



**The management of CML: current treatment
paradigms and future perspectives**
**An educational day for European fellows on
behalf of EUTOS for CML**

CEINGE & Faculty of Medicine, University Federico II, Naples

18 – 19 May 2009

**New generation TK inhibitors in front-line
therapy**

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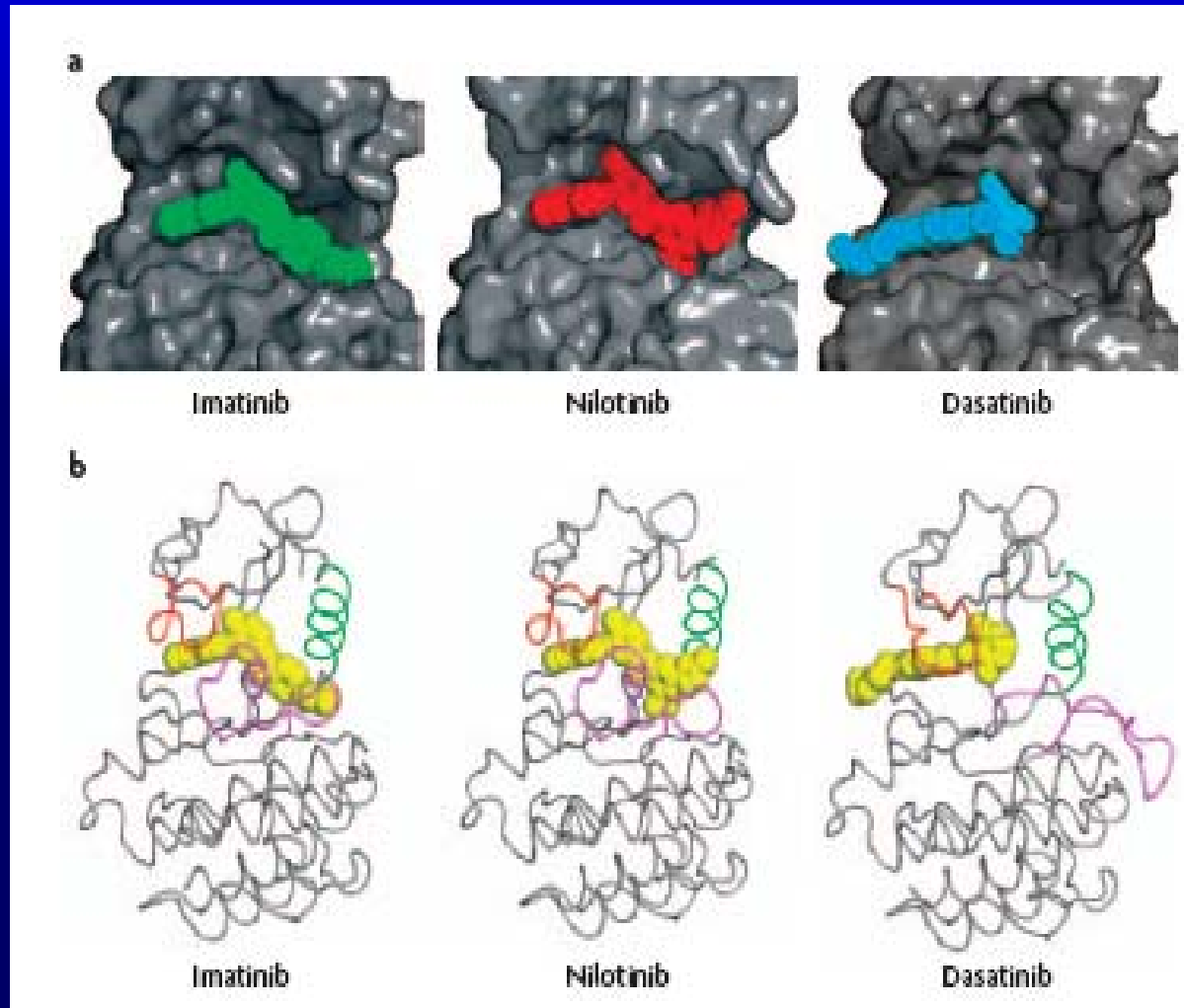
Rationale for testing II generation TKIs as first line treatment of CML treatment

- **The percentage of patients with CCyR, MMR, and CMR could increase by using selective BCR-ABL inhibitors with greater potency than Ima**
- **High risk Sokal is still associated with a lower front-line response rate to Ima**
- **A small percentage of cases (up to 4% per year) may lose response to Ima particularly during the first years of treatment (secondary resistance)**
- **Emergence of cells expressing Ima-resistant BCR-ABL mutants is frequently observed in secondary resistance**

New Tyrosine kinase inhibitors in clinical trials for CML

Inhibitor	Company	Targets	Route of administration	Developmental status
Nilotinib (AMN107)	Novartis	ABL, PDFGR, KIT, EPHB4	Oral	Approved
Dasatinib (BMS-354825)	Bristol-Myers Squibb	ABL, PDFGR, KIT, FGR, FYN, YES, LYN, HCK, LCK, SRC, EPHB4	Oral	Approved
Bosutinib (SKI-606)	Wyeth	ABL, FGR, LYN, SRC	Oral	Phase II
INNO-406 (NS-187)	Innovive	ABL, LYN, PDFGR, KIT	Oral	Phase I
MK-0457	Merk	Aurora kinases, FLT3, JAK2	I.V.	Phase II
PHA -739358	Nerviano	Aurora A, B, and C	I.V.	Phase II
AZD0530	Astra Zeneca	SRC family kinases	Oral	Phase II (solid tumors)

Structure of ABL in complex with Imatinib, Nilotinib and Dasatinib



The protein tyrosine kinase inhibitor Nilotinib
as first-line treatment of
Ph+ chronic myeloid leukemia (CML)
in early chronic phase:
a Phase II exploratory, multicenter study

GIMEMA Protocol CML 0307

Gianantonio Rosti

On Behalf of GIMEMA
CML WORKING PARTY

ASH 2008 –oral presentation



Rationale for using Nilotinib as first line treatment in CML

- **Nilotinib showed significant clinical activity in phase II clinical trials against Imatinib-resistant patients**
- **Rapid and durable hematological and cytogenetic responses to Nilotinib in phase II studies**
- **Favorable safety profile with minimal extra-hematological side effects**
- **Registration for treatment of CML patients in chronic or accelerated phase resistant or intolerant to preceding treatment**

Patients (18 Centres enrolled ≥ 1 Pt)

N = 73

Median Age, years (range)	51 (18-83)
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Male, %	51
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<u>Relative Risk</u>	Sokal	Hasford
• Low	45%	40%
• Intermediate	41%	59%
• High	14%	1%

Variant Translocations	14%
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Additional Chr. Abnormalities (ACA)	4%
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Der(9) deletions	10%
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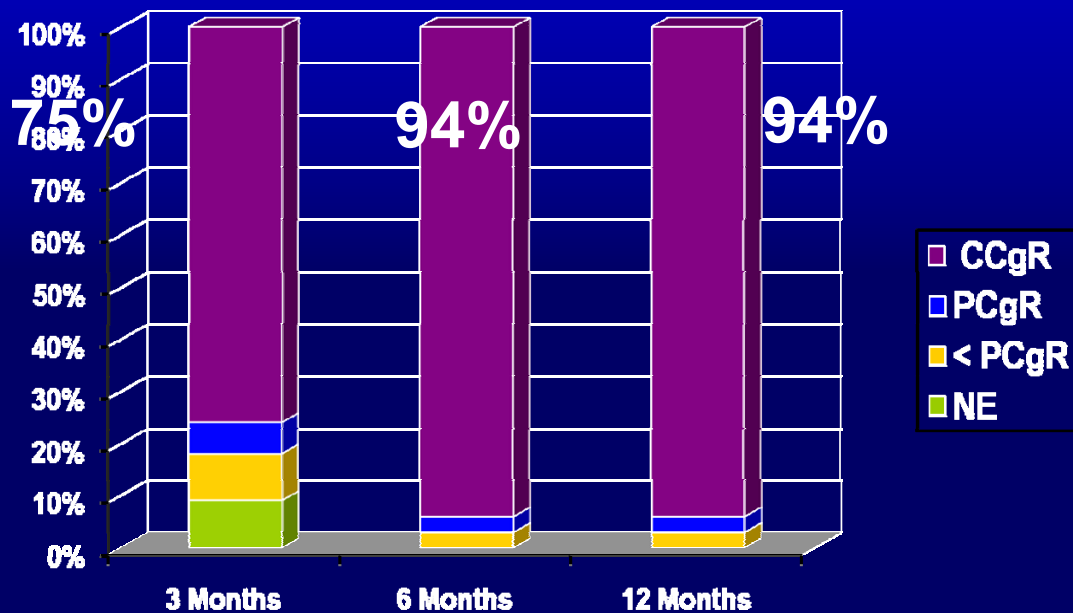
Nilotinib Exposure and Treatment Course

