



Nilotinib as First Line Treatment in Patients with Newly Diagnosed CML

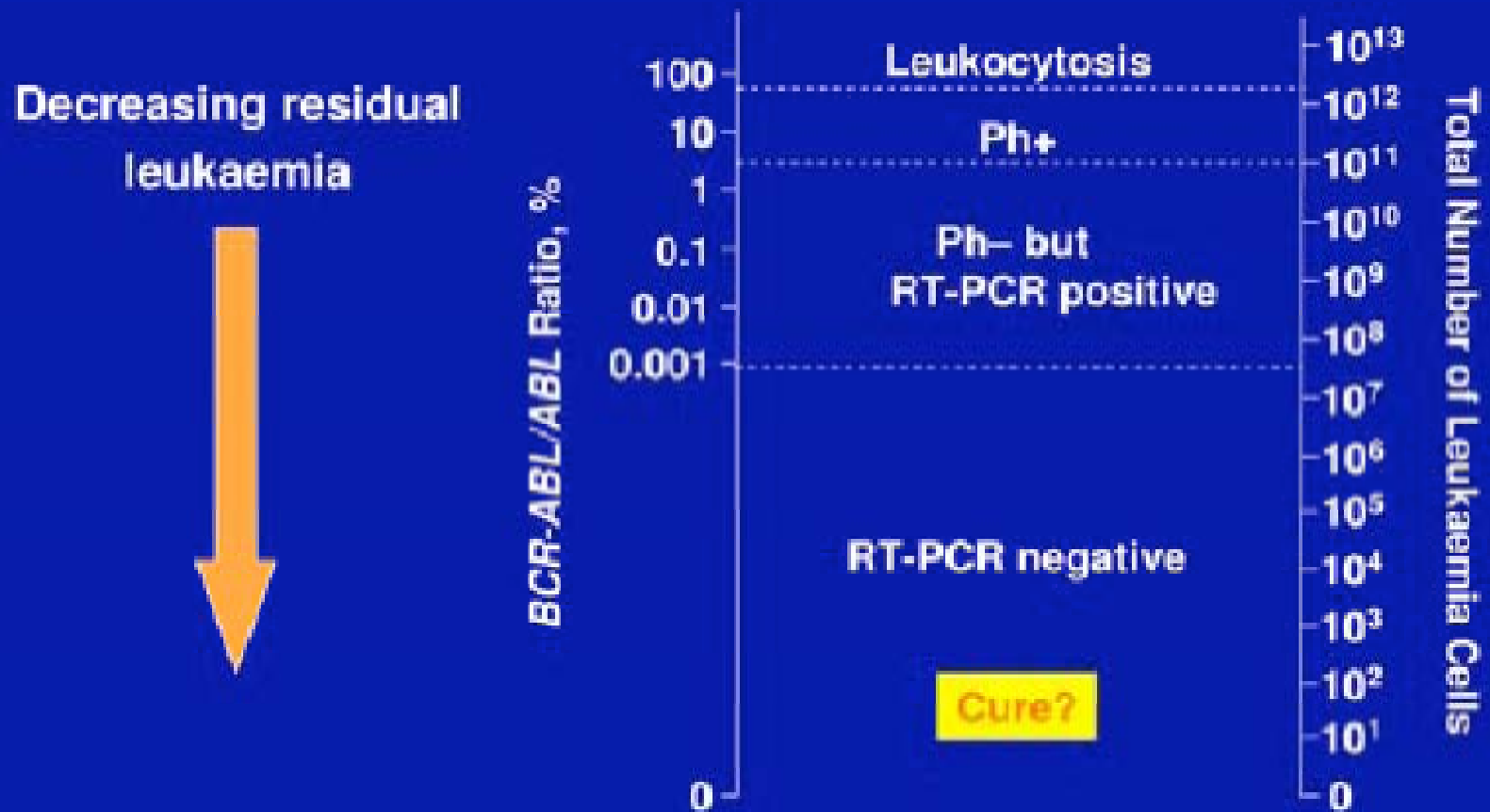
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Fauji Foundation Hospital
RAWALPINDI



CML- Goal of Treatment

- CML diagnosed in all phases
- Goals of treatment
 - Stabilize blood counts (haematological response)
 - Cytogenetic response
 - Overall complete molecular response
 - No BCR ABL transcripts detected in peripheral blood by quantitative RT-PCR

