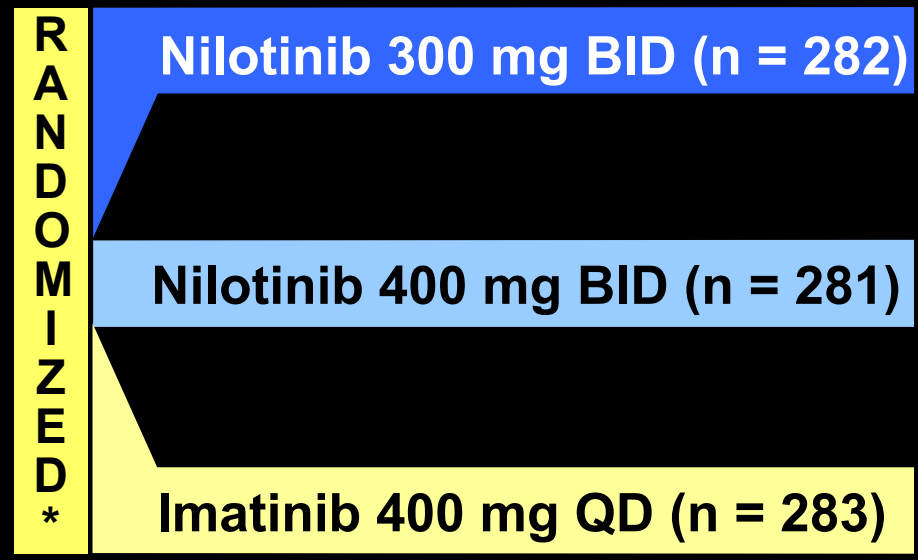


GIMEMA Protocol CML 0307

GIMEMA CML WP

Study Design and Endpoints

- N = 846
- 217 centers
- 35 countries

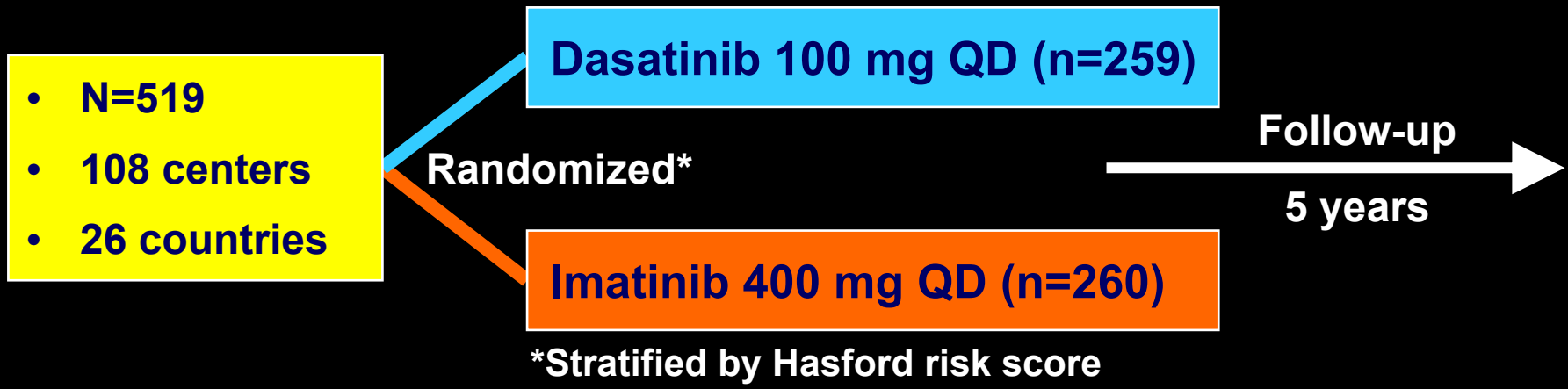


- Primary endpoint: MMR at 12 months
- Key secondary endpoint: Durable MMR at 24 months
- Other endpoints: CCyR by 12 months, time to MMR and CCyR, EFS, PFS, time to AP/BC on study treatment, OS including follow-up