N = 73

Median duration of nilotinib exposure, days (range)	337 (185-467)
Median dose intensity, mg/day (range)	781 (253-800)
Patients with dose interruptions, n (%)	36 (49)
Median cumulative duration of dose interruption, days (range)	19 (3-148)
Permanent withdrawal, n	2 (1ABP + 1 AE)
Progression to advanced phase, n	1 (dead BC)

CCgR (ITT)

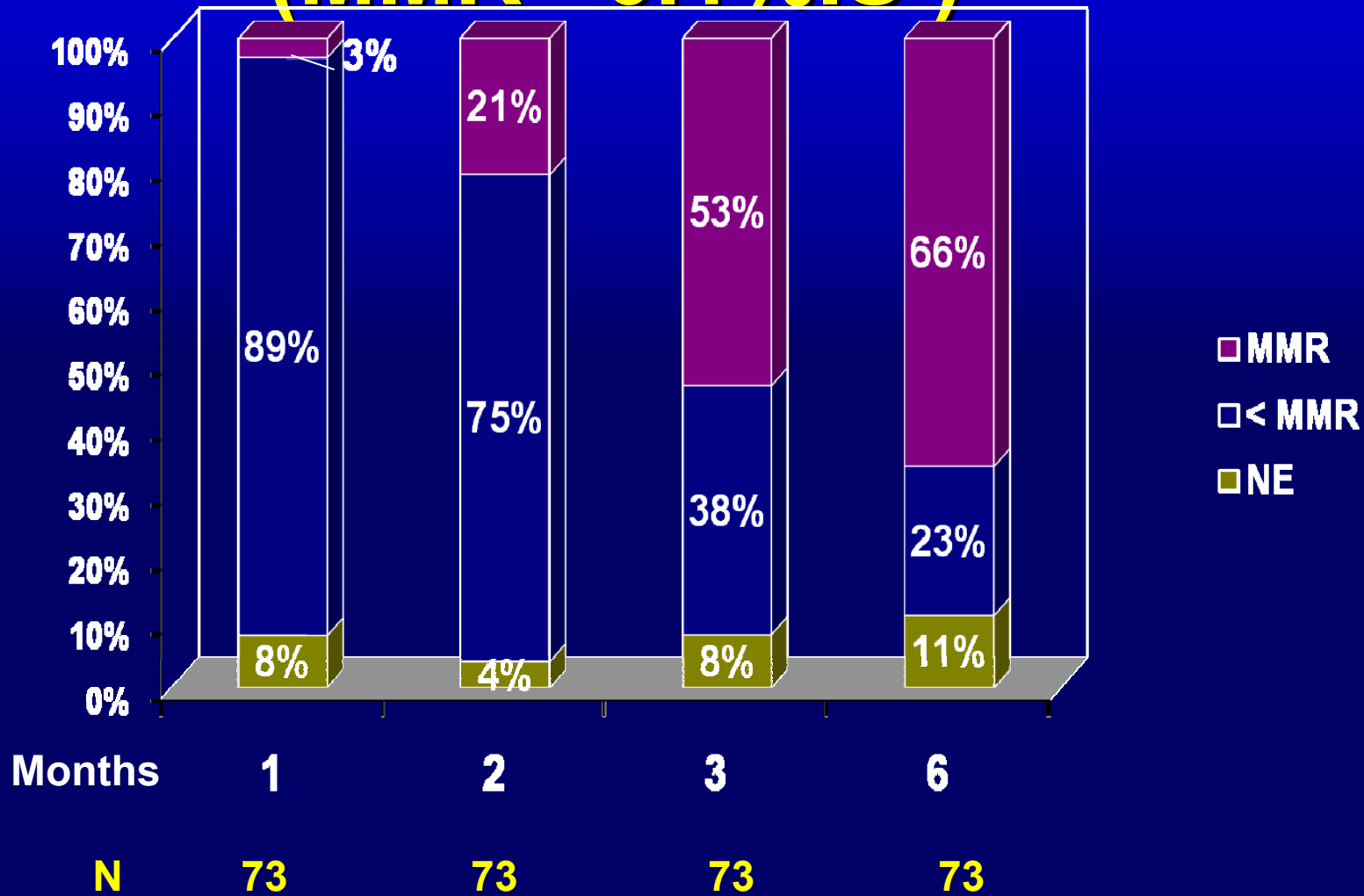
Patients with ≥ 12 mos follow-up



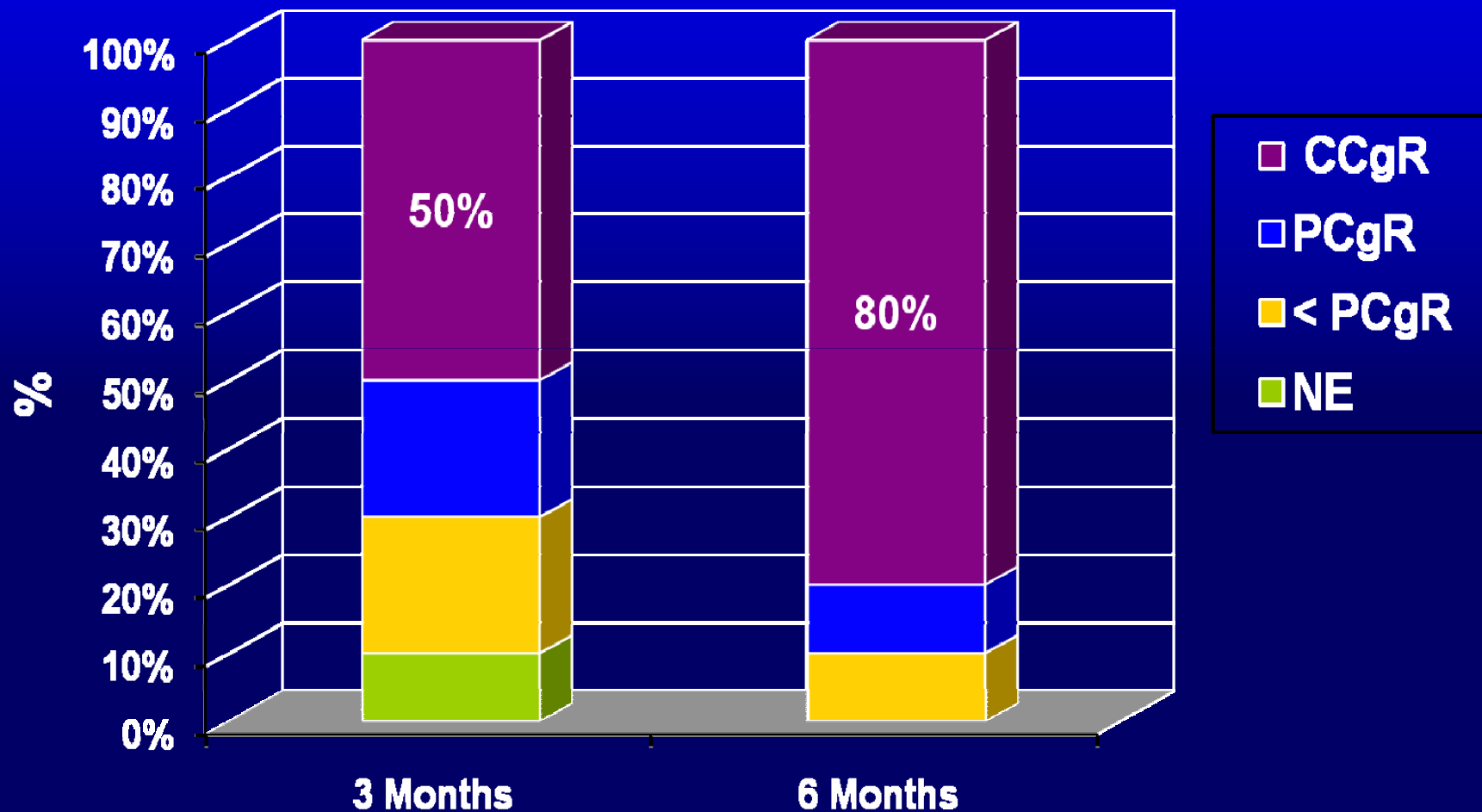
N
32

32

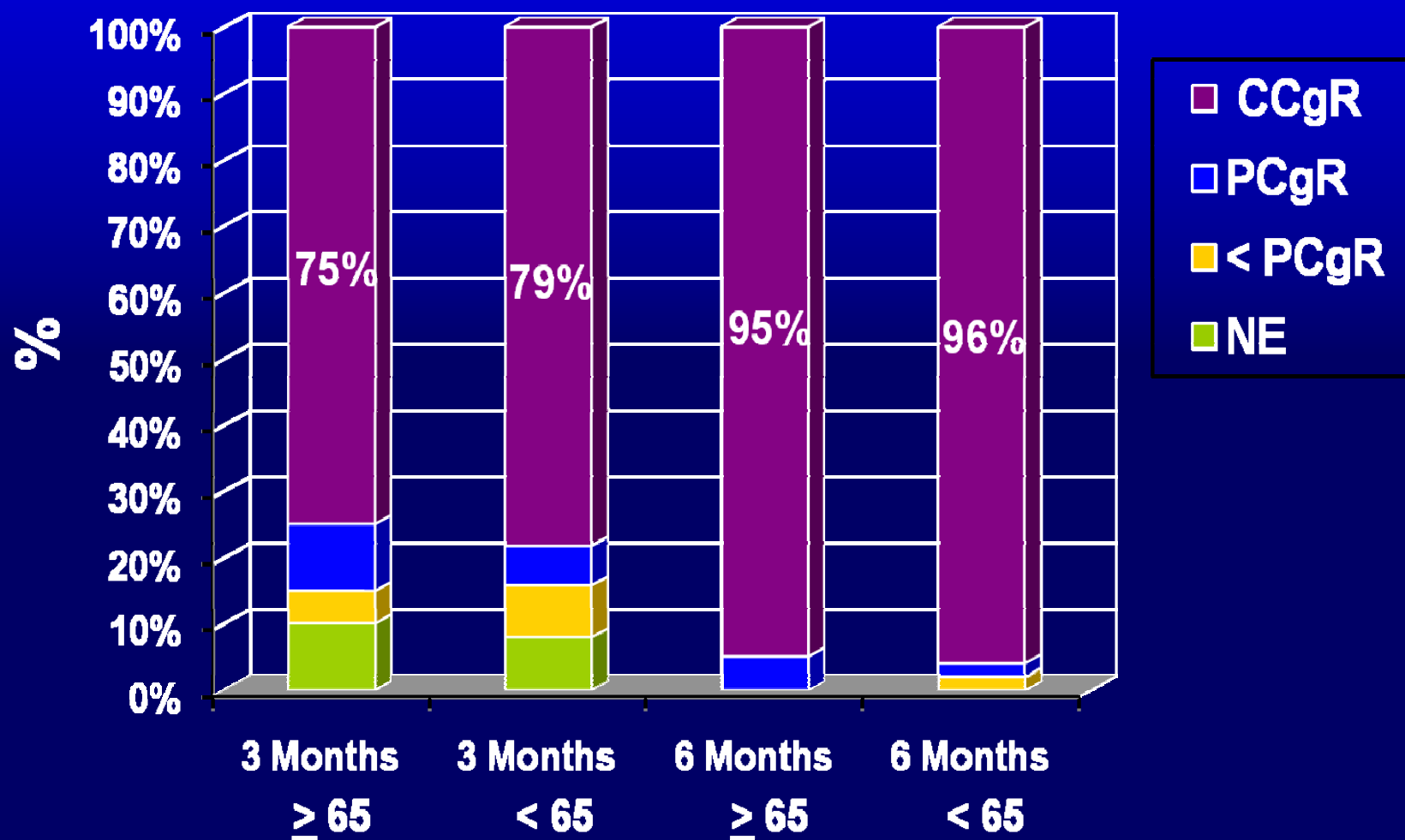
Kinetics of Molecular Response (ITT) (MMR < 0.1% IS)