Molecular Response



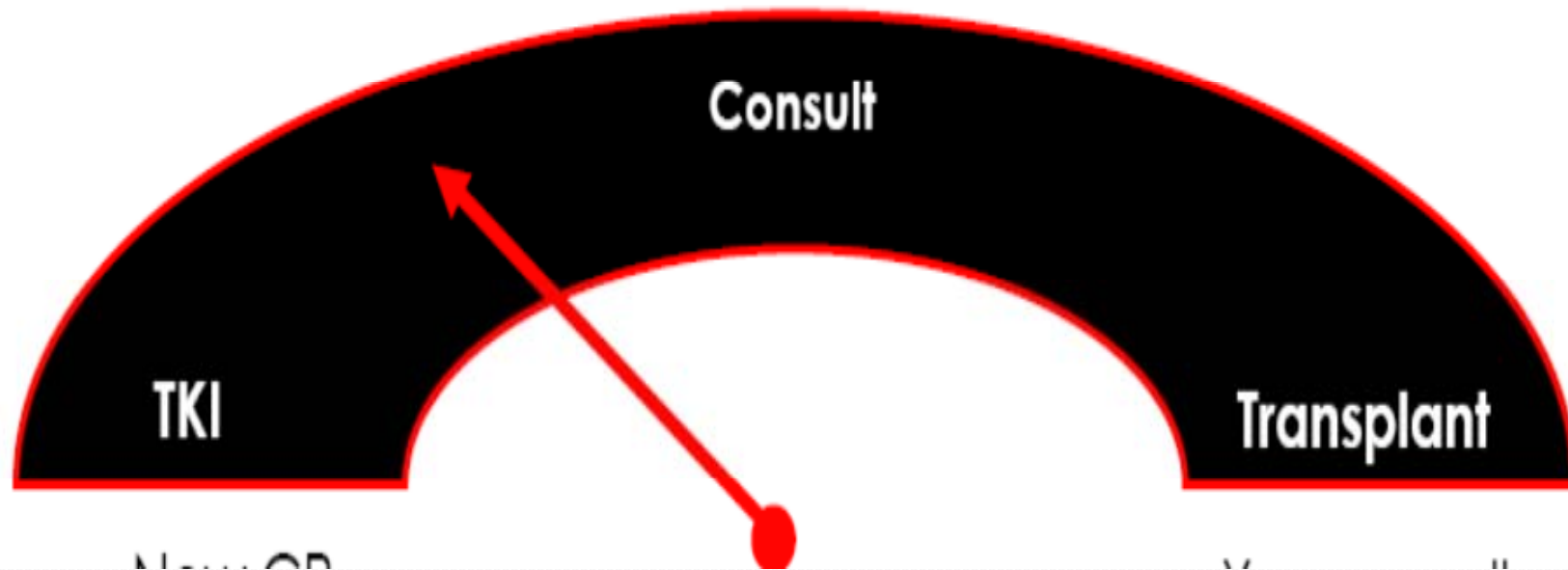
Reproduced with permission from Gelman J. *Curr Opin Hematol.* 2004;12:34.

Ph-, Philadelphia chromosome negative; RT-PCR, reverse transcription polymerase chain reaction.

1. Hughes TP et al. *N Engl J Med.* 2003;349:1423-1432. 2. Kantarjian HM et al. *Blood.* 2004;103:2873-2878.

3. National Comprehensive Cancer Network. *Clinical Practice Guidelines in Oncology* - v.1 2007. 4. Paschka P et al. *Leukemia.* 2003;17:1687-1694. 5. Baccarani M et al. *Blood.* 2006;108:1809-1820.