***Stratification by Sokal risk score**

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

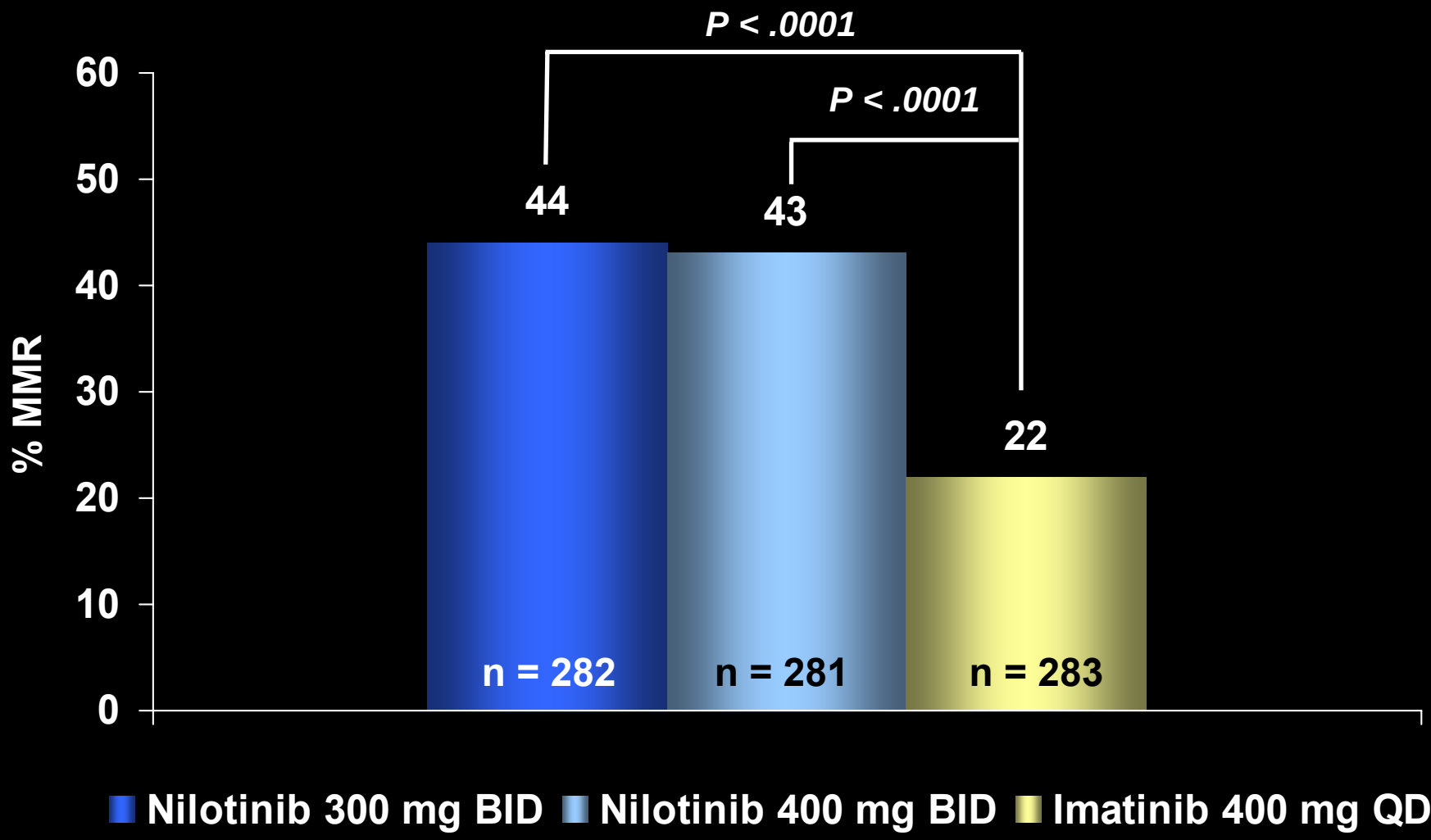
Dasatinib Versus Imatinib Study In Treatment-naïve CML: DASISION (CA180-056)