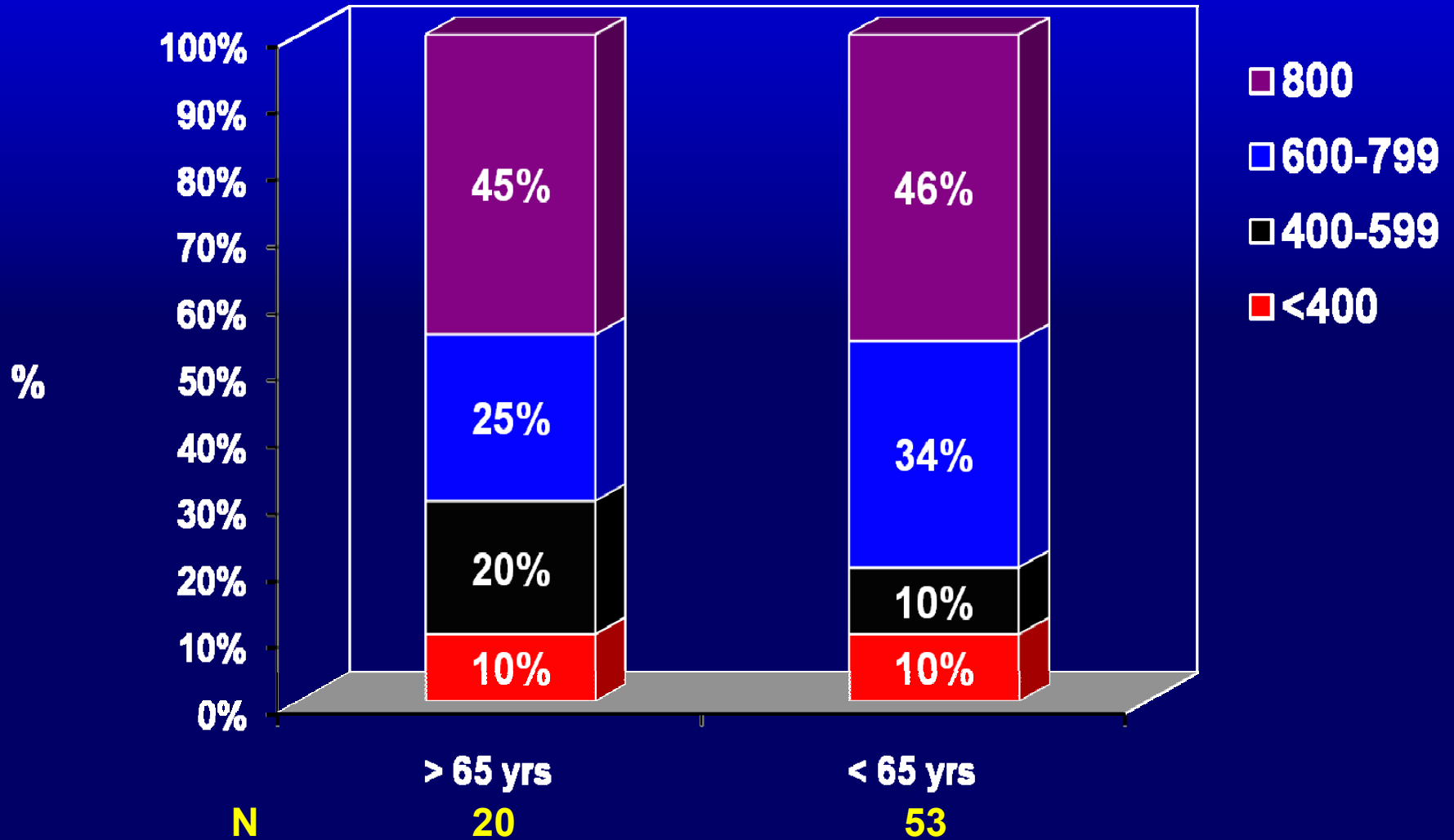
CCgR (ITT) in High Sokal risk



CCgR (ITT) by Age



Compliance by age (≥ 65 and < 65 yrs) (Mean daily nilotinib during the first 6 months)



NILOTINIB

Early CP

Grade 3 and 4 Hematologic Toxicity (n. 73)

	Grade 3 N (%)	Grade 4 N (%)	Grade 3 + 4 N (%)
Hemoglobin	-	-	-
PMN	2 (3)	1 (1)	3 (4)
Platelets	1 (1)	1 (1)	2 (3)

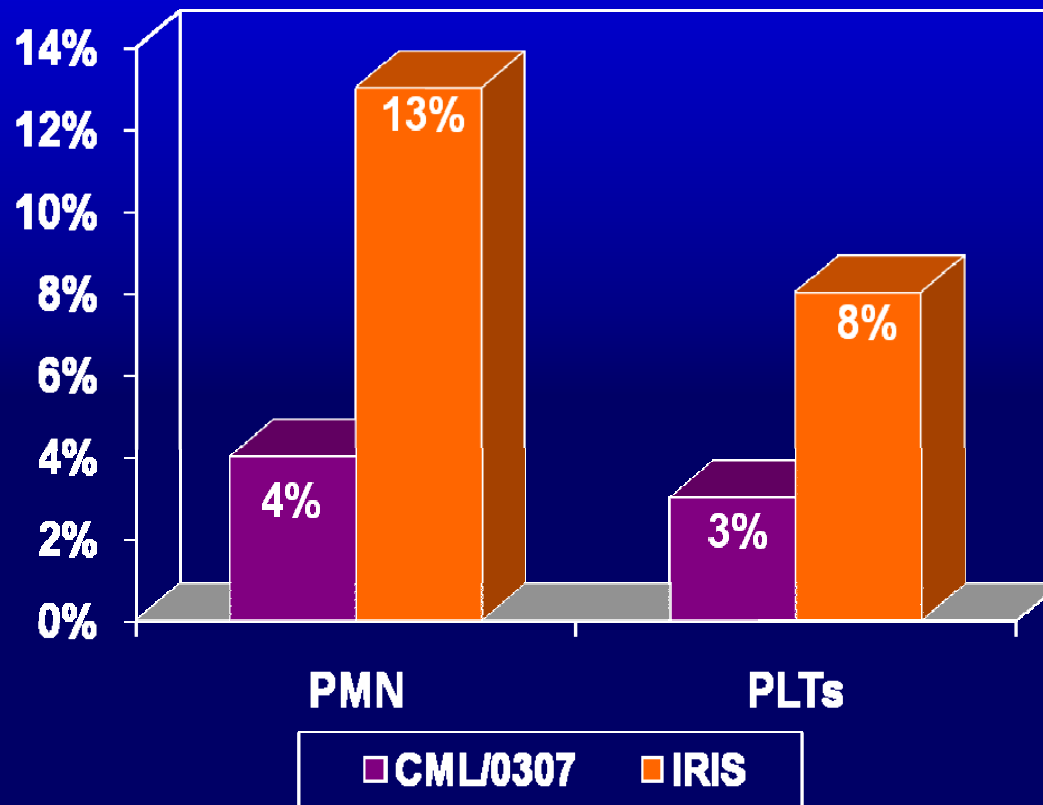
All events < 90 days (median: 61 days)

No dose reduction to 400 mg



Nilotinib and Imatinib in Early Chronic Phase

Grade 3 and 4 Hematologic Toxicity



NILOTINIB 400 Mg BID

Median exposure 11 months

IMATINIB 400 Mg QD

Median exposure 14 months (&)

Most Frequent Non-hematologic Adverse Events

Maximum grade - Regardless of Causality
(Percentage of patients with event; n = 73)