CML treat-o-meter



MAY 28, 2001

www.time.com

TIME

THERE IS NEW **AMMUNITION**
IN THE WAR AGAINST

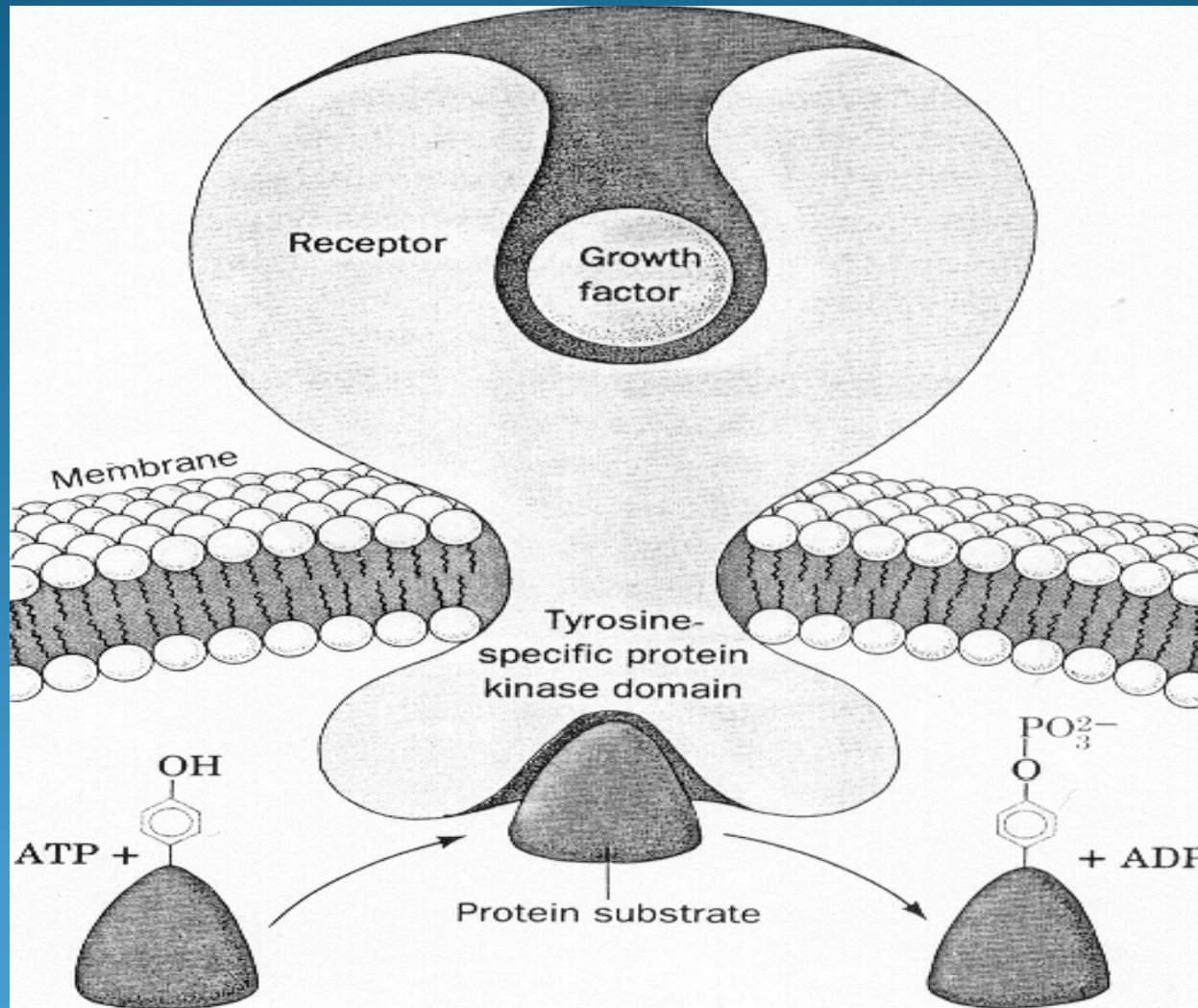
CANCER.

THESE ARE THE BULLETS.

Revolutionary new pills like **GLEEVEC**
combat cancer by targeting only the
diseased cells. Is this the breakthrough
we've been waiting for?