- **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 (measure of durability)
  - Progression-free survival
  - Overall survival

QD = once daily

Primary Endpoint - MMR Rate at 12 Months (ITT Population)*

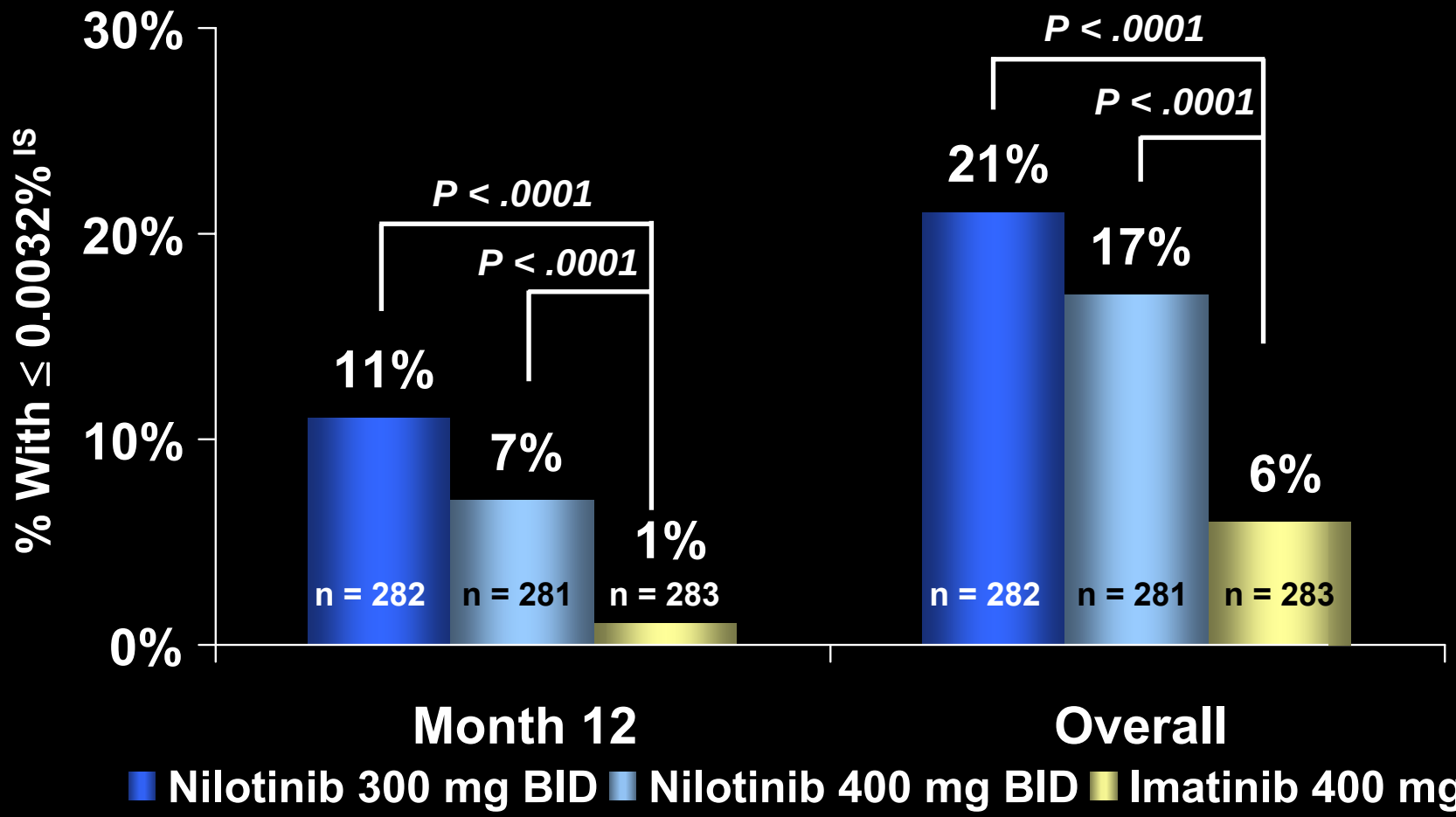


*Saglio G, et al. *NEJM*. E-pub ahead of print 5 June 2010.