Adverse Event	All Grades	Grade 1	Grade 2	Grade 3
Skin rash	42	22	15	5
Bone / Muscle pain	41	32	5	4
Headache	30	25	5	--
Fatigue	22	11	11	--
Pruritus	20	11	5	4
Dry eye	23	20	3	--
Epigastralgia	19	14	5	--
Nausea/vomiting	11	8	3	--
Abdominal pain	8	4	4	--
Diarrhea	7	4	3	--
Peripheral edema	4	3	1	--

Most Frequent Newly Occurring or Worsening Biochemical Lab Abnormalities

Maximum grade - Regardless of Causality
(Percentage of patients with event; n = 73)

	All Grades	Grade 1	Grade 2	Grade 3	Grade 4
Bilirubin (total)	53	15	22	16	--
ALT (GPT)	42	23	11	8	--
AST (GOT)	29	21	5	3	--
γ-GT	36	21	8	7	--
ALP	11	10	1	/	--
Lipase	29	14	7	4	4
Amylase	18	13	1	4	--
Creatinine	7	4	3	--	--

ECG MONITORING

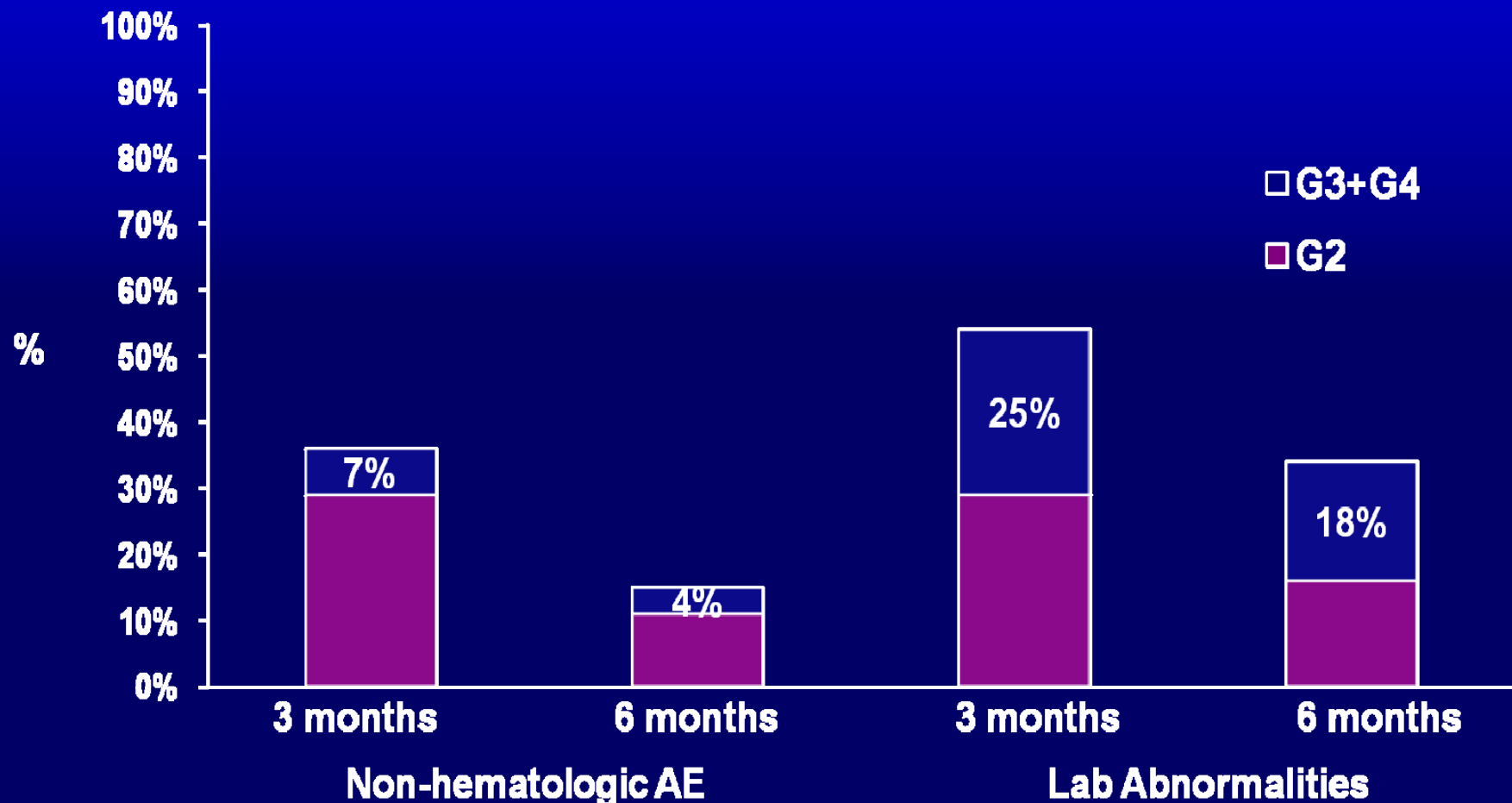
(540 ECGs in 73 patients)