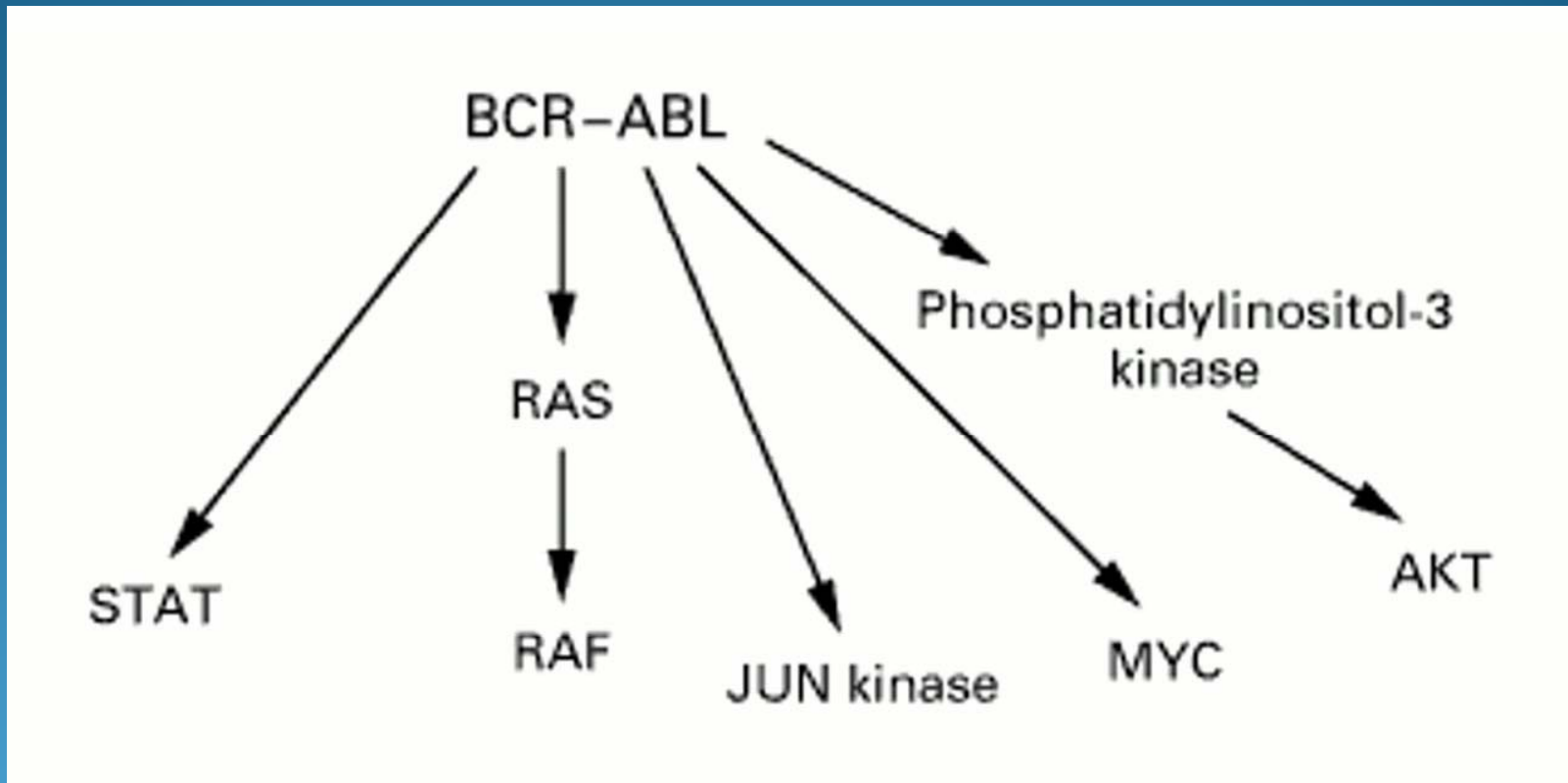


Tyrosine Kinase



Biochemistry 2nd Ed; 1995:1185

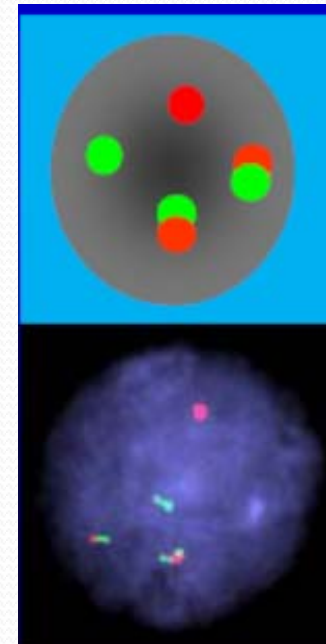
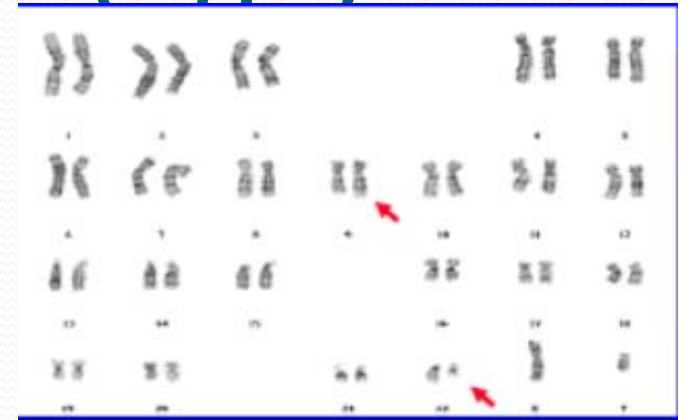
Bcr-Abl Signal Transduction Pathways



Sawyers CL. *NEJM*. 1999; 340(17):1331

Cytogenetic Response (CgR)

- How to assess CgR
Chromosome banding analysis (CBA)
of marrow cells, at least 20 metaphases
- FISH (Interphase)
- Not Recommended
- May substitute CBA if marrow cells
metaphases
cannot be obtained
- Marrow cells must be used since a
correlation
between FISH/blood has not yet been
fully established

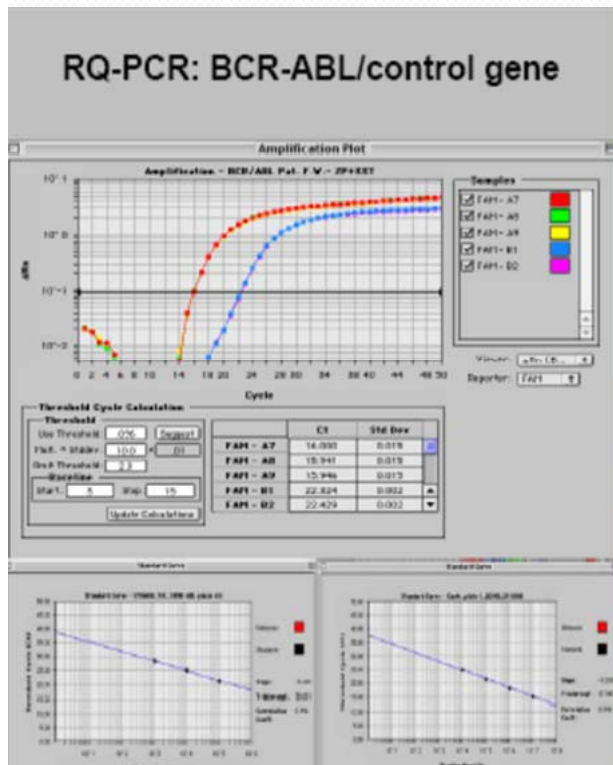


Definition of CgR

Definition	Method	Criteria
No CgR	CBA	>95% Ph ⁺ metaphases
Minimal CgR	CBA	66-95% Ph ⁺ metaphases
Minor CgR	CBA	36-65% Ph ⁺ metaphases
Partial CgR	CBA	1-35% Ph ⁺ metaphases
Complete CgR	CBA	No Ph ⁺ metaphases
	I-FISH	<1% ($\leq 1/200$) positive interphase nuclei