Data cut-off: 2Sept2009

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

Rates of Molecular Response of ≤ 0.0032%^{IS}* by 12 Months and Overall

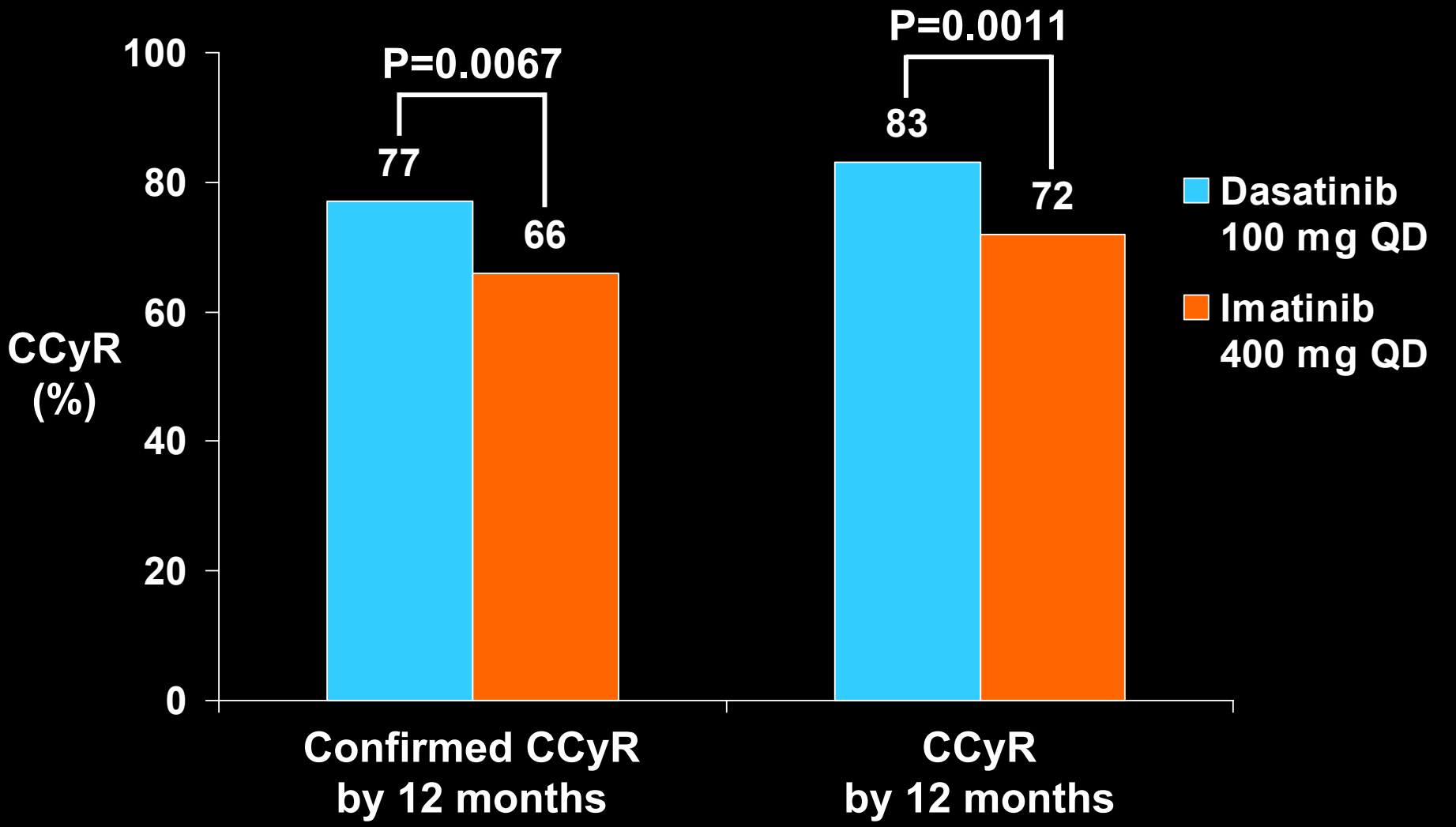


*ITT population

Data cut-off: 2Jan2010

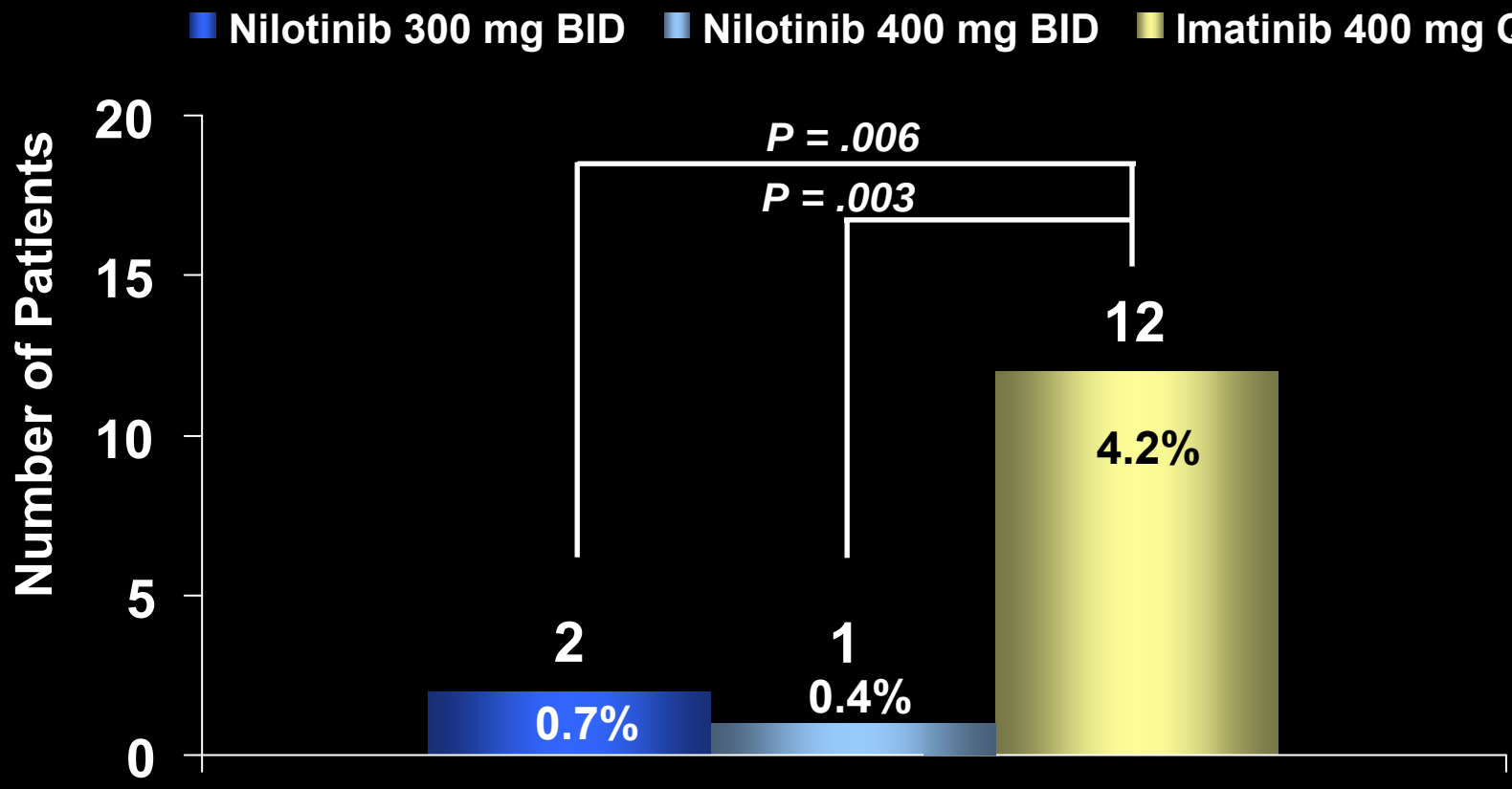
Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