	Percent of Patients with event
QTcF > 450 msec	3
QTcF > 500 msec	--

Transient and not clinically relevant ECG abnormalities observed in 20 (27%) patients

Incidence of Adverse Events by period

Maximum grade - Regardless of Causality
(Percentage of patients with event; n = 73)



Nilotinib Prescribing Information

Recommended management of Myelosuppression

- For CP, ANC < 1.0 x 10⁹/L and/or platelets < 50 x 10⁹/L:

1. Hold nilotinib

2. If counts improve within 2 weeks, resume at 400 mg BID

3. If above cytopenias correct > 2 weeks, start at 400 mg QD

4. Re-escalation may be considered

- Nilotinib may be given in combination with G-CSF, EPO, PLTs, if clinically indicated

GIMEMA CML0307 - Considerations

- **High and early rate of CCgR (97% at 6 months)**
- **High and early rate of MMoIR (66% at 6 months)**
- **Response rate is so high that it is impossible to detect any relationship with any factors**
- **Very high dose intensity**
- **Adverse events recorded so far are mainly of grade 1 and 2, easily managed.**
- **A longer follow-up needed to evaluate the effects of these early results on the long-term outcome**



MDACC-Nilotinib in early CP

MDACC-Nilotinib in early CP - Demographics (Patients no. 56, follow-up 12 months)

(%)

Age, median (range) 47 (21-81)