Molecular Response (RT-Q-PCR)

- Blood buffy-coat
- International scale



Complete
(CMoIR)

Undetectable BCR-ABL m RNA transcripts by RT-Q and/or nested PCR in two consecutive blood samples of adequate quality (sensitivity > 10⁴)

Major
(MMoIR)

Ratio of BCR-ABL to ABL (or other housekeeping genes) ≤ 0.1% on the international scale



Nilotinib compared with Imatinib in Patients with Newly Diagnosed CML-CP: Results from the International Randomized Phase III ENESTnd Trial

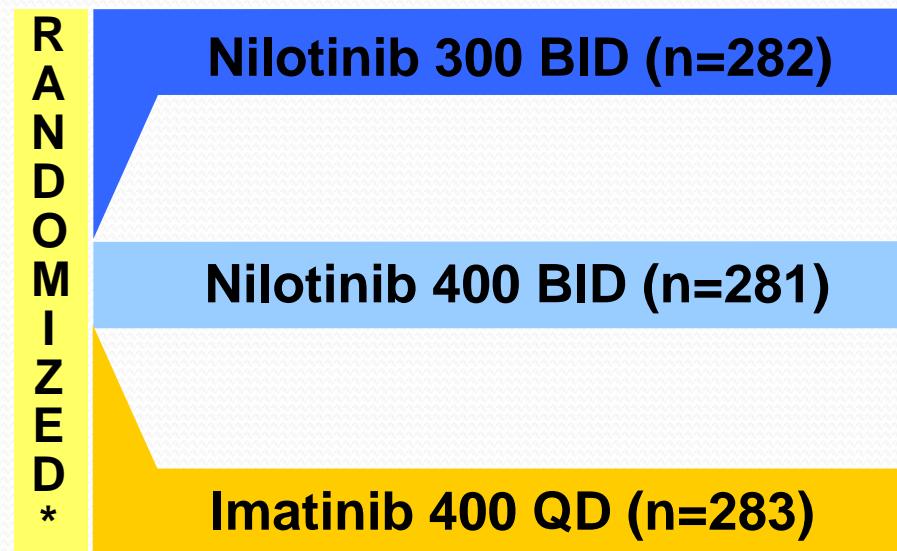
Giuseppe Saglio, Dong-Wook Kim, Surapol Issaragrisil, Philipp le Coutre, Josy Reiffers, Clarisse Lobo, Ricardo Pasquini, Richard Clark, Timothy Hughes, Andreas Hochhaus, Neil Gallagher, Albert Hoenekopp, Mei Dong, Ariful Haque, Hagop Kantarjian, and Richard Larson
on behalf of the ENESTnd Investigators

2009 ASH abstract (LBA-1) data only

Study Design and Endpoints

- **Primary endpoint:** MMR at 12 months
- **Secondary endpoint:** CCyR by 12 months
- **Other endpoints:** Time to and duration of MMR & CCyR, EFS, PFS, time to AP/BC, & OS

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



*Stratification by Sokal risk score

Follow-up 5 years

- **Extension study for patients with suboptimal response or failure**



Methods

- Primary endpoint was MMR at 12 months
- All patients had a minimum of 12 months of treatment or discontinued early; median follow-up was 14 months
- MMR was defined as a value of $\leq 0.1\%$ of BCR-ABL/control ratio using the IS
- MolR was assessed by RT Q-PCR at baseline, monthly for 3 months and every 3 months thereafter
 - Samples were analyzed at a single central PCR laboratory
- Major secondary endpoint was CCyR by 12 months based on bone marrow; FISH not permitted

Patient Characteristics

- Baseline demographics and disease characteristics were well balanced among the 3 treatment arms
- Patients with high Sokal Risk Scores were balanced at 28% in the 3 treatment arms

