Chronic Myeloid Leukemia
- ASH 2016 -

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Leukemias: overview

- **Acute Lymphoblastic Leukemia (ALL)**
- **Acute Myeloid Leukemia (AML)**
- **Chronic Lymphocytic Leukemia**
- **Chronic Myeloid Leukemia (CML)**

CML - clinical features

- approximately 4500 new US cases per year
- median age at presentation 53 years
- men comprise approximately 60 percent of cases
- disease is clinically divided into two phases
  - chronic phase
  - accelerated/ blast crisis phase

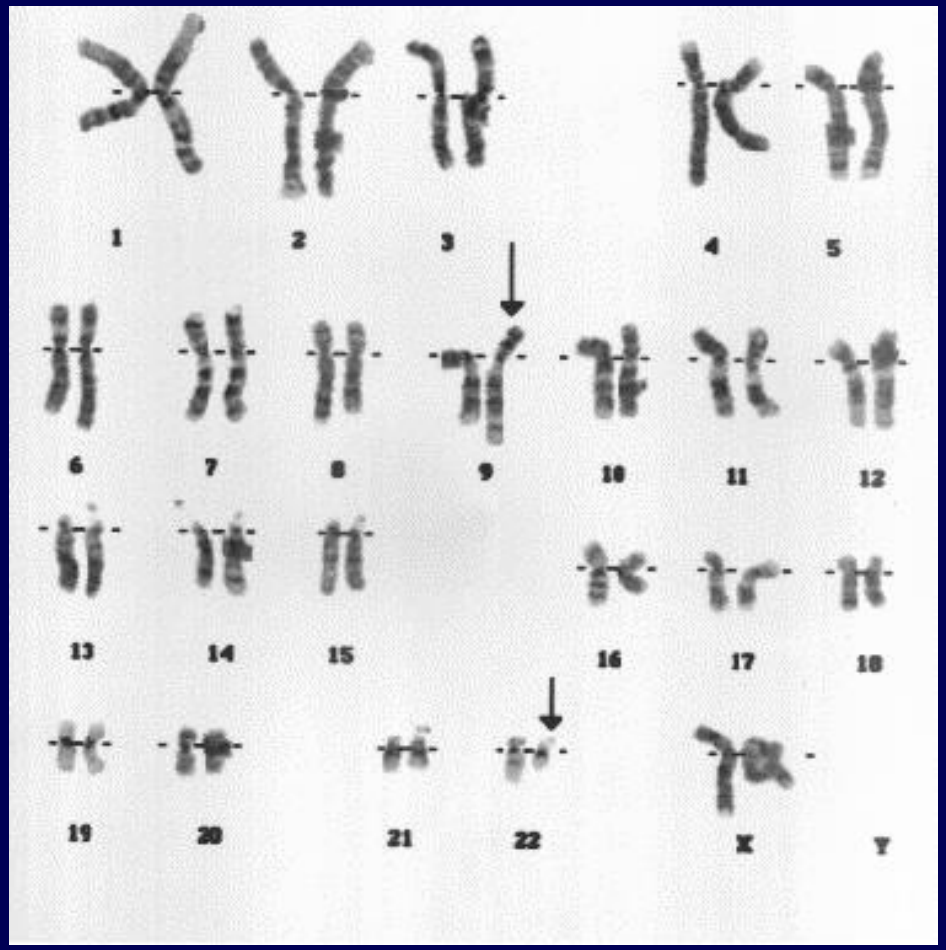
CML - chronic phase

- approximately 40 percent of patients are without symptoms (fatigue)
- 85 percent of newly diagnosed CML cases are chronic phase
- median duration of chronic phase (prior to 2000) approximately 4-6 years
  - After 2000 - unknown, greater than 10 years
- interventions can lead to durable responses in chronic phase
  - Medical therapy (interferon, TKIs)
  - Stem cell transplantation

CML - blast crisis phase

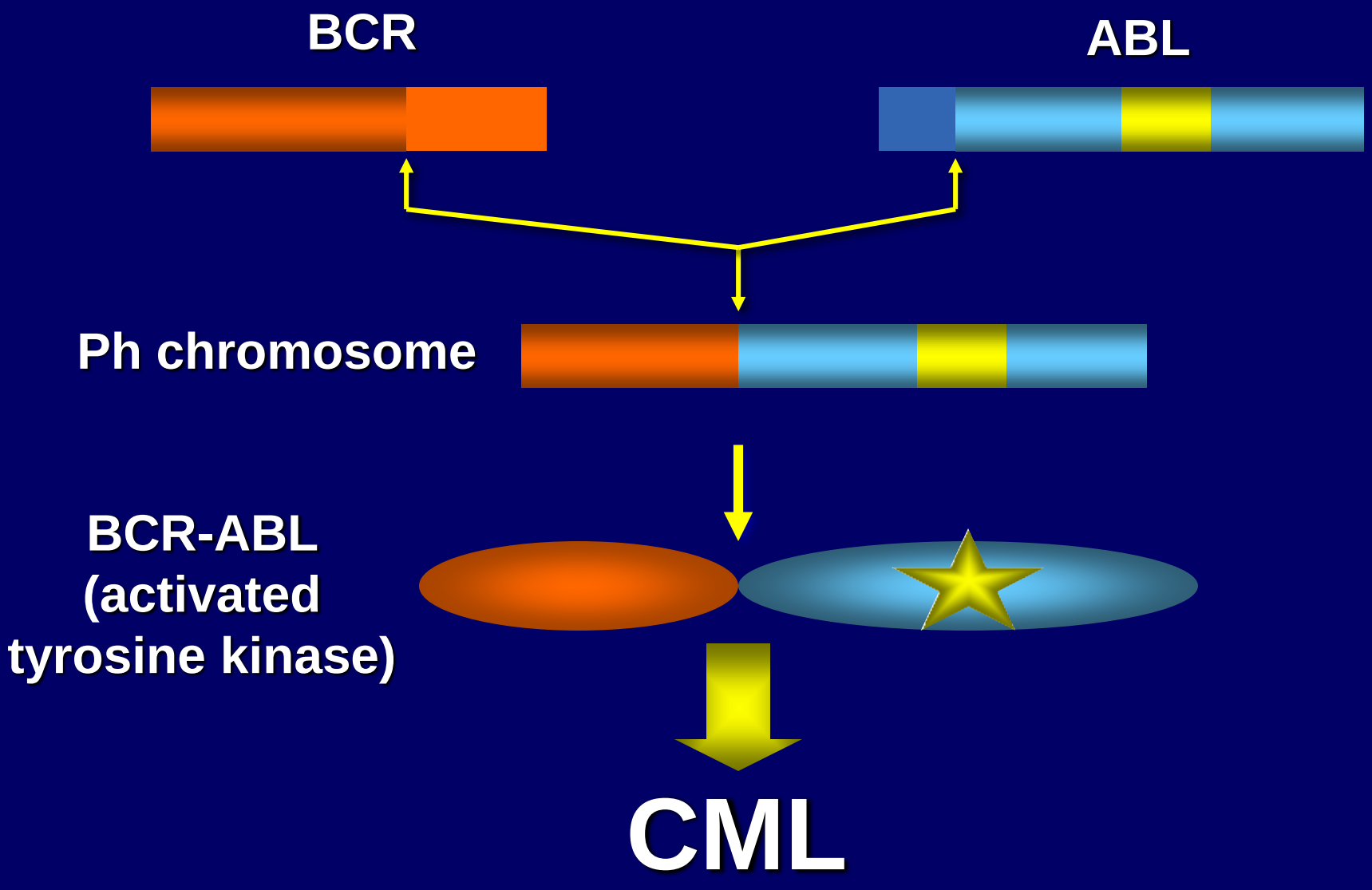
- **failure of normal development of blood cells**
- **responds poorly to medical intervention**
  - **bleeding, infections, anemia common**
- **median survival approximately 6 months**

First hint at the cause of CML:



Forrest et al, 2008; Bakshi et al, 2008; Image courtesy of Larry Beauregard, Jr., PhD.

The Philadelphia (Ph) Chromosome Leads to CML



Clinical Course: Phases of CML

Chronic phase	Advanced phases	
	Accelerated phase	Blastic phase (blast crisis)
Median 4–6 years stabilization	Median duration up to 1 year	Median survival 3–6 months

**loss of p53; trisomy 8; second Ph; PAX5 deletion; others*

Chronic Phase CML - Goals of Therapy

- Prevention of disease transformation to blast phase
  - Chronic phase CML is not immediately life-threatening, so if blast phase can be prevented indefinitely, patients will be "functionally" cured
  - Will almost certainly require lifelong therapy
    - Chronically administered therapies should ideally be well-tolerated and minimally intrusive to everyday life
- True disease cure - enabling patients to be off all therapies
  - Allogeneic stem cell transplantation (~70% cure rate)
    - ~20% risk of short-term death (1-2 years)
    - ~50-60% risk of chronic graft vs host disease
      - "trading one disease for another"
  - Interferon-alpha
    - Low, but real, likelihood of effecting deep and durable molecular remissions (more than 20 years)
    - Difficult for many patients to tolerate
      - Long-acting preparation may be better tolerated
        - Signs of efficacy in CML as well as polycythemia vera

MONITORING DISEASE IN PATIENTS WITH CML

Tools to Monitor Response and Resistance in CML

- Complete Blood Count (CBC)
- Cytogenetics (Quantification of Cells Containing the Philadelphia Chromosome in the Bone Marrow)
- Molecular [Polymerase Chain Reaction (“PCR”) to Quantify the Amount of BCR-ABL in the Blood or Bone Marrow]

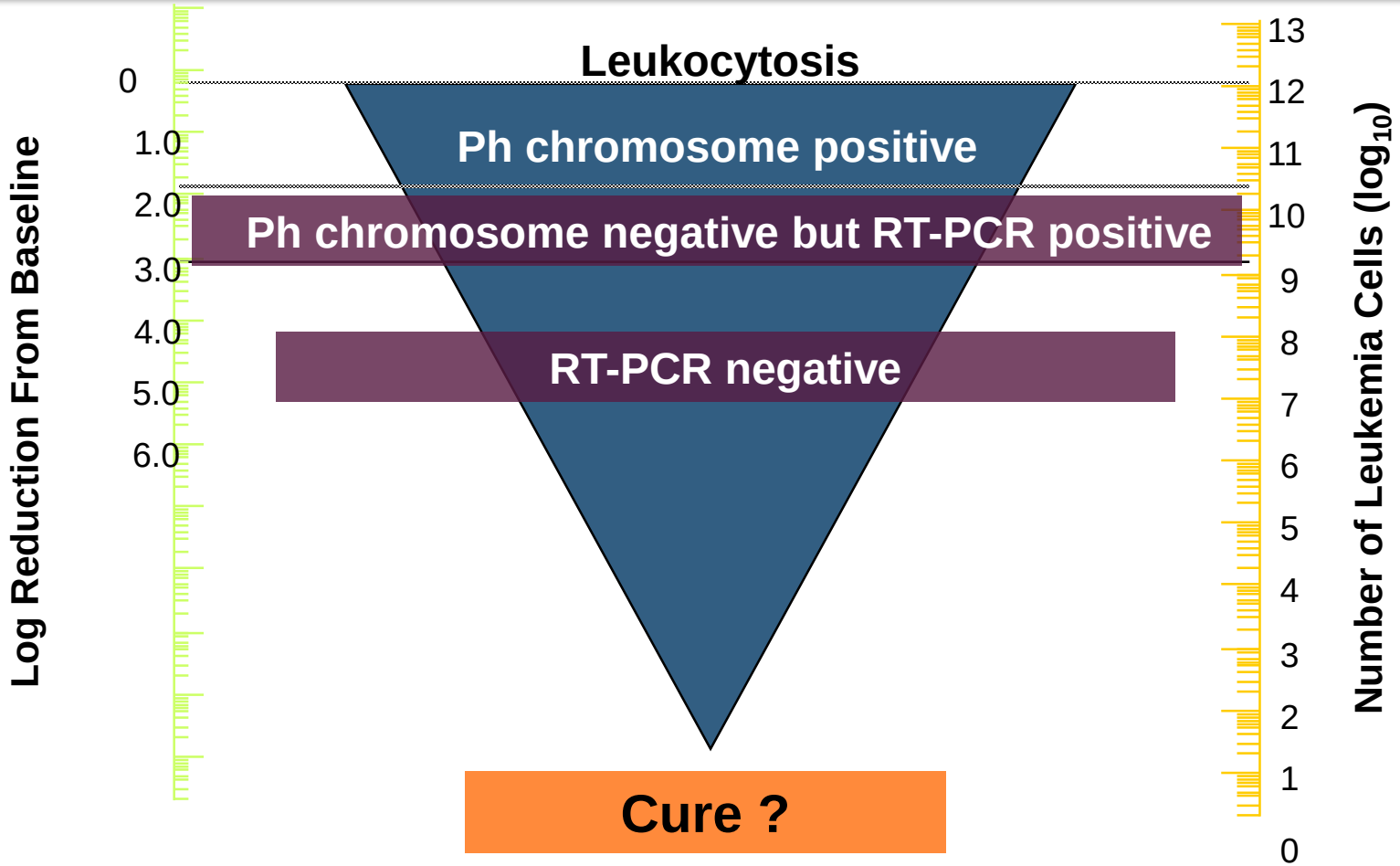
Treatment Response

Level of Response	Definition
Complete hematologic response (CHR)	Normal CBC and differential, no extramedullary disease
Minor cytogenetic response	35%–90% Ph-positive metaphases*
Partial cytogenetic response (PCyR)†	1%–34% Ph-positive metaphases*
Complete cytogenetic response (CCyR)†	0% Ph-positive metaphases*
Major molecular response (MMR)	≥3-log reduction of BCR-ABL
Complete molecular response	Negativity by RT-PCR (≥4.5 log reduction of BCR-ABL

***Cytogenetic response is based on analysis of at least 20 metaphases.**
†PCyR + CCyR = major cytogenetic response (MCyR).