CCyR Rate By 12 Months Was Superior For Dasatinib Over Imatinib



EHA 2010, Abstract # 725

Progression to AP/BC on Study Treatment*



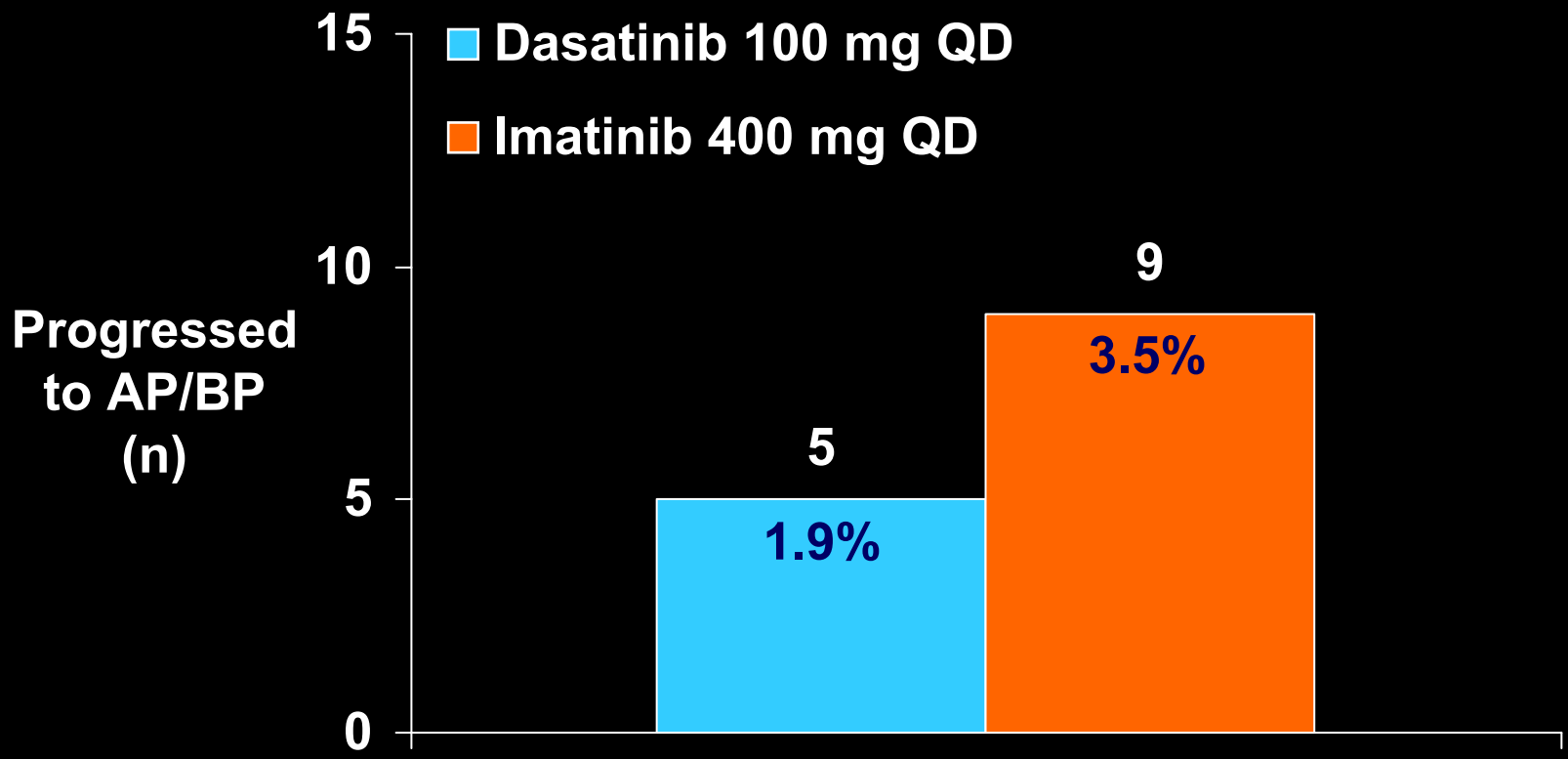
With a median follow-up of 18.5 months.
P-values are based on log-rank test stratified by Sokal risk group vs imatinib for time to AP/BC.