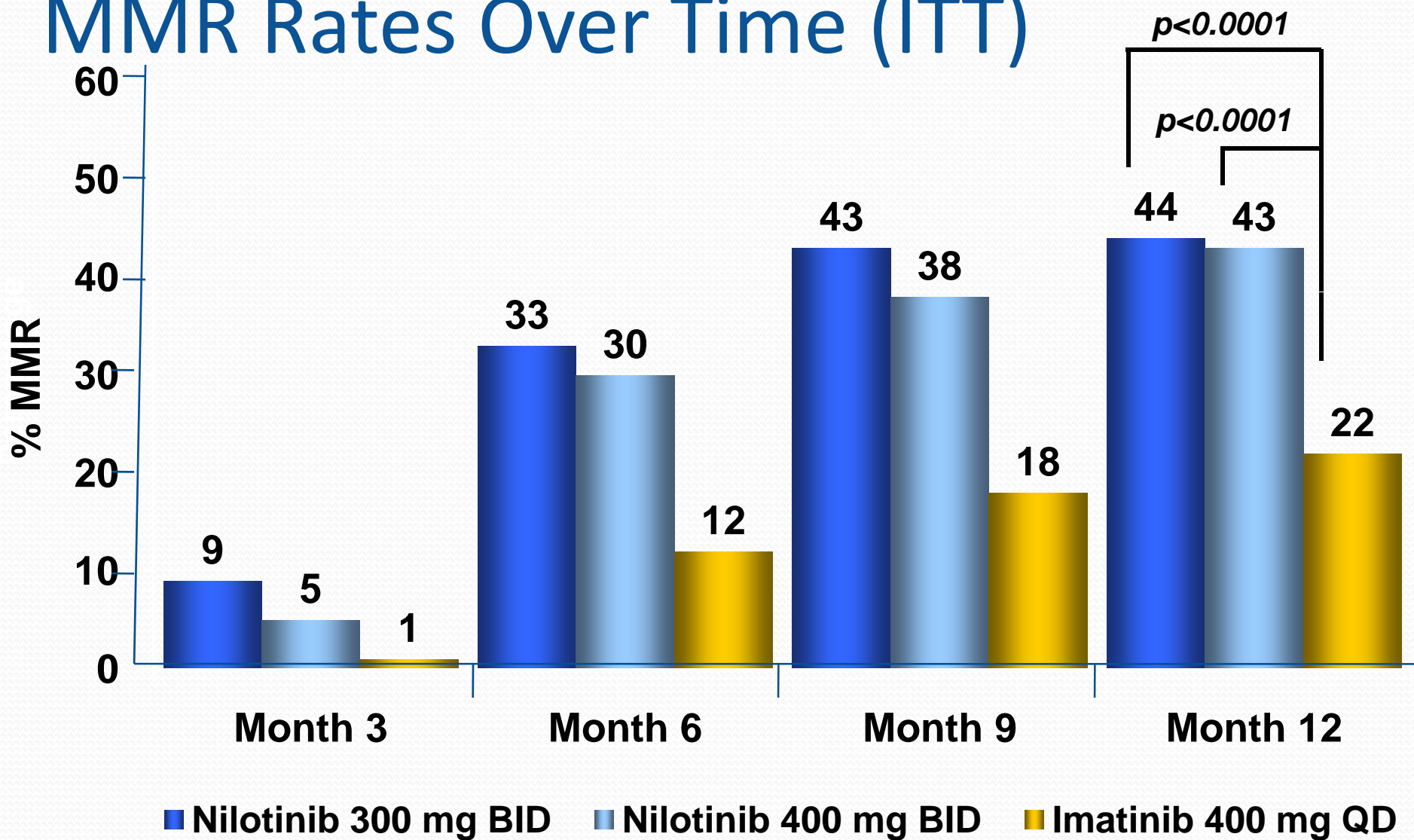
	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Imatinib 400 mg QD
Sokal score high Risk	28%	28%	28%

Patient Disposition

	Nilotinib 300 mg BID	Nilotinib 400 mg BID	Imatinib 400 mg QD
Median dose intensity mg/day	592	779	400
Patients ongoing in study, %	84	82	79
Discontinuation due to AEs or lab abnormalities, %*	7	11	9

* Discontinuation due to adverse events or laboratory abnormalities

MMR Rates Over Time (ITT)