Adapted from NCCN Clinical Practice Guidelines in Oncology: chronic myelogenous leukemia. V.3.2008. http://www.nccn.org. Accessed 02/04/2008; Deininger MW. *Hematology Am Soc Hematol Educ Program*. 2005;174-182.

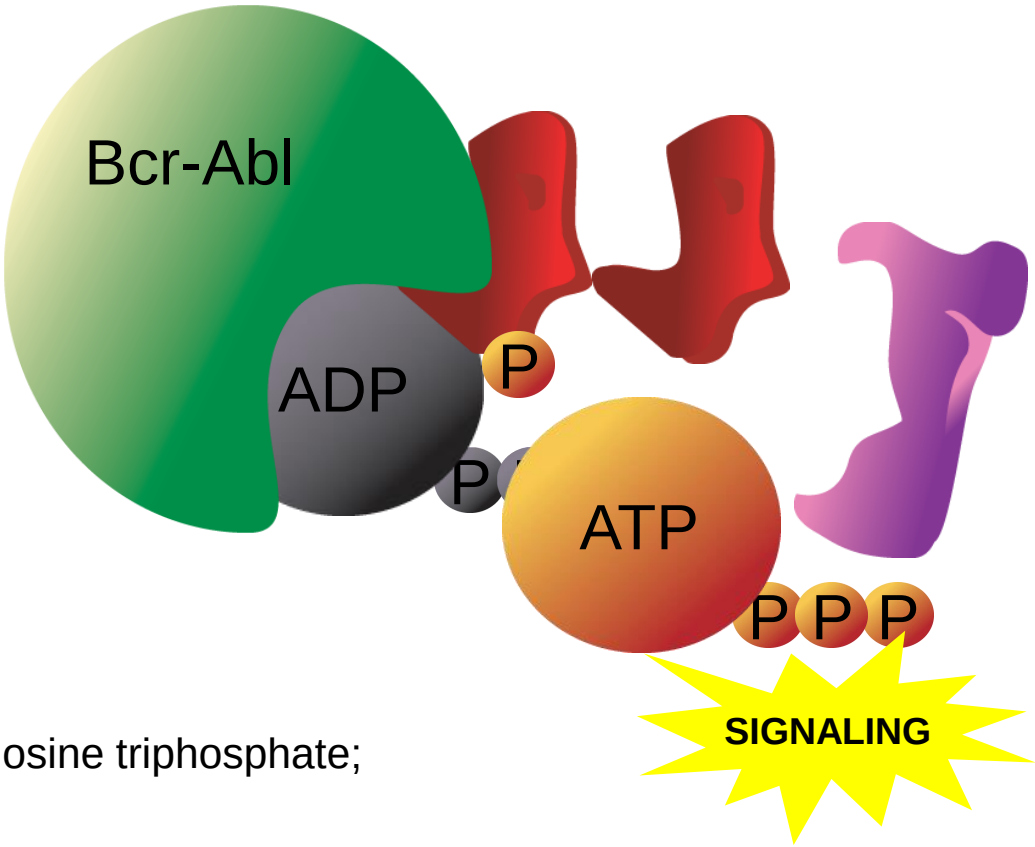
Log Reduction of BCR-ABL Transcripts in Patients Responding to Treatment



RT-PCR = real-time polymerase chain reaction; Ph = Philadelphia.

Normal Bcr-Abl Signaling*

- The kinase domain activates a substrate protein, eg, PI3 kinase, by phosphorylation
- This activated substrate initiates a signaling cascade culminating in cell proliferation and survival

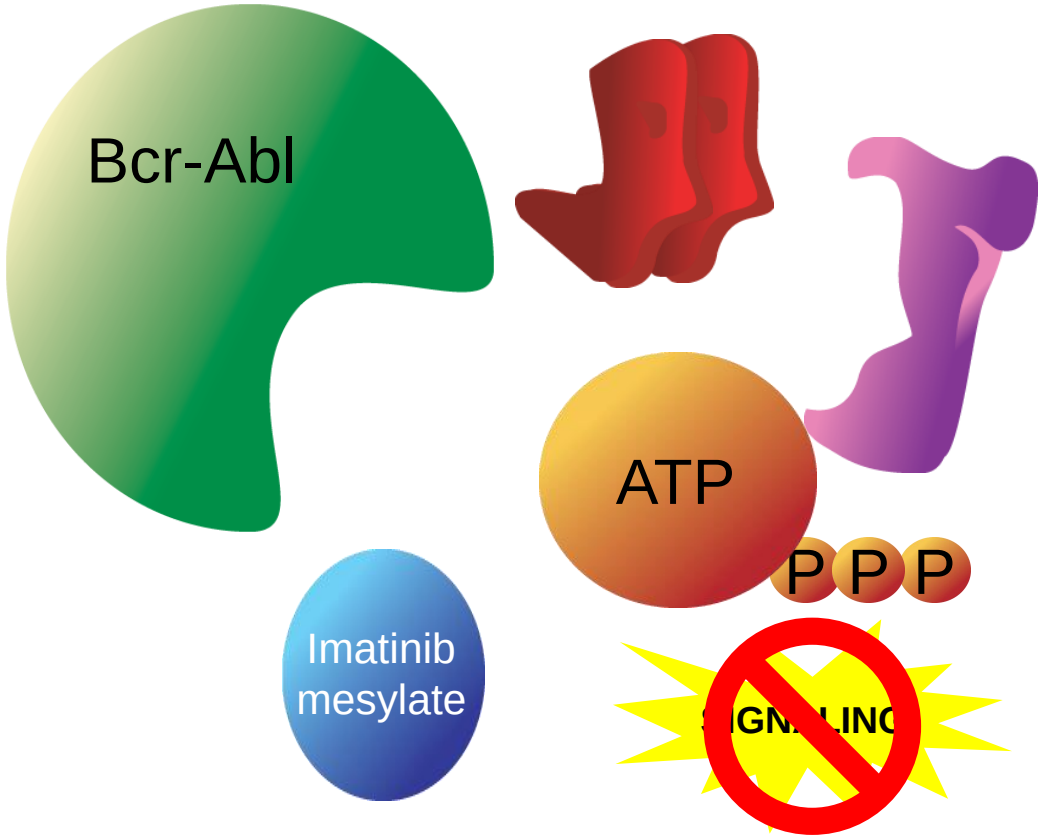


ADP = adenosine diphosphate; ATP = adenosine triphosphate; P = phosphate.

Savage and Antman. *N Engl J Med.* 2002;346:683
Scheijen and Griffin. *Oncogene.* 2002;21:3314.

Imatinib Mesylate - a BCR-ABL-*selective* inhibitor: Mechanism of Action*

- Imatinib mesylate occupies the ATP binding pocket of the Abl kinase domain
- This prevents substrate phosphorylation and signaling
- A lack of signaling inhibits proliferation and survival



Savage and Antman. *N Engl J Med.* 2002;346:683.

Imatinib (Gleevec) - Clinical Efficacy

Phase I Trials

Stage of CML	Response Rate (%)	
	Hematologic	Major Cytogenetic
Chronic Phase (IFN-failure)	98	31
Myeloid Blast Crisis	55	11
Lymphoid Blast Crisis, t(9;22)-associated ALL	70	15

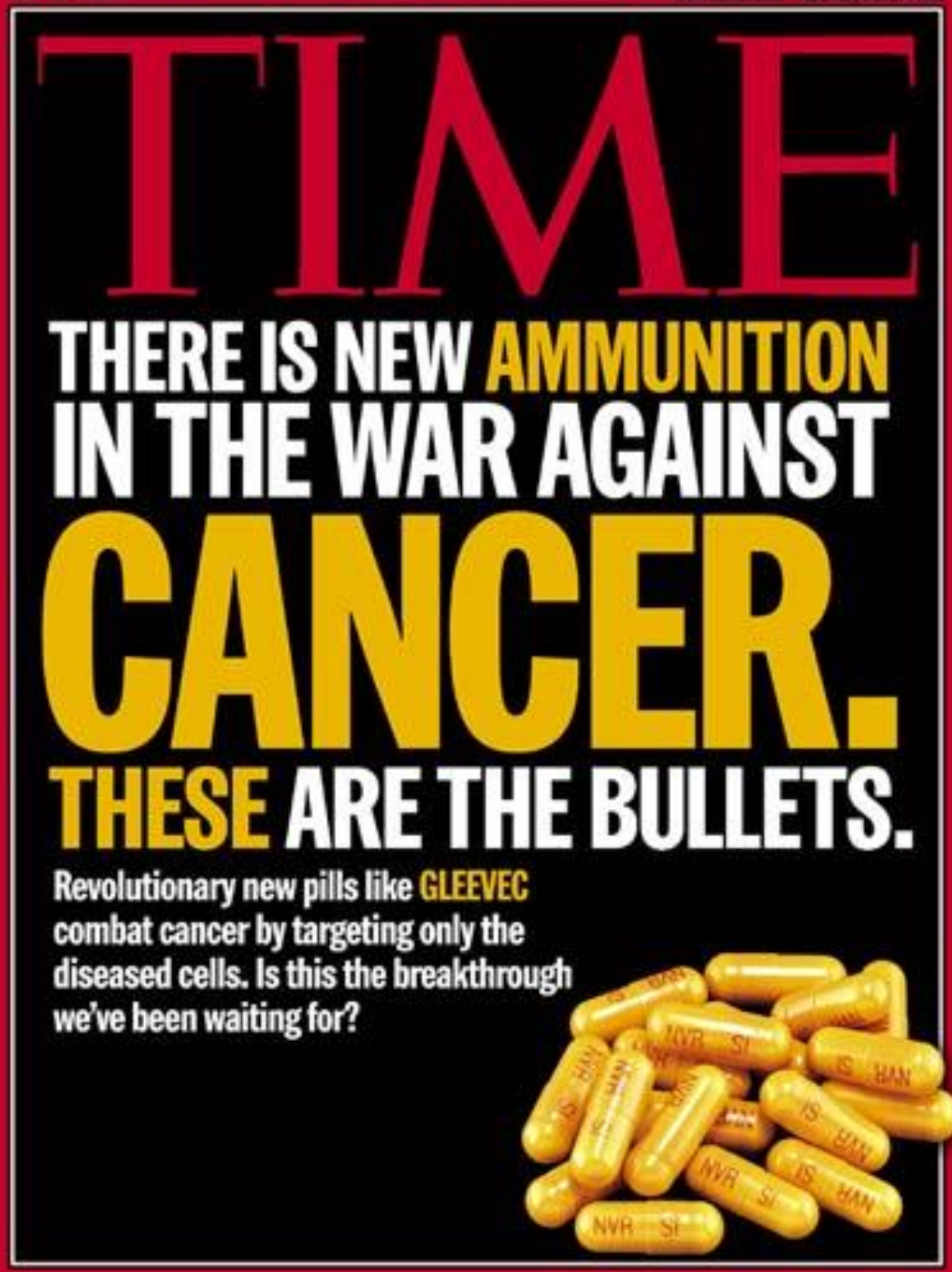
Druker et al, NEJM 344 (2001)