Sokal Risk

- Low 45%
- Intermediate 45%
- High 5%

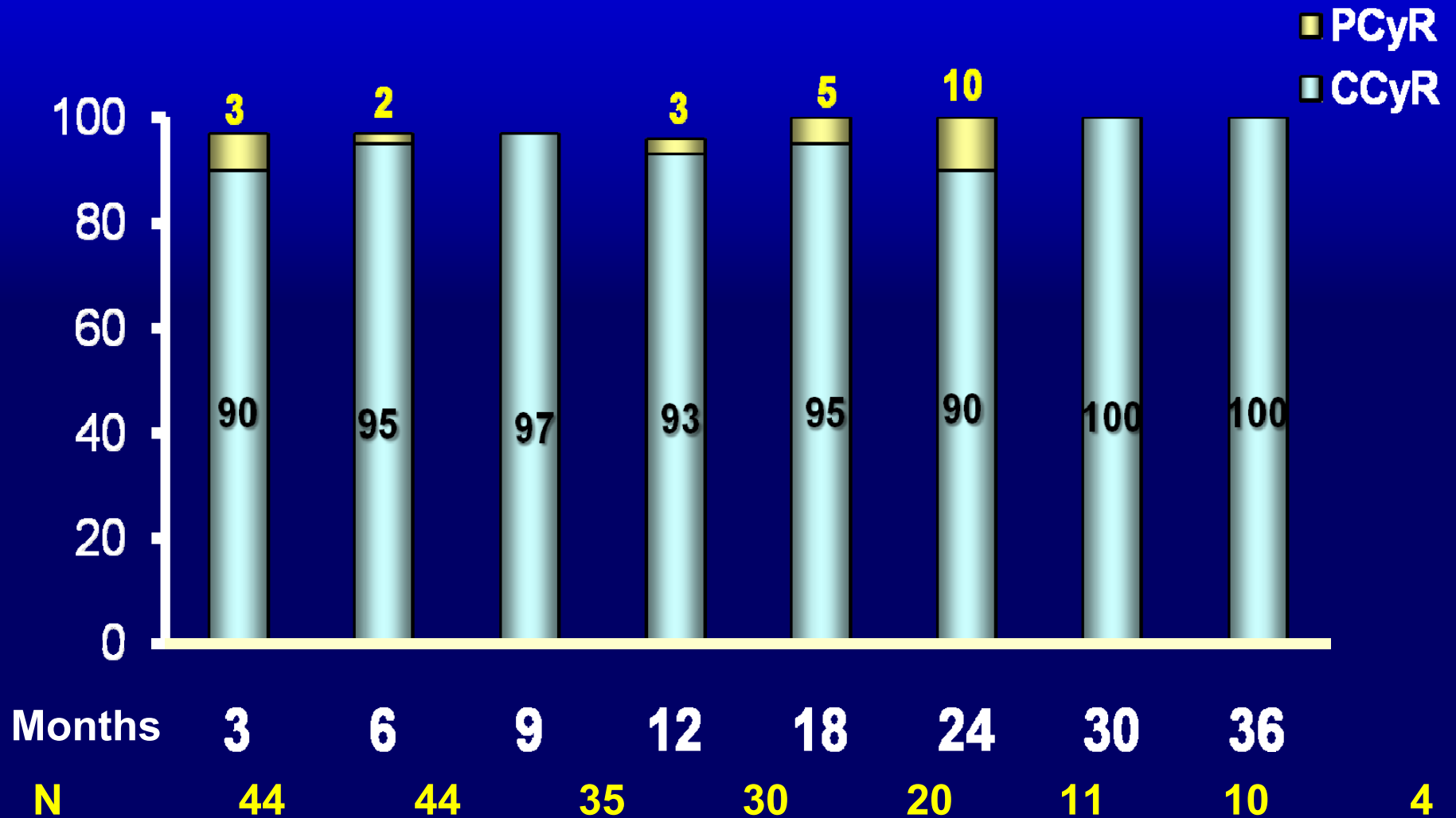
Variant translocation 6%

Accelerate phase 5%

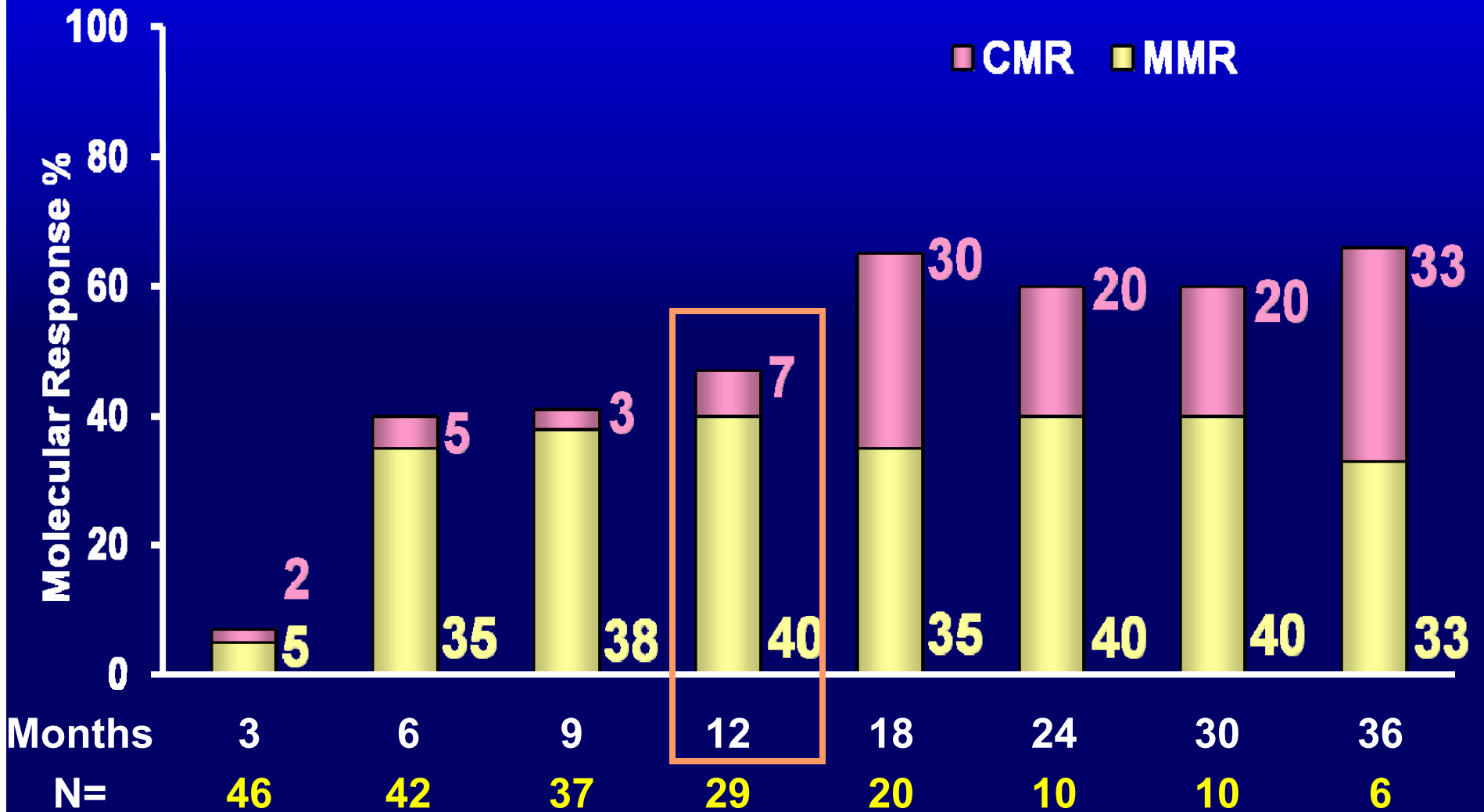
Der(9) 19%

Pretreatment (Imatinib <1mo) 16%

Nilotinib in Early CP CML (MDACC) Major Cytogenetic Response by time

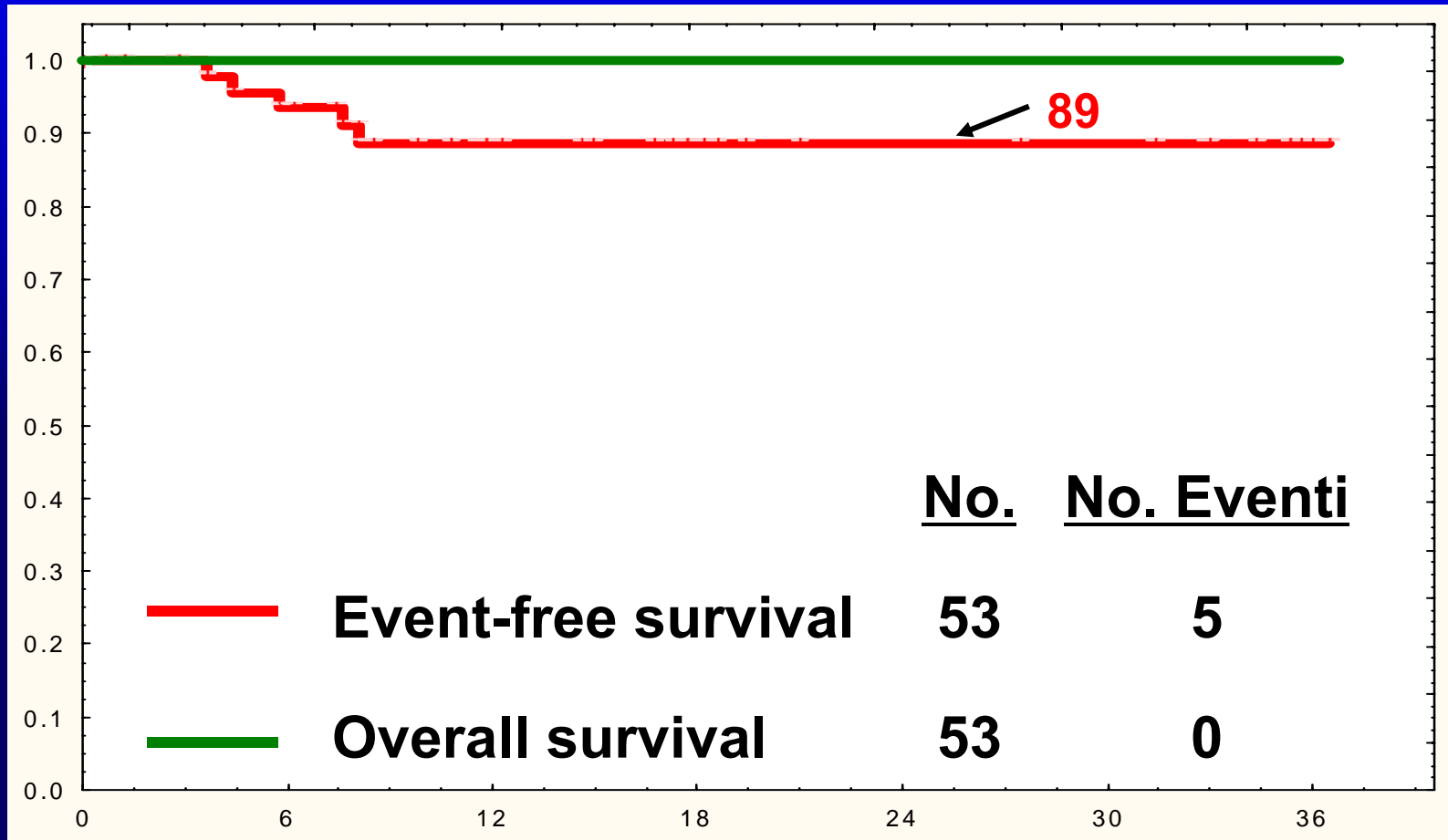


Nilotinib in Early CP CML (MDACC) Molecular response by time



Nilotinib in Early CP CML (MDACC) Event-Free Survival

Cumulative Proportion Free of Events



Months

Events: Loss of CHR, Loss CCyR, drug discontinuation, progression to AP/BC, death