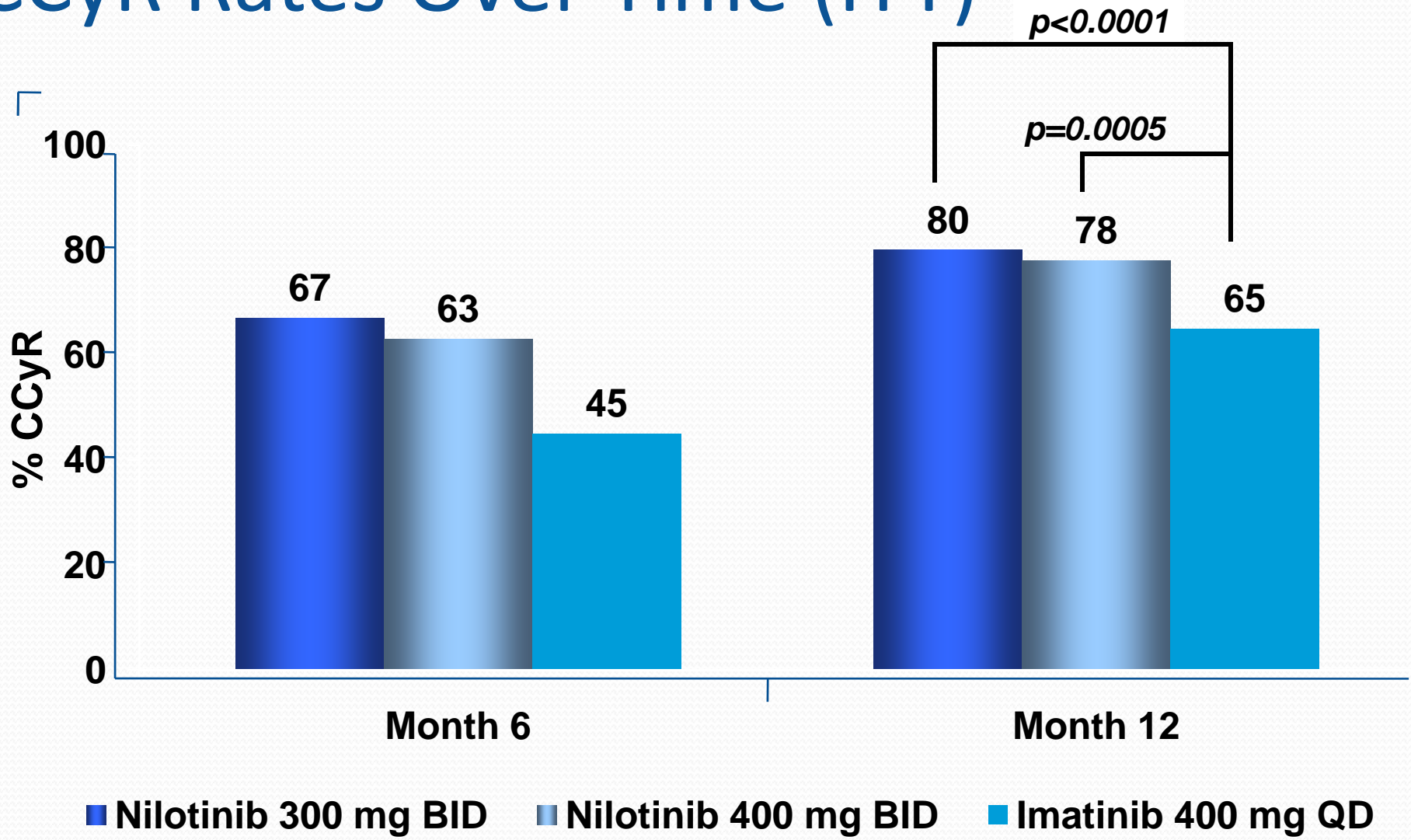


Molecular Response Rates

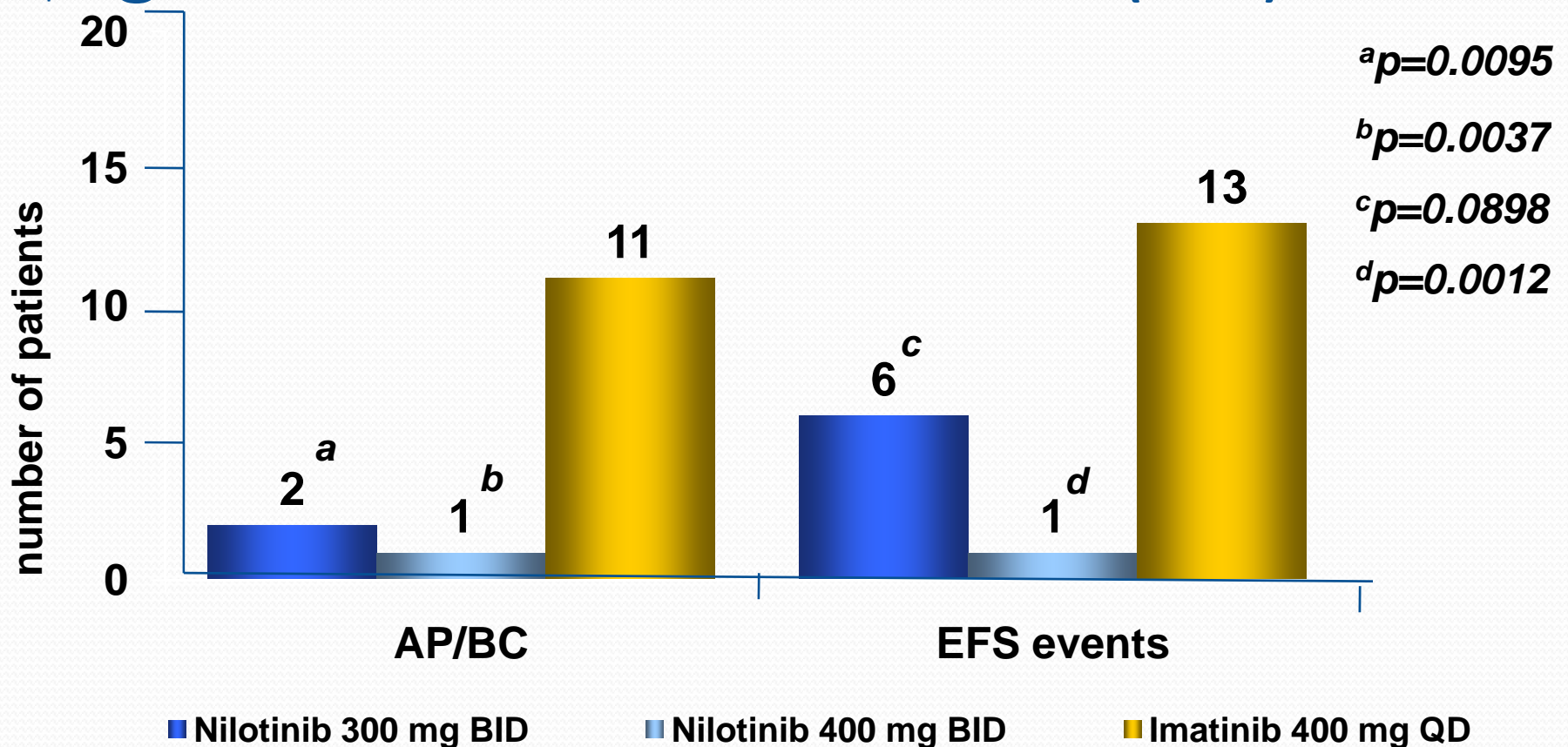
	Nilotinib, 300 mg BID (N = 282)	Nilotinib, 400 mg BID (N = 281)	Imatinib, 400 mg QD (N = 283)
Overall MMR, %	57%	54%	30%
High-risk Sokal , MMR (12 months), %	41%	32%	17%
Time to MMR, months	5.7	5.8	8.3