Imatinib (Gleevec) - *Clinical Efficacy*

Phase III Trials (Chronic Phase CML)

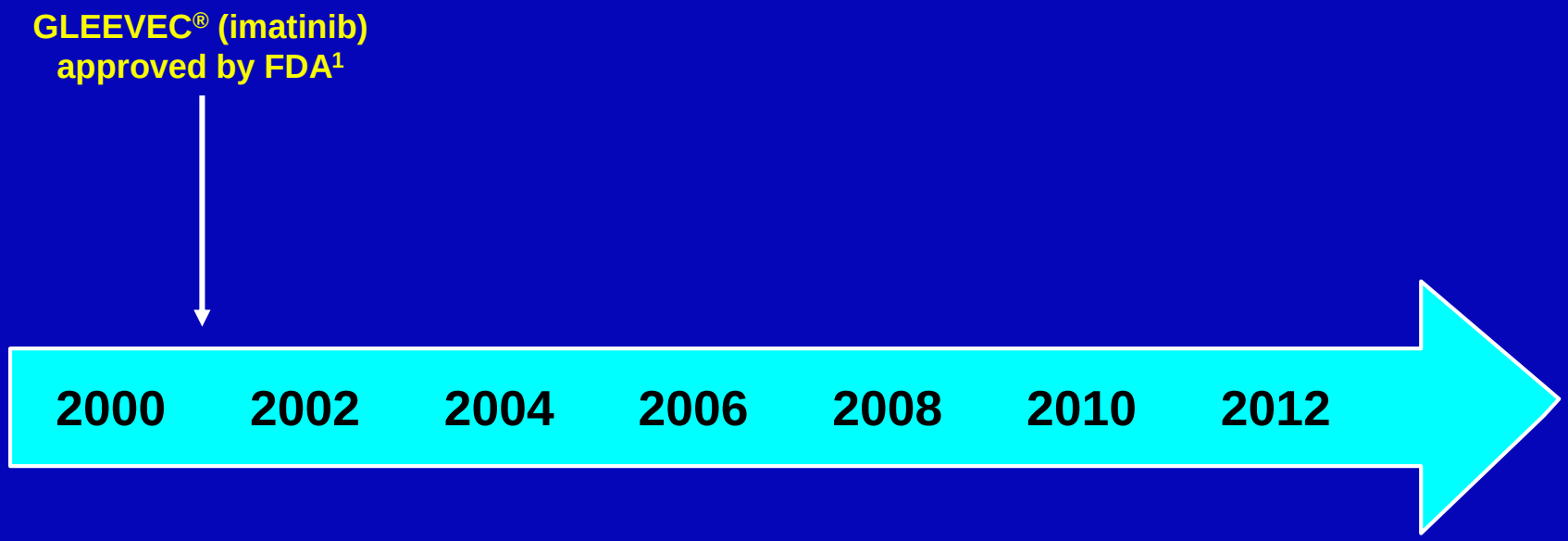
Treatment	Response Rate (%)	
	Hematologic	Major Cytogenetic
Imatinib	94	83
Interferon + Ara-C	55	20

O'Brien et al, NEJM, 2003



FDA Approval, May 2001

Evolving CML Treatment Landscape

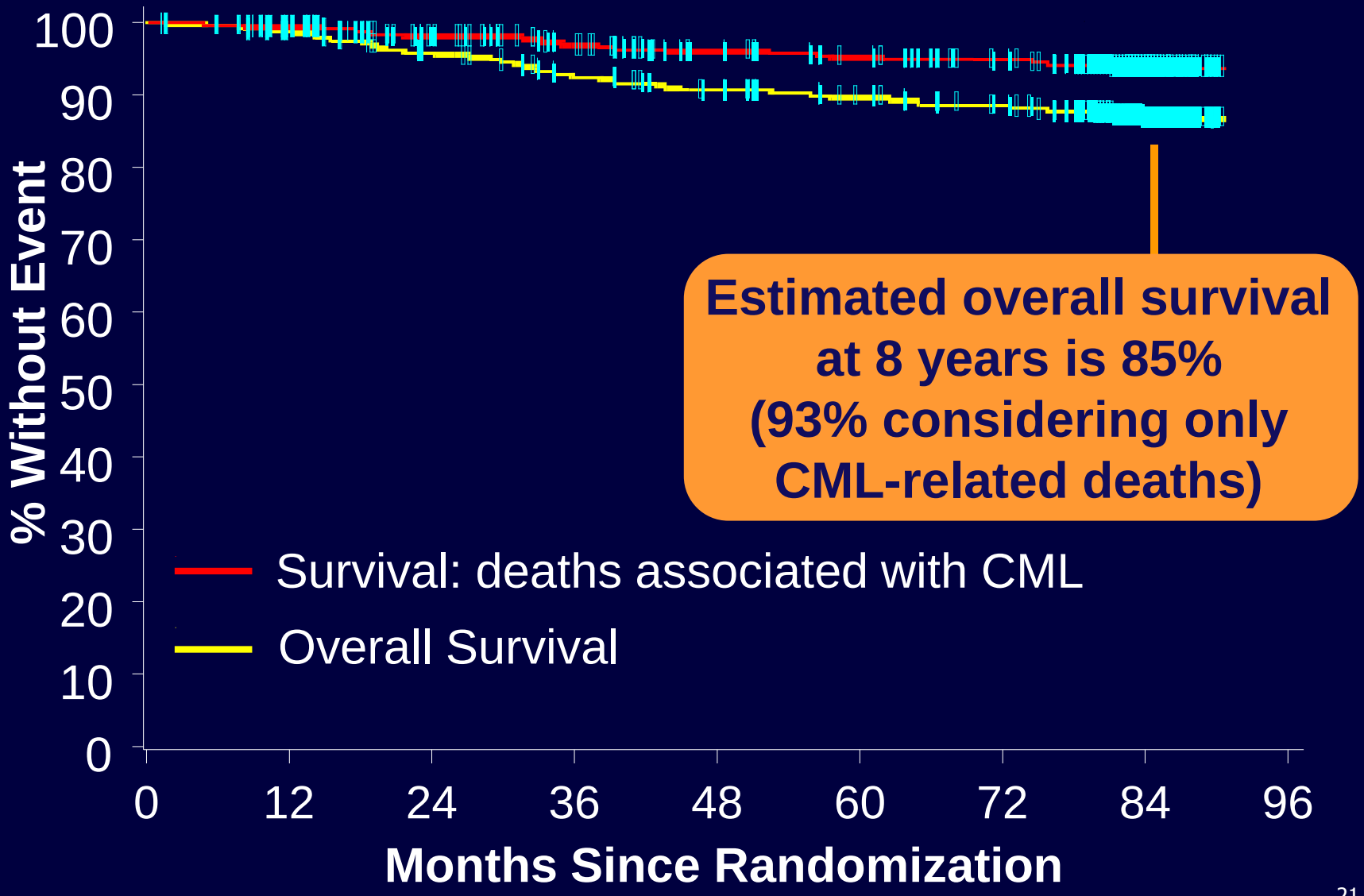


IMATINIB AS FRONTLINE THERAPY FOR CML

7-8 year update of newly-diagnosed Chronic Phase CML patients treated with 400 mg daily imatinib

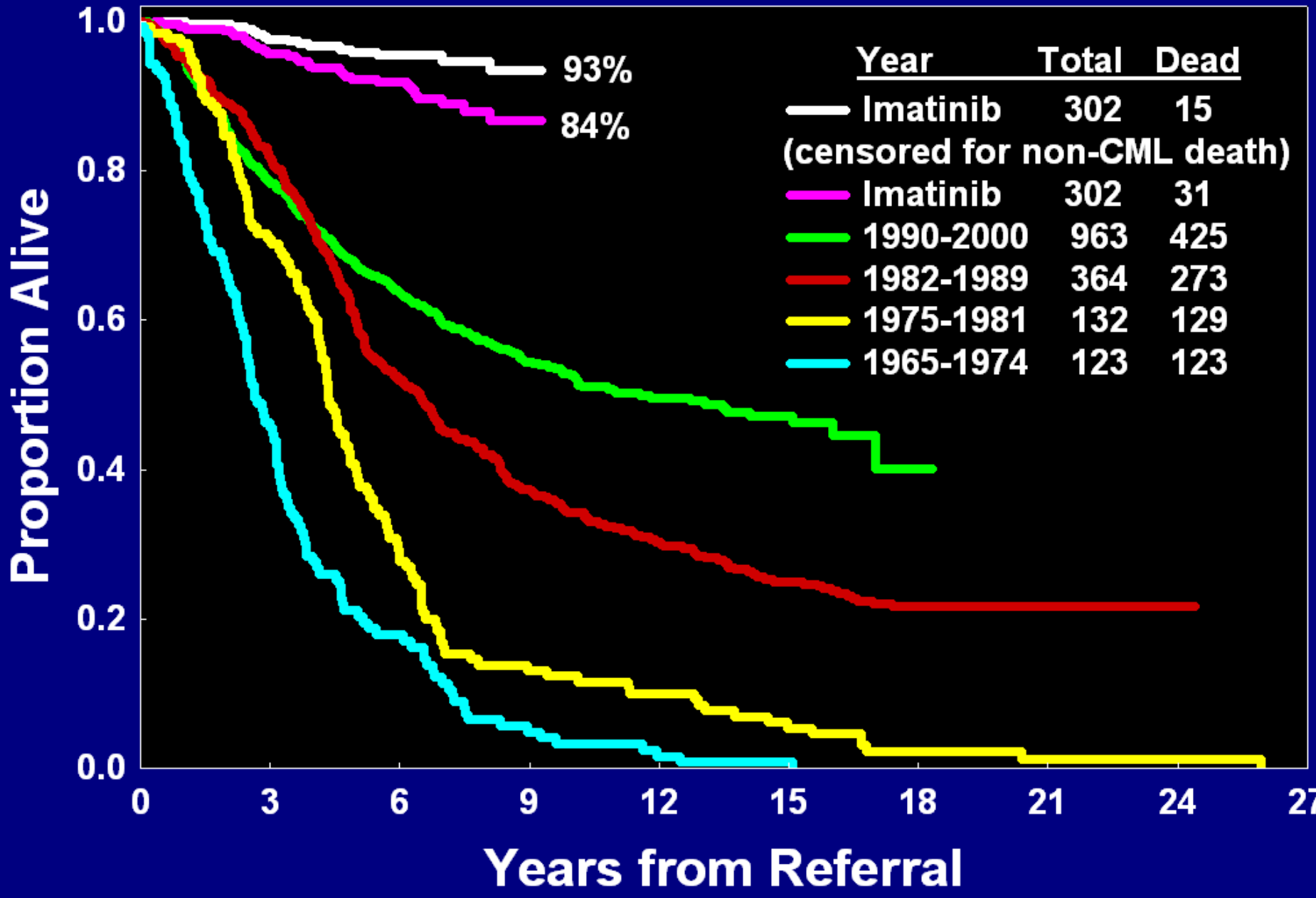
O'Brien et al. ASH 2008, Abstract 186

Overall Survival (ITT Principle): Imatinib Arm



Deininger et al. ASH 2009. Abstract 1126

CML Survival at MDACC. 1965-Present (N=1884)