*ITT population

Data cut-off: 2Jan2010

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

Progression To Accelerated Or Blastic Phase



- No patient who achieved MMR progressed to accelerated or blast phase
- 2 patients who achieved CCyR progressed to accelerated or blast phase (1 with dasatinib, 1 with imatinib)

EHA 2010, Abstract # 725

Nilotinib and Dasatinib in Newly Diagnosed CML-CP: (QTcF data)

These data are from separate studies

Study	ENESTnd Nilotinib 300 mg BID (n = 282)[a]	ENESTnd Nilotinib 400 mg BID (n = 281)[a]	ENESTnd Imatinib 400 mg QD (n = 283)[a]	DASISION Dasatinib 100 mg QD (n = 259)[b]	DASISION Imatinib 400 mg QD (n = 260)[b]
QT >500 msec	0	0	0	0.4	0.4
QTcF increase from baseline > 60 ms	<1	<1	0	5[c]	5[c]

a. Saglio G, et al. N Engl J Med. E-pub ahead of print 5 June. 2010.
b. Kantarjian/Shah, et al. *N Engl J Med*. E-pub ahead of print 5 June. 2010.
c. Kantarjian H, et al. ASCO 2010 oral presentation.

Study Drug-Related Non-laboratory Adverse Events (≥ 10% in Any Group)

% of Patients Treated	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	33	0
Muscle spasms	7	0	6	<1	26	<1
Diarrhea	8	<1	6	0	24	1
Vomiting	5	0	9	1	16	0
Rash	32	<1	37	3	12	1
Headache	14	1	22	1	8	0
Pruritus	15	<1	13	<1	5	0
Alopecia	8	0	13	0	4	0
Myalgia	10	<1	10	0	10	0
Fatigue	11	0	9	<1	9	<1

Data cut-off: 2Jan2010

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

Study Drug-Related Fluid Retention (All Grades)

% of Patients Treated	Nilotinib 300 mg BID n = 279	Nilotinib 400 mg BID n = 277	Imatinib 400 mg QD n = 280
Peripheral edema	5	6	14
Eyelid edema	<1	2	14
Periorbital edema	<1	<1	13
Facial edema	<1	2	9
Weight gain	3	1	6
Pericardial effusion	<1	0	<1
Pleural effusion	<1	0	0