- Nilotinib induced significantly higher MMR compared to imatinib
- Median time to MMR faster for nilotinib
- MMR higher in patients with high Sokal Risk Scores treated with nilotinib

CCyR Rates Over Time (ITT)



Progression to AP/BC and EFS (ITT)



- No patient who achieved MMR progressed to AP/BC
- 3 patients who achieved CCyR on imatinib progressed to AP/BC

*p-values are based on log-rank test stratified by Sokal risk group vs imatinib for time to EFS and time to AP/BC



Safety and Tolerability

- Both drugs were well-tolerated
- No patients in any treatment arm showed a QTcF interval > 500 msec at any time
- No decrease from baseline in mean LVEF anytime during treatment in any arm



Conclusions

- Nilotinib, at both 300 mg BID and 400 mg BID, is superior to imatinib with higher rates of MMR and CCyR
- Significantly fewer patients on nilotinib progressed to AP/BC
- Nilotinib is effective across all Sokal risk groups
- Nilotinib is generally well-tolerated
- Incidence of SAE's and AE's leading to discontinuation was lowest in the nilotinib 300mg BID arm
- The results of ENESTnd suggest that nilotinib may become the standard of care in newly diagnosed CML

Seize the opportunity

Nilotinib: 1st line data





Nilotinib in Newly Diagnosed CML-CP Patients: ENESTnd

Objective: to compare the efficacy and safety of 300 or 400 mg bid nilotinib vs 400 mg qd IM in pts with newly diagnosed Ph+ CML-CP

Key messages and takeaways:

- Nilotinib, at both 300 mg BID and 400 mg BID, is superior to imatinib with higher rates of MMR and CCyR
- Significantly fewer patients on nilotinib progressed to AP/BC, demonstrating nilotinib has superior disease control in the front-line treatment of CML
- Nilotinib is effective across all Sokal risk groups
- Nilotinib is generally well-tolerated
- Incidence of SAEs and AEs leading to discontinuation was lowest in the nilotinib 300 mg BID arm
- The results of ENESTnd suggest that nilotinib will become the standard of care in newly diagnosed CML



Nilotinib in Newly Diagnosed CML-CP Patients: MDACC

Objective: To investigate efficacy and safety of nilotinib as first-line therapy pts with CML-CP

Key messages and takeaways:

- Nilotinib treatment resulted in rapid and significant cytogenetic and molecular responses
- Nearly all patients achieved CCyR within 12 months on nilotinib



Nilotinib in Newly Diagnosed CML-CP Patients: GIMEMA

Objective: to analyze the safety profile of nilotinib 800 mg daily in the CML early CP setting

Key messages and takeaways:

- Nilotinib 800 mg daily is feasible, safe and very effective in early CP CML
- The safety profile of nilotinib is predictable
- Majority of AEs were short in duration and easily managed

A nighttime photograph of a city skyline, featuring the Space Needle in the foreground. The sky is dark blue with a full moon in the upper left. The city lights are visible, and the Space Needle is illuminated.

Has the sun set on transplants?

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