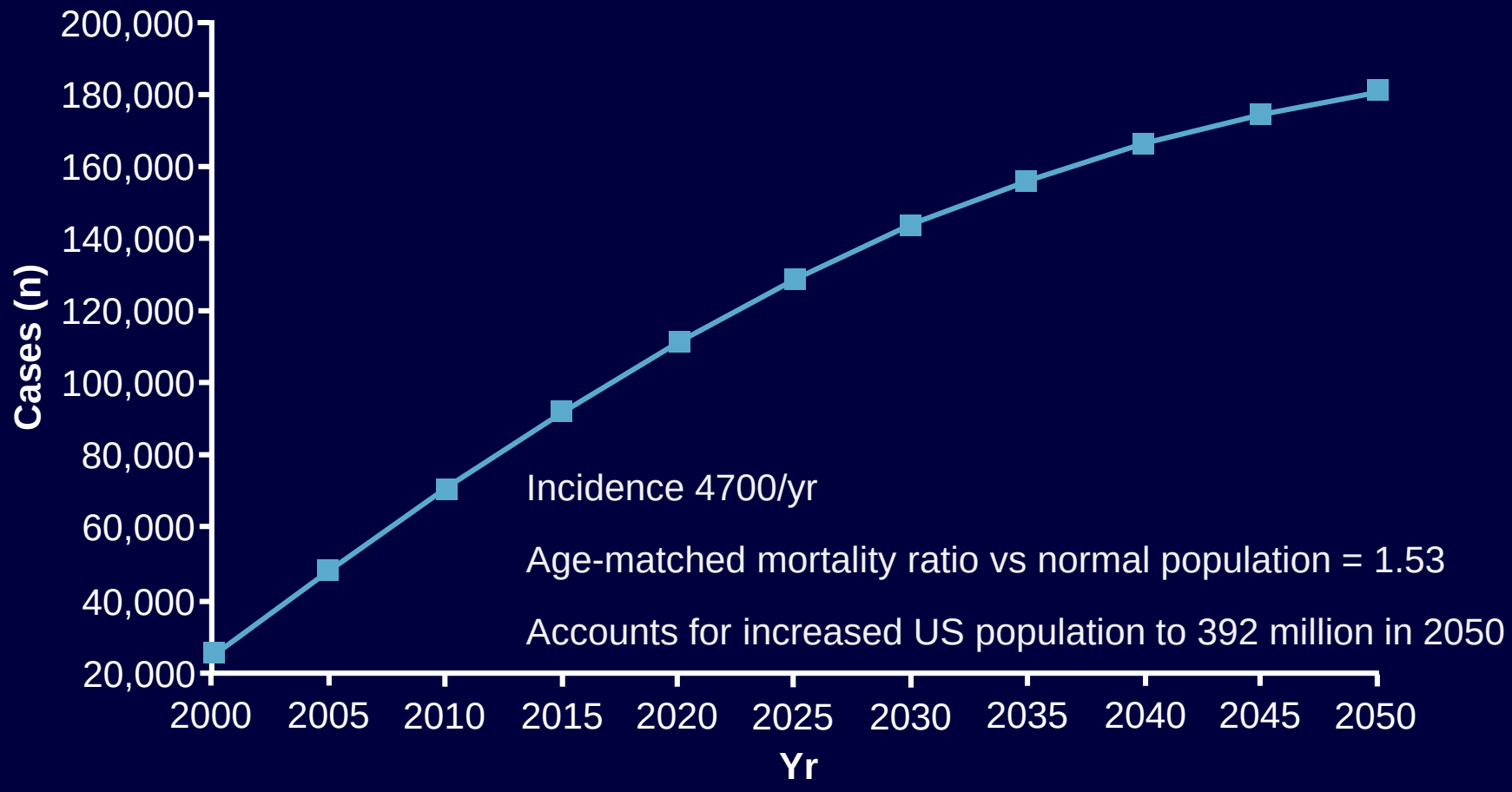
Incidence And Mortality Of CML

Year	Number of Cases	Number of Deaths (%)
1997	4300	2400
2007	4570	490

Based on current data,
median survival is expected to exceed 15-20 years.

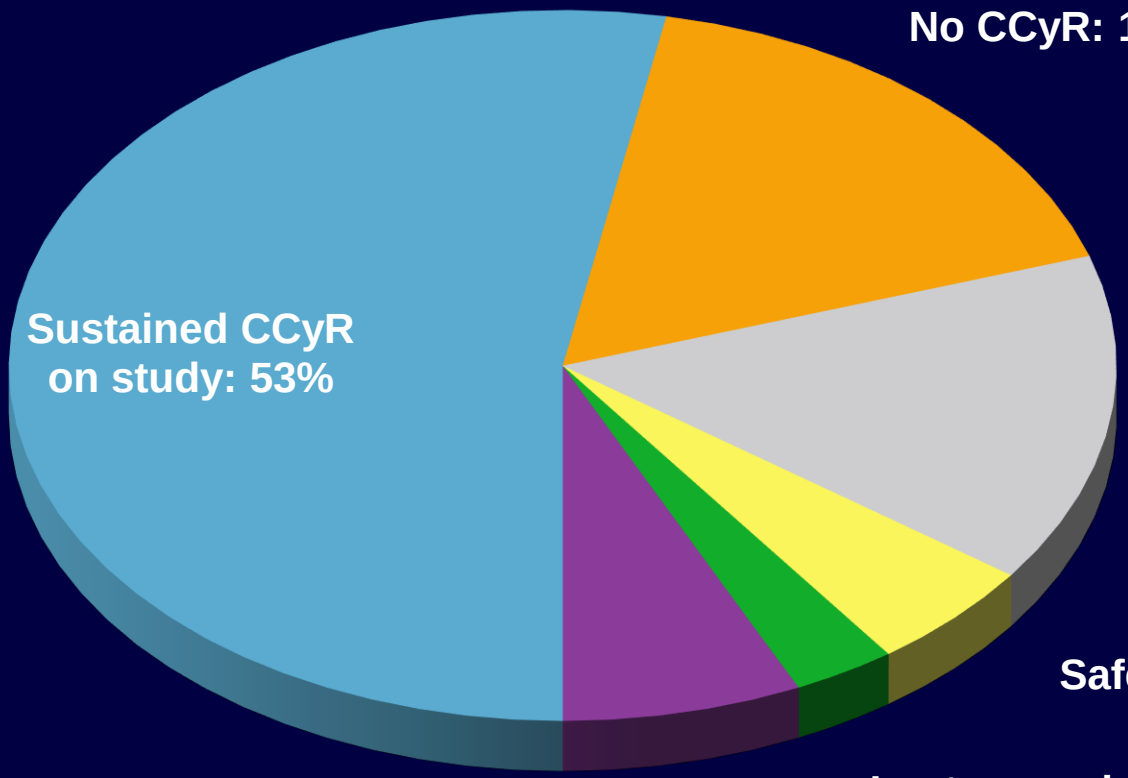
Parker et al, 1997; Jemal et al, 2007; Alvarez et al, 2007.

Estimate of Rapidly Increasing CML Prevalence



Huang X, et al. Cancer. 2012;118:3123-3127.

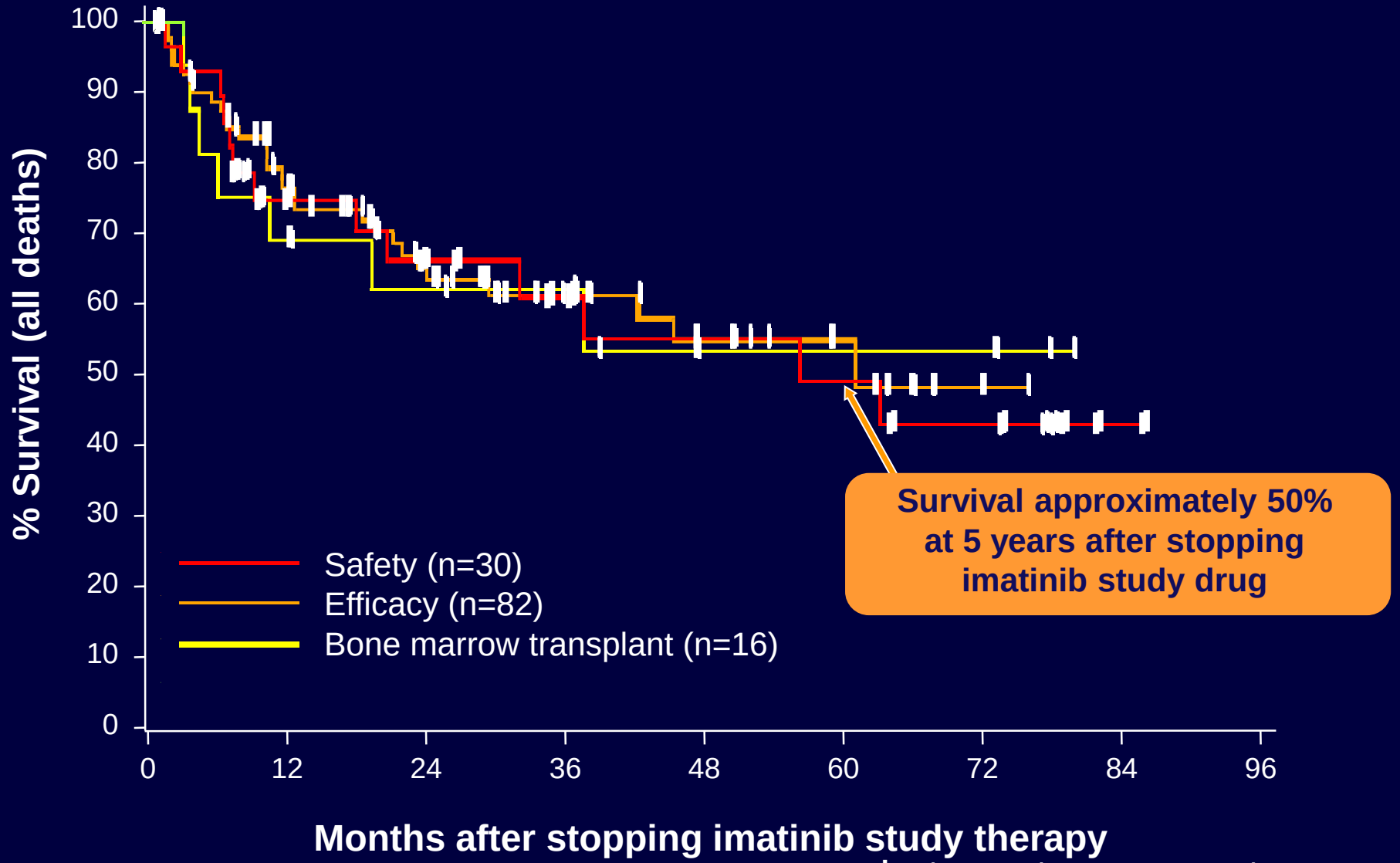
Imatinib: IRIS 8-Yr Update Shows 37% Have Unacceptable Outcome



*Unacceptable outcome.

Deininger M, et al. ASH 2009. Abstract 1126.

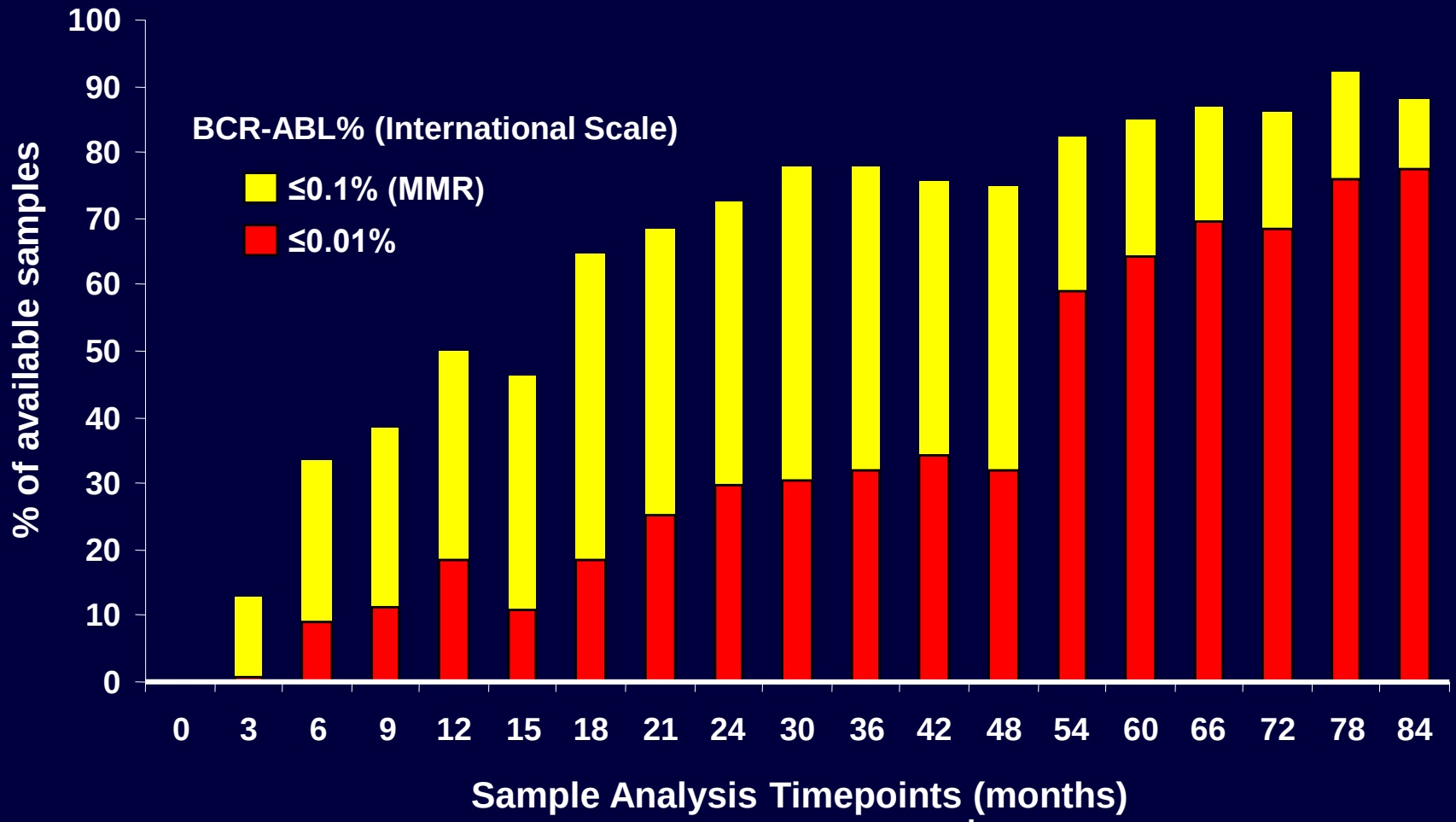
Survival of Patients Who Discontinued Imatinib Study Therapy