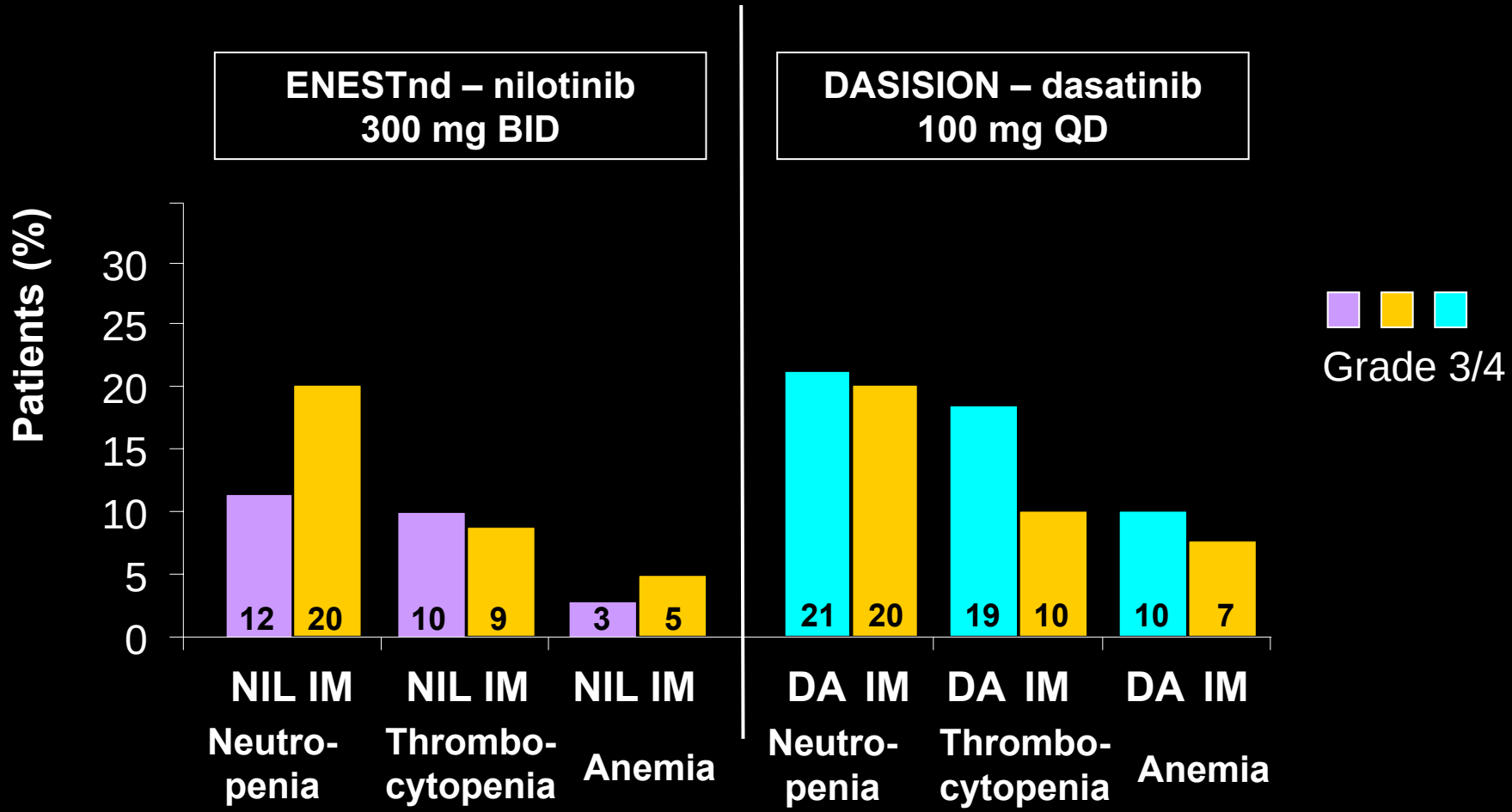
- Grade 3/4 AEs were rarely observed in any treatment arm (<1%)
- There was no clinically relevant prolongation in QT interval or decrease in LVEF

Data cut-off: 2Jan2010

Larson R. A. et al.JCO 28:7s ASCO 2010 (suppl; abs 6501, Oral)

These data are from separate studies

Nilotinib* and Dasatinib** in Newly Diagnosed CML-CP: Summary of Hematologic Adverse Events



*Saglio G, et al. NEJM. E-pub ahead of print 5 June 2010.

**Kantarjian / Shah et al. NEJM. E-pub ahead of print 5 June 2010.

Fluid Retention / Serosal inflammation: DASISION

	DASISION Dasatinib 100 mg QD (n = 259)	DASISION Imatinib 400 mg QD (n = 260)
Fluid retention (All grade)	**19%**	**42%**
Superficial edema (All grade)	**9%**	**36%**
Pleural effusion Grade 1	**2%**	**0**
Grade 2	**8%**	
Treatment interruptions for PE, n	19	--
Dose reductions for PE, n	8	--
Diuretics, n	12	--
Corticosteroids, n	7	--
Thoracenteses, % (n)	1.2% (3)	--
Discontinuations due to PE	1.2% (3)	--

Kantarjian /Shah, et al. *N Engl J Med*. E-pub ahead of print 5 June. 2010.

Gianantonio Rosti, MD
University of Bologna
Bologna, Italy