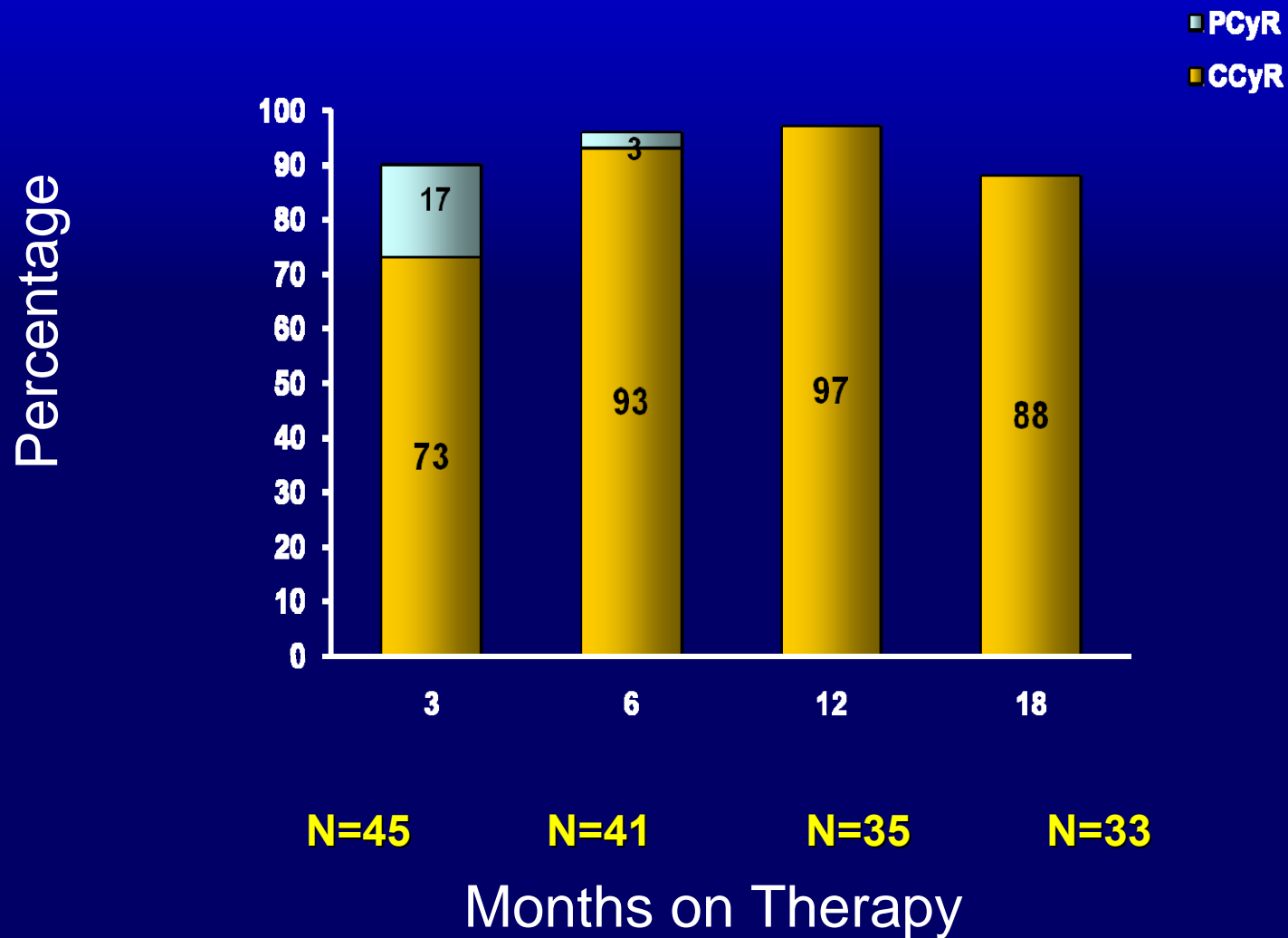
Efficacy of Dasatinib in Patients with Previously Untreated Chronic Myelogenous Leukemia (CML) in Early Chronic Phase (CML-CP)

Jorge Cortes, Susan O'Brien*, Gautam Borthakur*, Dan Jones*, Farhad Ravandi*, Charles Koller*, Ofelia Mesina*, Alessandra Ferrajoli*, Jianqin Shan* and Hagop Kantarjian