O'Brien et al. ASH 2008, Abstract 186

Molecular Response Rates

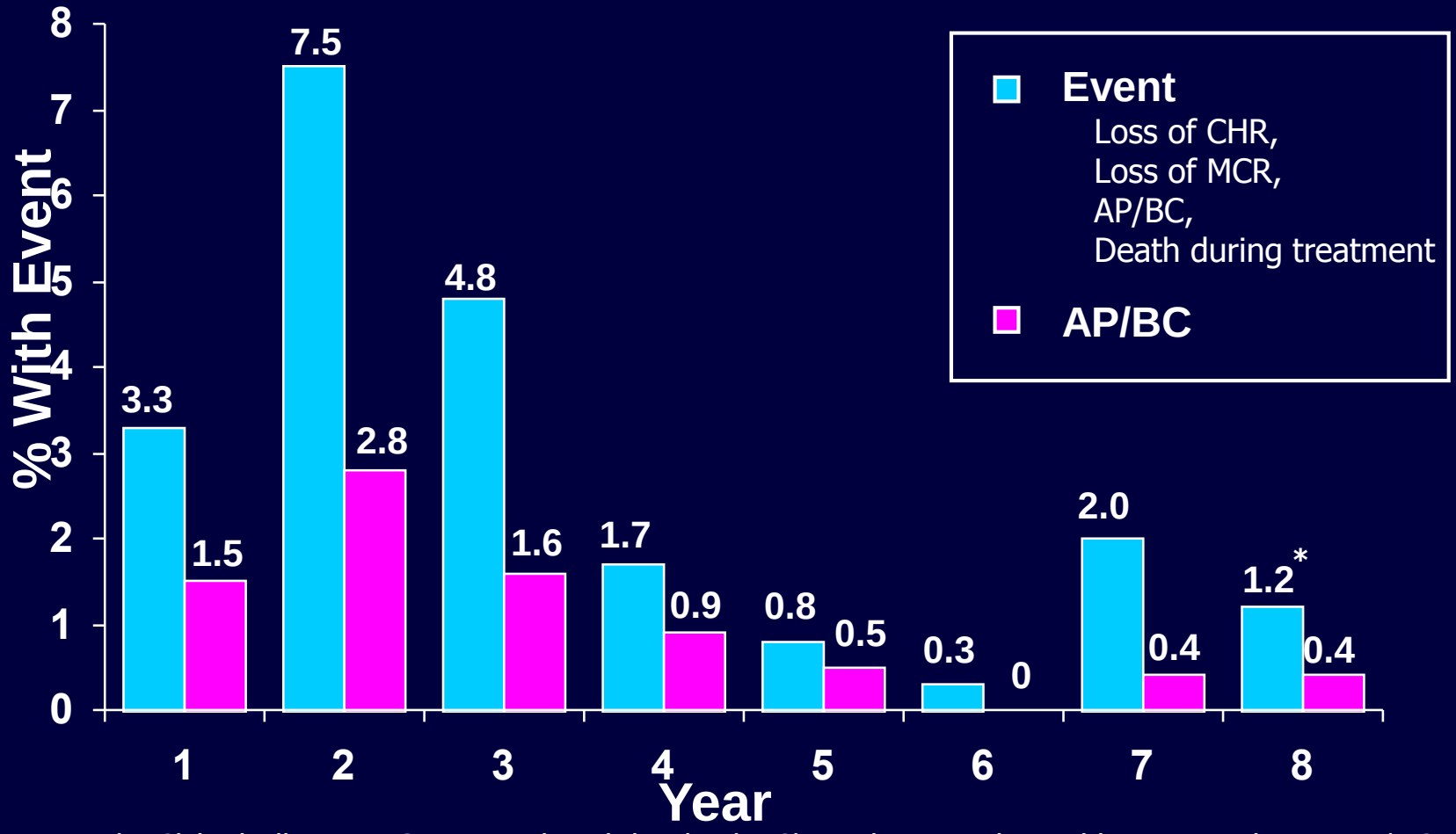
- Major molecular response (MMR) and the depth of molecular response increase over time



O'Brien et al. ASH 2008, Abstract 186

Annual Event Rates: Imatinib Arm

- KM estimated EFS at 8 years = 81%
- KM estimated rate without AP/BC at 8 years = 92%



*Total events (n=3) including two CML-unrelated deaths (n=2), and one patient with progression to AP/BC

Deininger et al. ASH 2009, Abstract 1126

Most Frequently Reported AEs: First-Line Imatinib

Most Common Adverse Events (by 5 Years)	All Grade AEs Patients, %	Grade 3/4 AE's Patients %
Superficial Edema	60	2
Nausea	50	1
Muscle cramps	49	2
Musculoskeletal pain	47	5
Diarrhea	45	3
Rash/skin problems	40	3
Fatigue	39	2
Headache	37	<1
Abdominal pain	37	4
Joint pain	31	3

- Only Serious Adverse Events (SAEs) were collected after 2005
- Grade 3/4 adverse events decreased in incidence after years 1-2

O'Brien et al. ASH 2008, Abstract 186

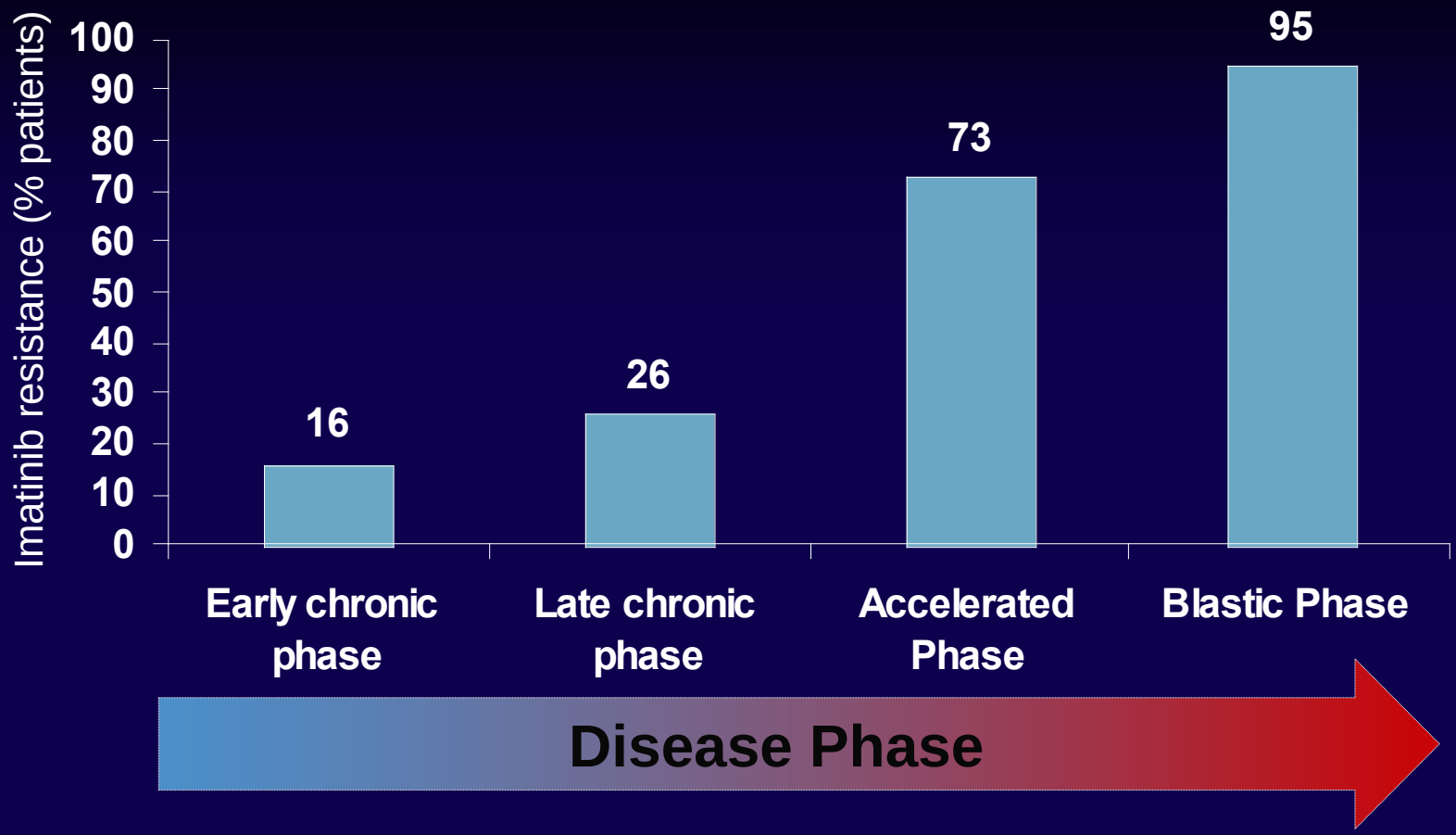
Imatinib - Conclusions

- Imatinib (400 mg daily) remains the standard dose for chronic phase CML patients
- 85% overall survival with imatinib exceeds that of all other CML therapies, with 7% patients dying from CML after eight years
- 82% of patients treated with imatinib achieved a CCyR
  - 55% of all imatinib randomized patients are still on study treatment, and nearly all of these are in CCyR
- Responses are typically durable, and the annual risk of progression generally decreases with time
- No new safety findings seen with long term follow-up

IMATINIB-RESISTANT DISEASE

How is it defined?