MD Anderson Cancer Center, Houston, TX

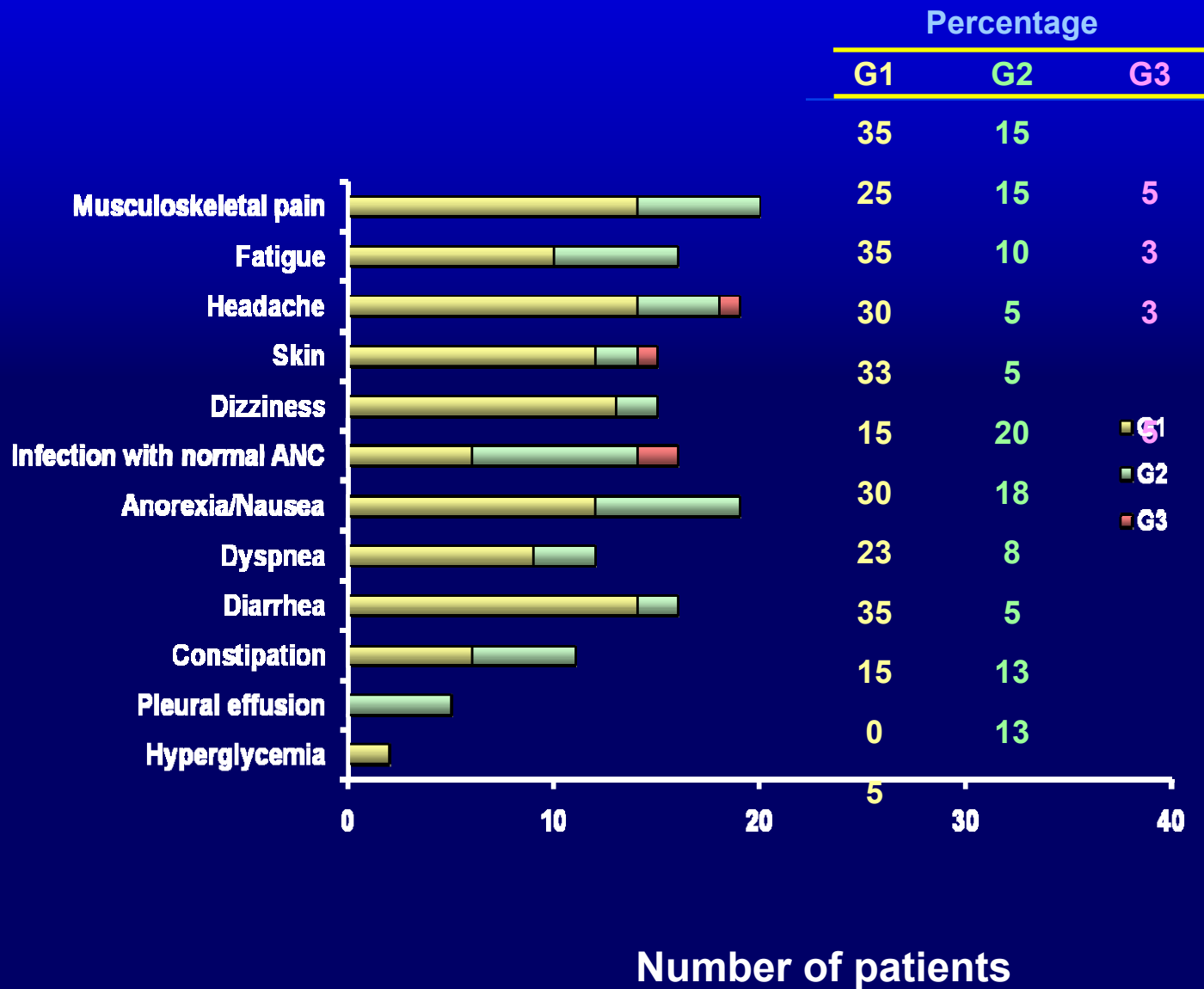
Dasatinib in Early CP CML

Major Cytogenetic Responses



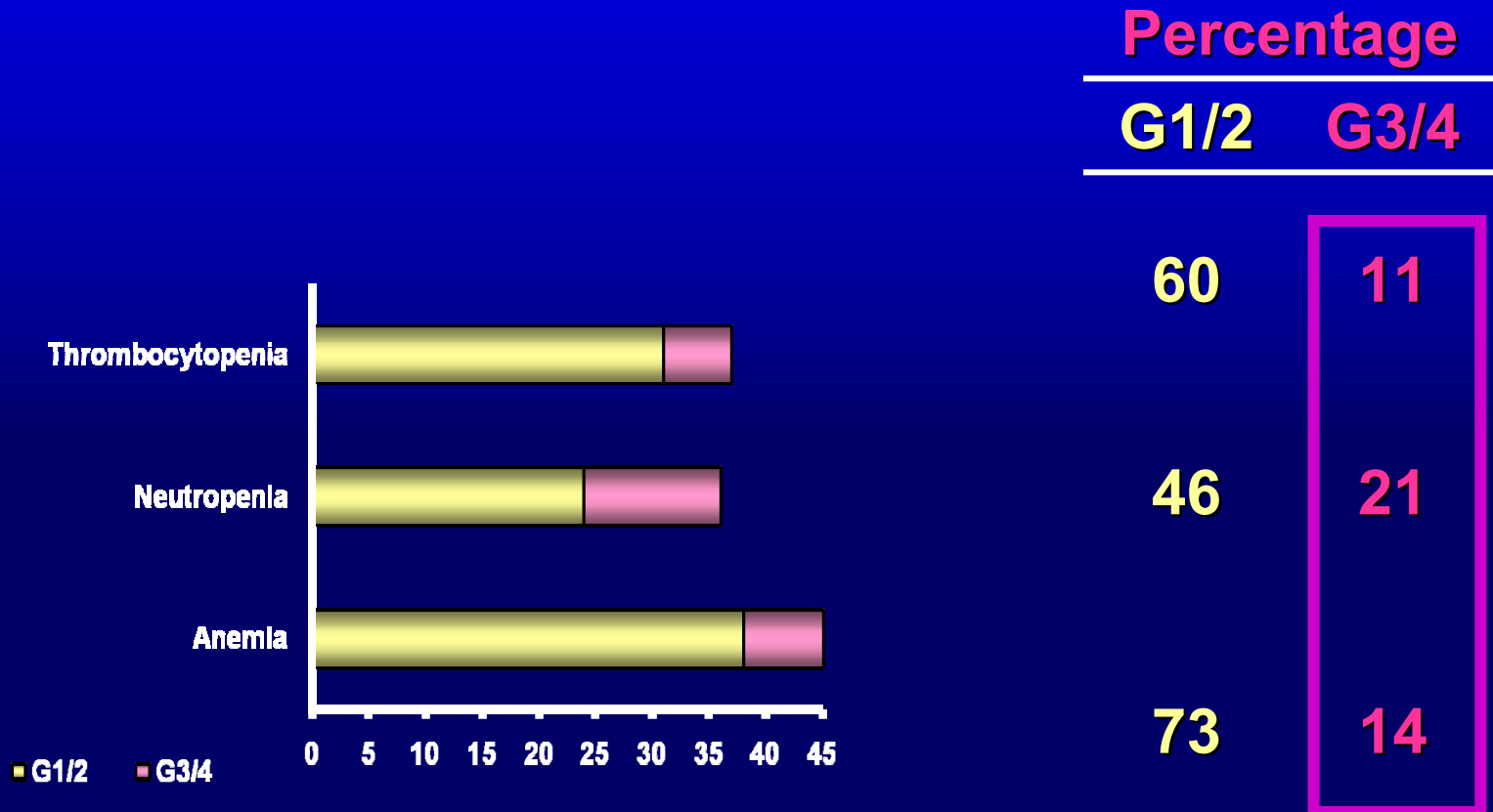
Dasatinib in Early CP CML

Non-Hematologic Adverse Events



Dasatinib in Early CP CML

Hematologic Adverse Events



Number of patients (Total N = 52)

Front-Line LMC-FC (Tasigna e Dasatinib) - ASH 2008

	Nilotinib – GIMEMA Abs #181	Nilotinib (MDACC) Abstract #446	Dasatinib (MDACC) Abstract #182
Patients (no.)	73	49	50
CCyR	75% @ 3 mo 94% @ 6 mo 94% @ 12 mo	93% @ 3 mo (42/45) 100% @ 6 mo (36/36) 96% @ 12 mo (26/27)	73% @ 3 mo (33/45) 93% @ 6 mo (38/41) 97% @ 12 mo (34/35)
MMR	66% @ 6 mo-ITT >75% @ 6 mo - best response	45% a 6 mo 52% a 12 mo	34% a 12 mo (12/35) 48% a 18 mo (12/25)
FU, median	7 mo 32/73 pz @ 12 mo (44%)	13 mo	24 mo
Treatment interruptions	49% @ \geq 3 mo	36%	54%
Dose reductions	29%	32%	38%
Pleural effusions	NA	2% (n=1)	21% (n=2; Gr 3-4)
Myelosuppression	4%- neutropenia 3% - thrombocytopenia	12% - neutropenia 10%- thrombocytopenia	21% - neutropenia 11%- thrombocytopenia
Lipase Hyperbilirubinemi a	4% 15%	6% 8%	NR

Consideration

- **II generation TKIs show high in vitro efficiency against both wt and mutated form of BCR/ABL protein**
- **Given the good bioavailability, potency against target translates into impressive clinical efficacy as first line CML treatment**
- **Low off-target effects ensure good safety profile**

Future Perspectives

- **To Evaluate long term efficacy of new generation of TKIs both as second line and as front-line agents in CML treatment**
- **To use TKIs in combination (association or rotation)**

COMBINATIONS.....

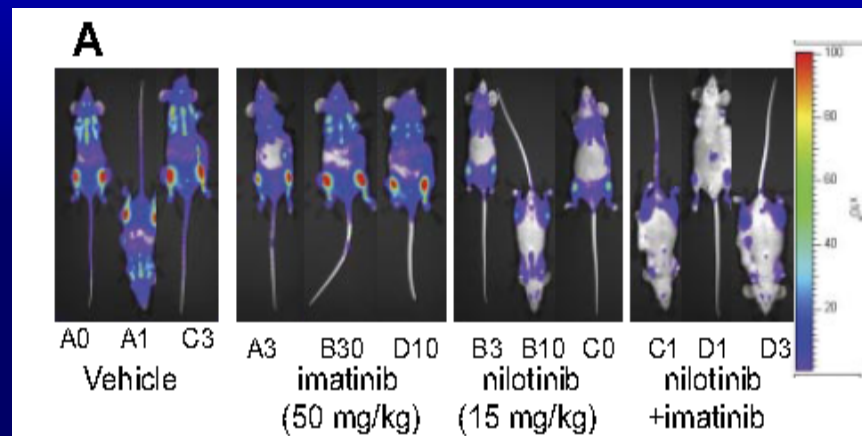


your_one_in_a_million_Group

Beneficial effects of combining nilotinib and imatinib in preclinical models of BCR-ABL⁺ leukemias

Ellen Weisberg,¹ Laurie Catley,¹ Renee D. Wright,¹ Daisy Moreno,¹ Lolita Banerji,¹ Arghya Ray,¹ Paul W. Manley,² Juergen Mestan,² Dorian Fabbro,² Jingrui Jiang,¹ Elizabeth Hall-Meyers,¹ Linda Callahan,¹ Jamie L. DellaGatta,¹ Andrew L. Kung,¹ and James D. Griffin¹

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Imatinib increases the intracellular concentration of nilotinib, which may explain the observed synergy between these drugs

Deborah L. White, Verity A. Saunders, Steven R. Quinn, Paul W. Manley, and Timothy P. Hughes

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GIMEMA

Gruppo Italiano Malattie Ematologiche dell'
Adulto

Front-line treatment of Philadelphia positive (Ph pos), BCR-ABL positive, chronic myeloid leukemia (CML) with two tyrosine kinase inhibitors (TKI) (Nilotinib and Imatinib). A phase II exploratory multicentric study.

GIMEMA Protocol CML 0108/NILIM



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