The Rate of Loss of Response to Imatinib Associated with the Phase of CML

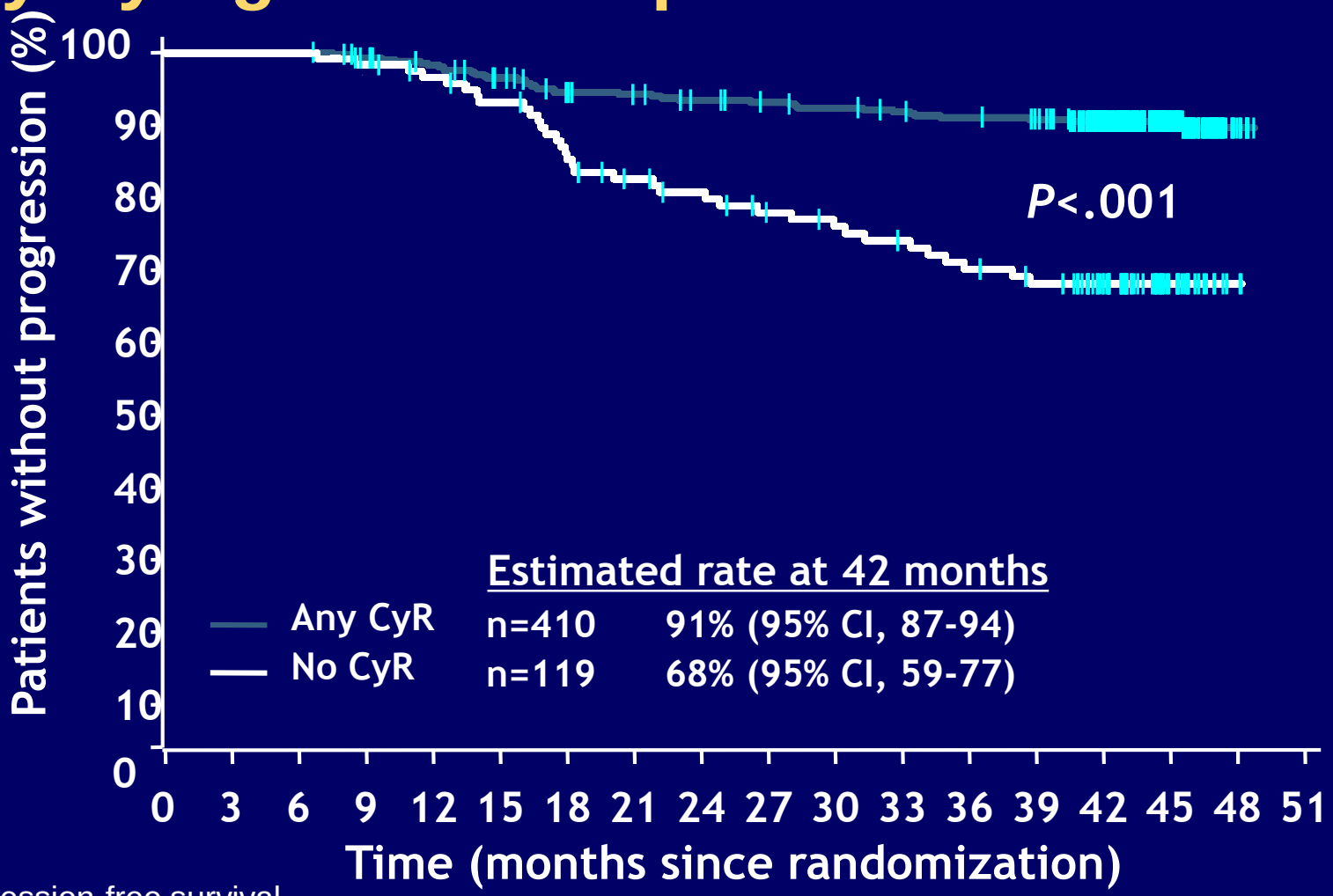


Patients in early CP (disease duration not greater than 6 months) were followed for 42 months. All other patients had been previously treated with interferon and were followed for 48 months.

Shah. *Hematology Am Soc Hematol Educ Program*. 2005;183-187.

RECOGNIZING IMATINIB RESISTANCE

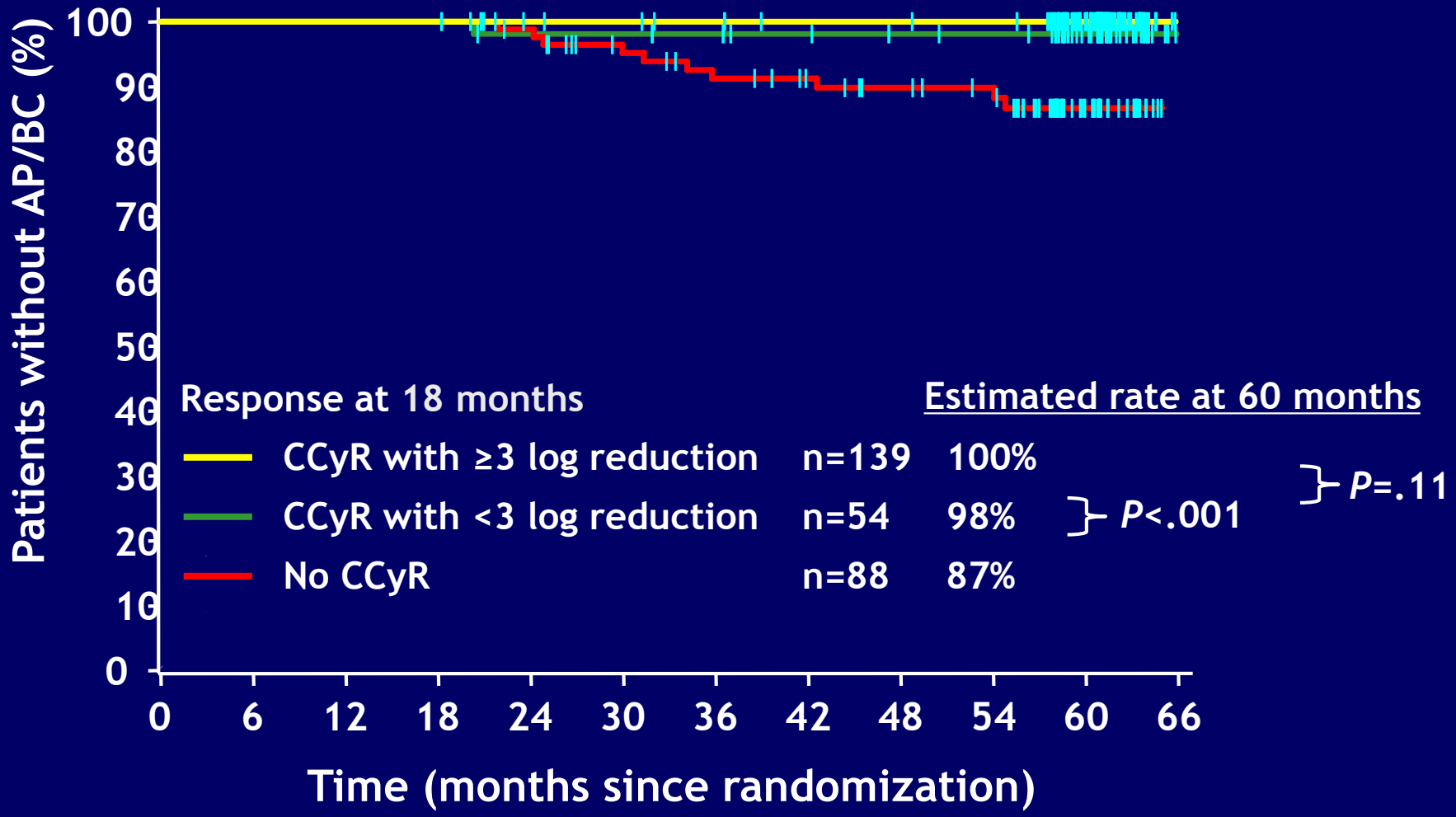
Progression-free Survival on Imatinib by Cytogenetic Response at 6 Months



PFS=progression-free survival.

Adapted from O'Brien SG et al. *N Engl J Med.* 2003;348:994-1004; Findings noted by Druker B, MD (written communication, January 2007).

Imatinib Survival Without Accelerated Phase/Blast Crisis by Molecular Response: IRIS Study



Druker B et al. *N Engl J Med*. 2006;355:2408-2417.

Imatinib Resistance and Intolerance in Chronic Phase CML Definitions

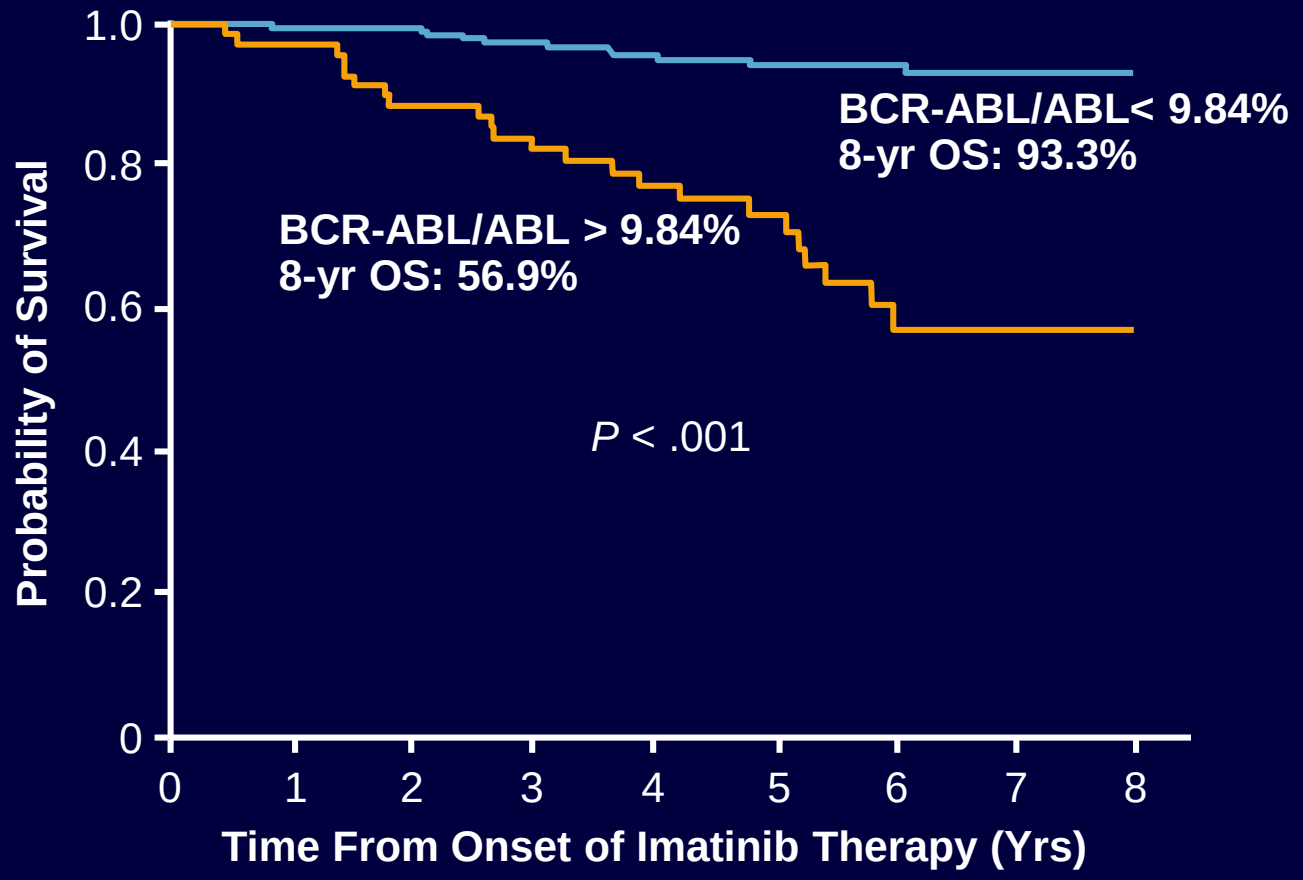
- Resistance can be defined as primary (lack of acceptable initial response) or secondary (loss of an established response)
  - **Primary hematologic resistance** refers to failure to achieve a CHR within 3-6 months of initiating imatinib (~2-4 % of cases*)
  - **Primary cytogenetic resistance** can be defined as:
    - Lack of any cytogenetic response by 6 months
    - Lack of CCyR by 18 months (~25% of cases*)
- Secondary resistance refers to progression after an established hematologic or cytogenetic response – increasing worsening cytogenetics/PCR, increasing white blood cell count, or disease transformation to accelerated/blast phase

***These categories are NOT mutually exclusive**

IMATINIB-RESISTANT DISEASE

Can it be identified earlier than six months, ideally by less invasive methods than bone marrow aspiration?

BCR-ABL/ABL after 3 Mos of Imatinib Predicts OS Outcomes (Hammersmith)



Marin D, et al. J Clin Oncol. 2012;30:232-238.

Molecular Response after 3 Months of Imatinib Treatment Correlates with Outcome

- In 282 patients with CP-CML who were treated at the UK Hammersmith hospital, patients with a BCR-ABL transcript level >9.84% after three months of imatinib had inferior survival probability at 8 years (56.9 vs 93.3%)[1]
- In 949 CP-CML patients treated with one of four imatinib-containing regimens in Germany, a BCR-ABL level of >10% was associated with a higher incidence of treatment failure at 12 months (17.4% vs 2.5%), at 18 months (20.7% vs 5.8%) and disease progression (8.1% vs 2.7%) when compared with patients whose BCR-ABL level was <10%[2], and significantly superior overall survival (95% vs 87%)[3].

[1]Marin D, et al. J Clin Oncol. 2012;30:232-238.

[2]Hanfstein B, et al, ASH 2010 abstract #360

[2]Hehlmann R, et al, ASH 2013 abstract #6510

Indications for Testing/Monitoring Strategy

Cytogenetics and PCR

- At diagnosis of CML
  - Baseline cytogenetics and PCR
- While patient is responding
  - BM cytogenetics at 3 and/or 12 mo (and at 18 mo if no CCyR by12)
  - Blood for PCR for BCR-ABL every 3 mo
- After patient achieves CCyR
  - Blood BCR-ABL PCR every 3 mo, every 3-6 months after three years
  - BM cytogenetics only as clinically indicated
- When BCR-ABL transcripts rises (PCR) by 1 log
  - Evaluate compliance
  - BM cytogenetics and ABL mutation analysis for substantial rise

ABL Mutation Testing

- Chronic phase
  - Inadequate initial response to treatment
    - No 1-log reduction in PCR or MCyR at 3 mo,
    - No CCyR by 12-18 mo
  - Any loss of response (WBC, cytogenetics, or 1 log increase in PCR)
  - Progression to accelerated of blast phase
- Accelerated and blast phase
  - Any loss of response (WBC, cytogenetics, or PCR)

Modified from NCCN Clinical Practice Guidelines in Oncology: chronic myelogenous leukemia. V.2.2013. http://www.nccn.org.

Defining TKI Failure

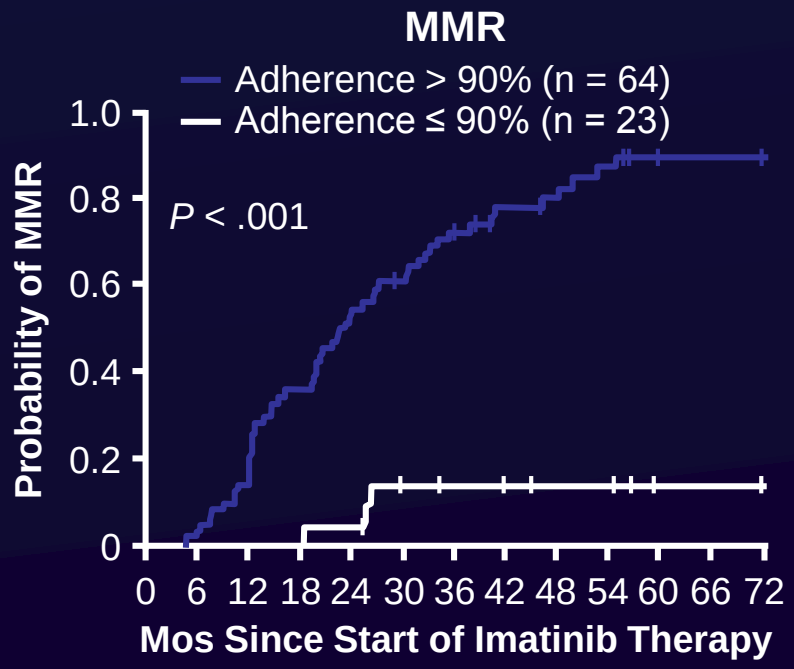
	NCCN[1]
Months	**Failure**
3	**< 1-log PCR reduction or lack of MCyR**
12	**< MMR or <CCyR**
18	**< MMR or <CCyR**
Anytime	**Loss of hematologic response, cytogenetic response or molecular response; progression to accelerated/blast phase CML**

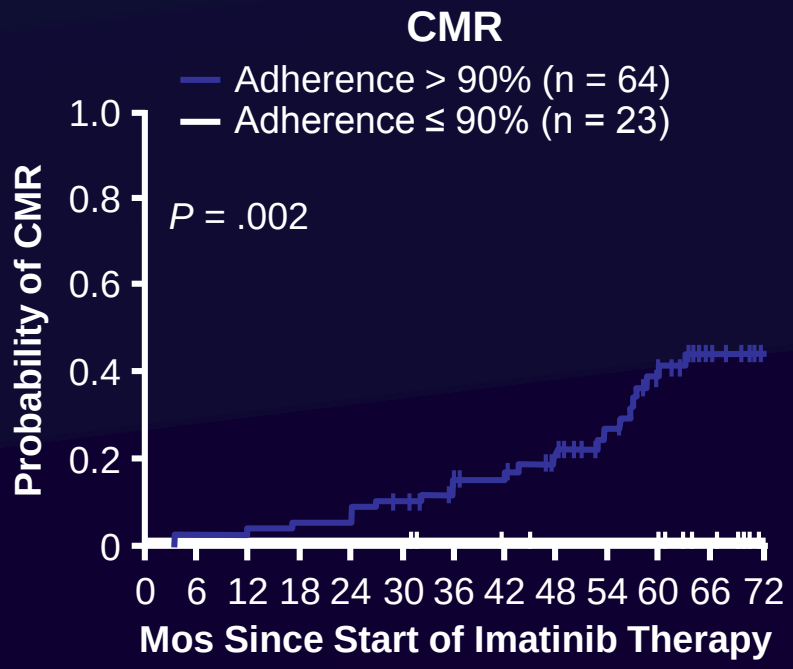
CHR, complete hematologic remission; CyR, cytogenetic response; PCyR, partial cytogenetic response; MCyR (0-7/20 Ph+ metaphases), major cytogenetic response; CCyR, complete cytogenetic response (0/20 Ph+ metaphases); MMR, major molecular response (3-log reduction).

1. NCCN Oncology Guidelines

Long-Term Adherence to Imatinib Is Critical for Achieving Molecular Response

- Adherence to imatinib tracked for 3 mos in 87 consecutive CML patients with CCyR using microelectronic monitoring devices





Marin D, et al. J Clin Oncol. 2010;28:2381-2388.

IMATINIB-RESISTANT DISEASE

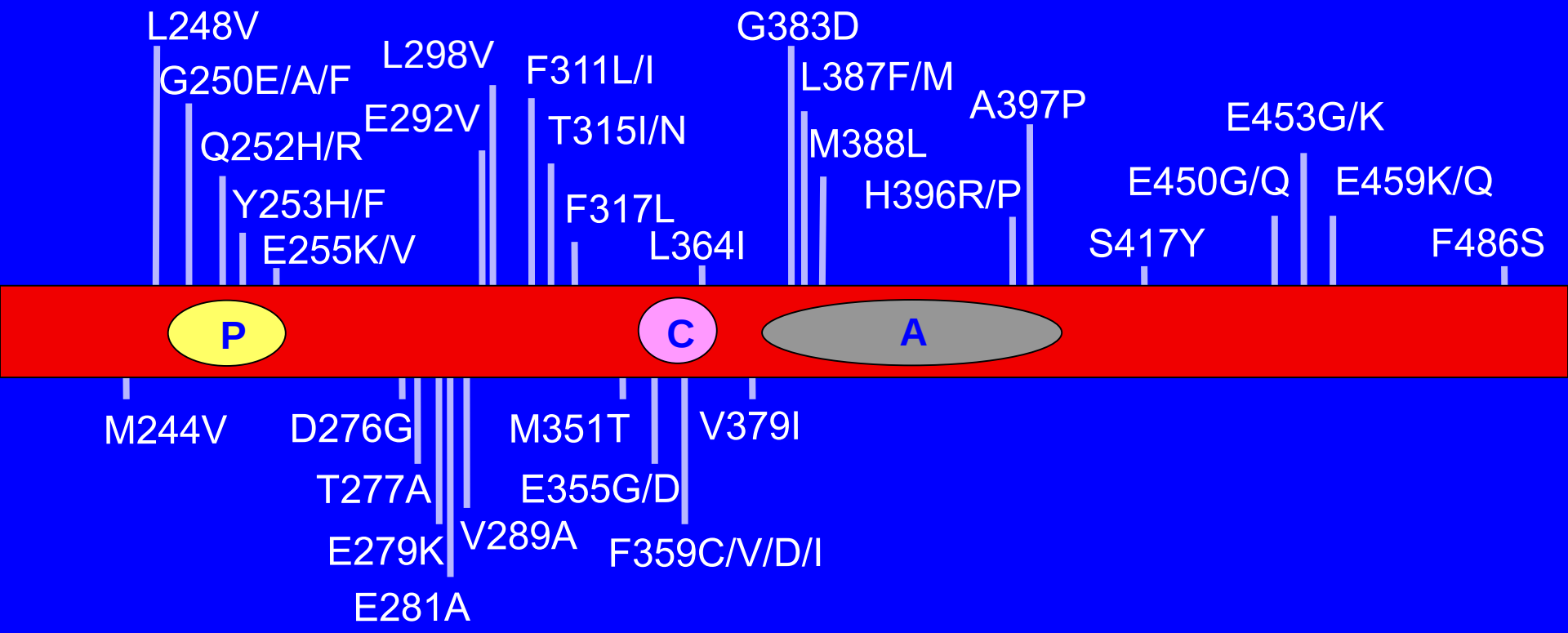
What are its causes?

Clinical Resistance to Imatinib Mechanisms

- **Primary resistance**
  - Insufficient inhibition of BCR-ABL
    - Can be due to low plasma levels, activity of drug pumps, etc
  - Individual variation in normal bone marrow reserve (low levels of normal hematopoietic stem cells in some patients)

- **Secondary resistance**
  - Outgrowth of one or more clones harboring an imatinib-resistant BCR-ABL kinase domain mutation (most common)
  - Overproduction of BCR-ABL (e.g. via genomic amplification)
  - BCR-ABL-independent mechanisms (poorly understood)

(Incomplete) map of *BCR-ABL* kinase domain mutations associated with clinical resistance to imatinib

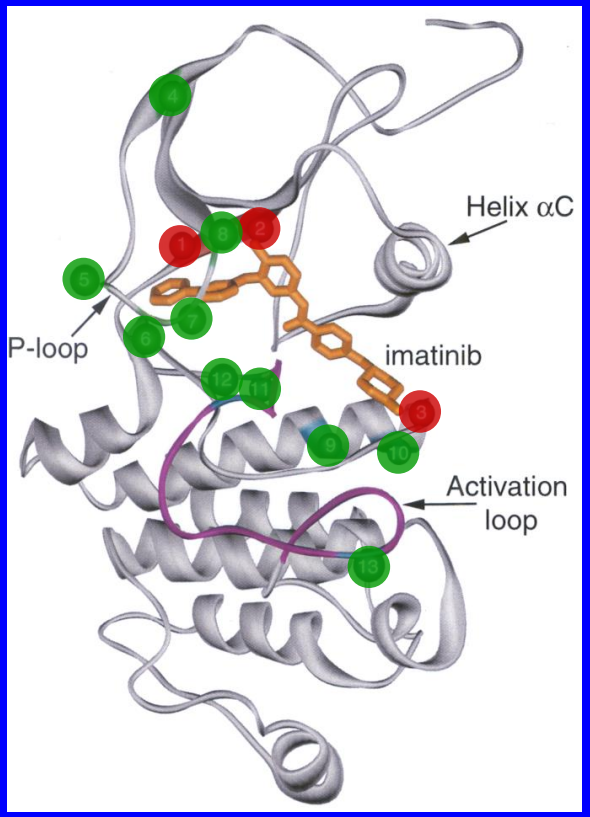


Gorre et al, 2001; von Bubnoff et al, 2002; Branford et al, 2002; Hofmann et al, 2002; Roche-L'Estienne et al, 2002; Shah et al, 2002; Hochhaus et al, 2002; Al-Ali et al, 2004

Courtesy Tim Hughes

Role of Kinase Conformation in Imatinib Resistance

- Point mutations in Bcr-Abl kinase domain can destabilize the inactive conformation



Mutations that directly affect imatinib binding

Mutations that affect the conformation required to bind imatinib

Shah NP et al. *Cancer Cell.* 2002;2:117-125.

Molecular Mechanisms of Resistance to Imatinib — Implications

BCR-ABL kinase inhibitors that are:

(1) more potent than imatinib and
(2) have activity against imatinib-resistant kinase domain mutations

may be of significant therapeutic benefit to imatinib-resistant and -intolerant patients

“Second-generation” ABL Kinase Inhibitors for Imatinib-Resistant/Intolerant CML

FDA-approved

Dasatinib

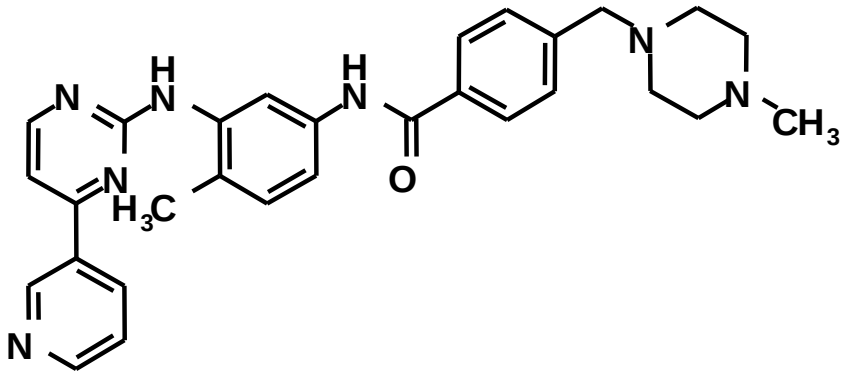
Nilotinib

Bosutinib

In vitro, these agents are more potent than imatinib, and are active against nearly all imatinib-resistant mutations tested in the laboratory with the notable exception of BCR-ABL/T315I

Dasatinib is a BCR/ABL inhibitor that is much more potent than imatinib in vitro

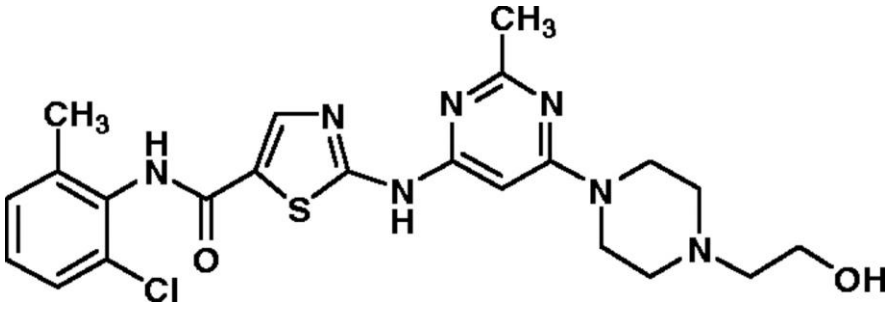
Imatinib (STI571)



1x

Binds inactive conformation

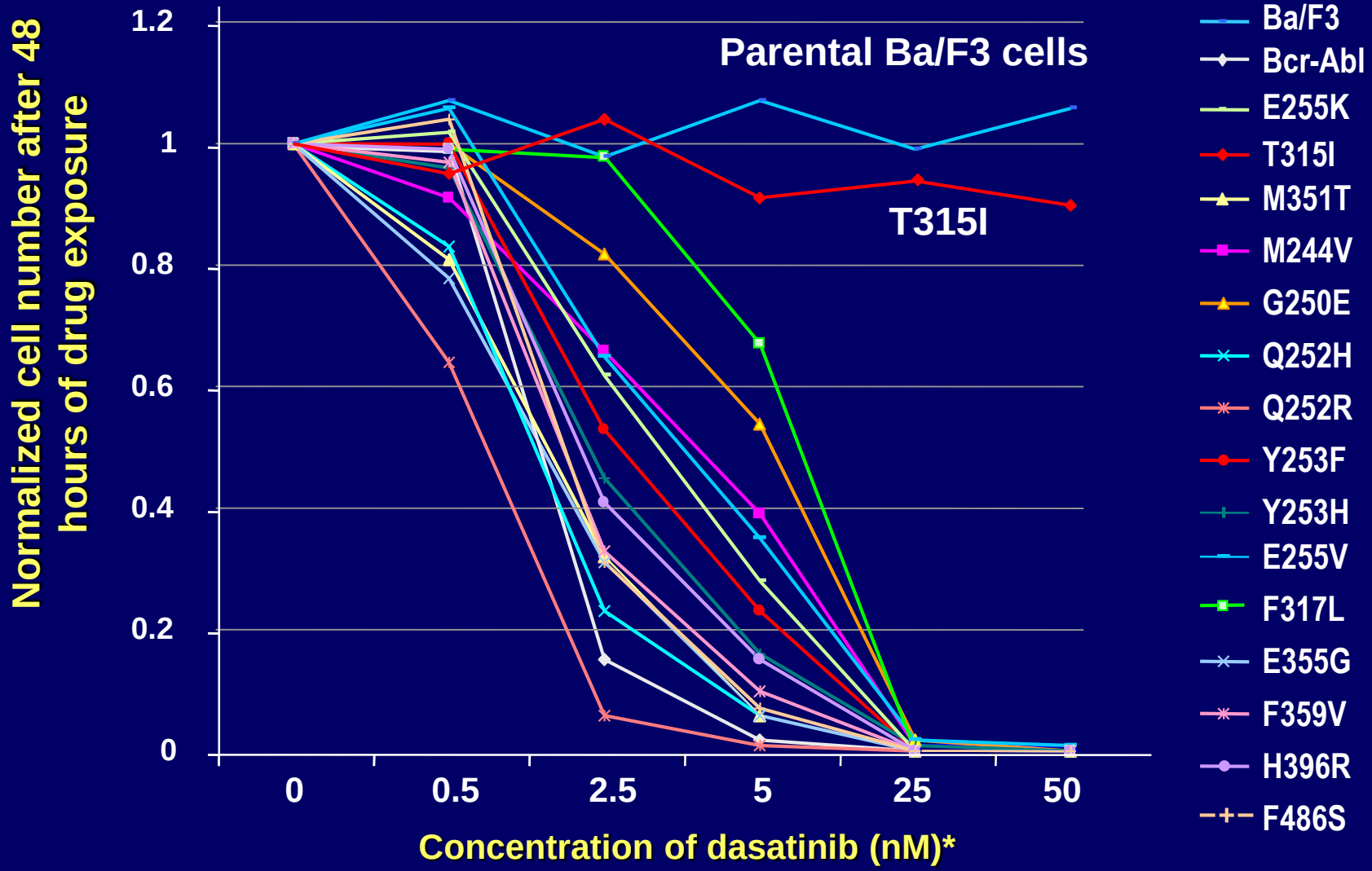
Dasatinib (BMS-354825)



300x

Binds active conformation

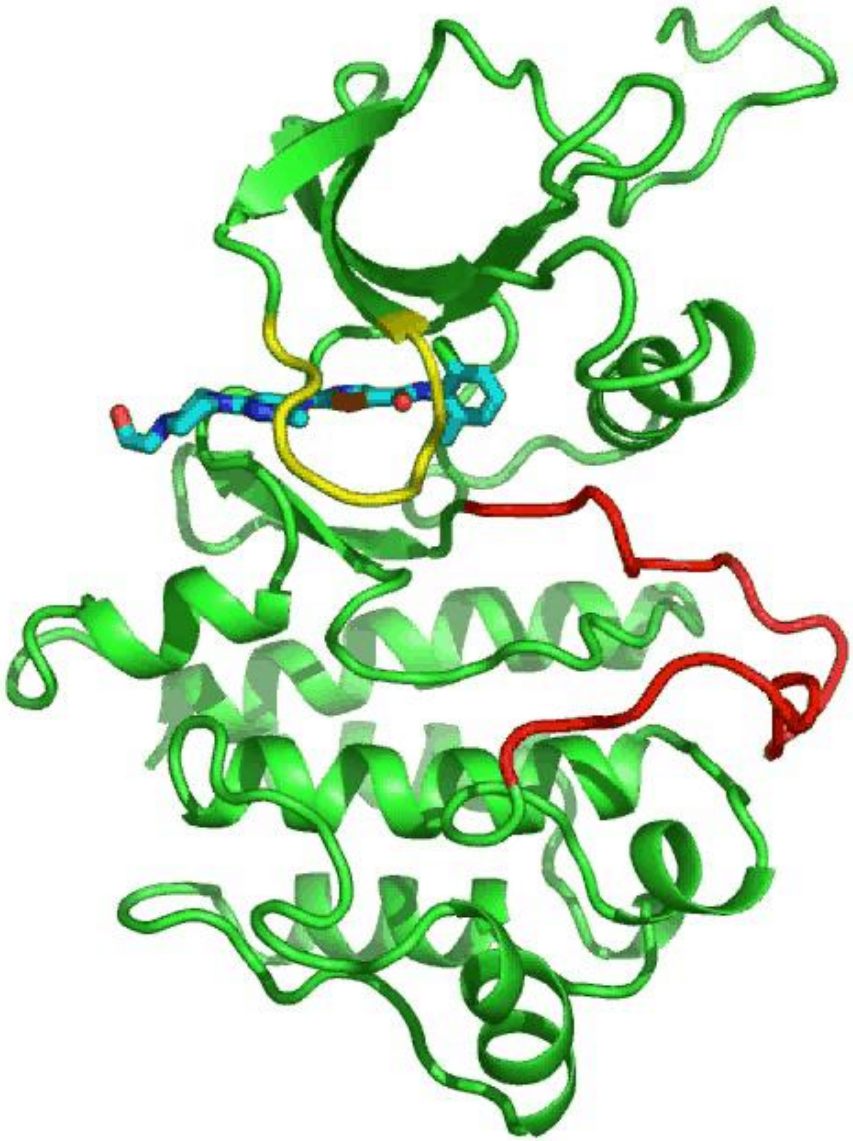
Dasatinib Inhibits Growth of 14/15 Imatinib-Resistant BCR-ABL-Expressing Ba/F3 Cell Lines in vitro



Shah et al, Science, 2004

**Dasatinib is 300-400 more potent than imatinib in vitro*

Differential binding of dasatinib (BMS-354825) and imatinib to ABL kinase



Dasatinib: Predicted Efficacy Against Known Mechanisms of Clinical Resistance to Imatinib

- **BCR-ABL kinase domain point mutation**

  - (except T315I-associated cases)

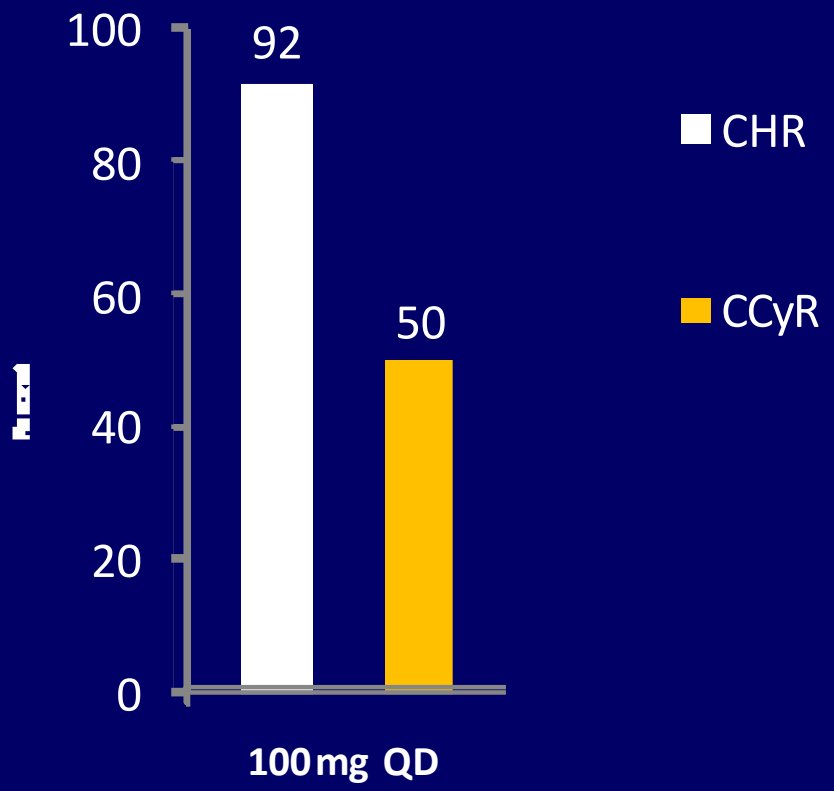
- **BCR-ABL overexpression**

  - (increased potency)

- **BCR-ABL-independent resistance**

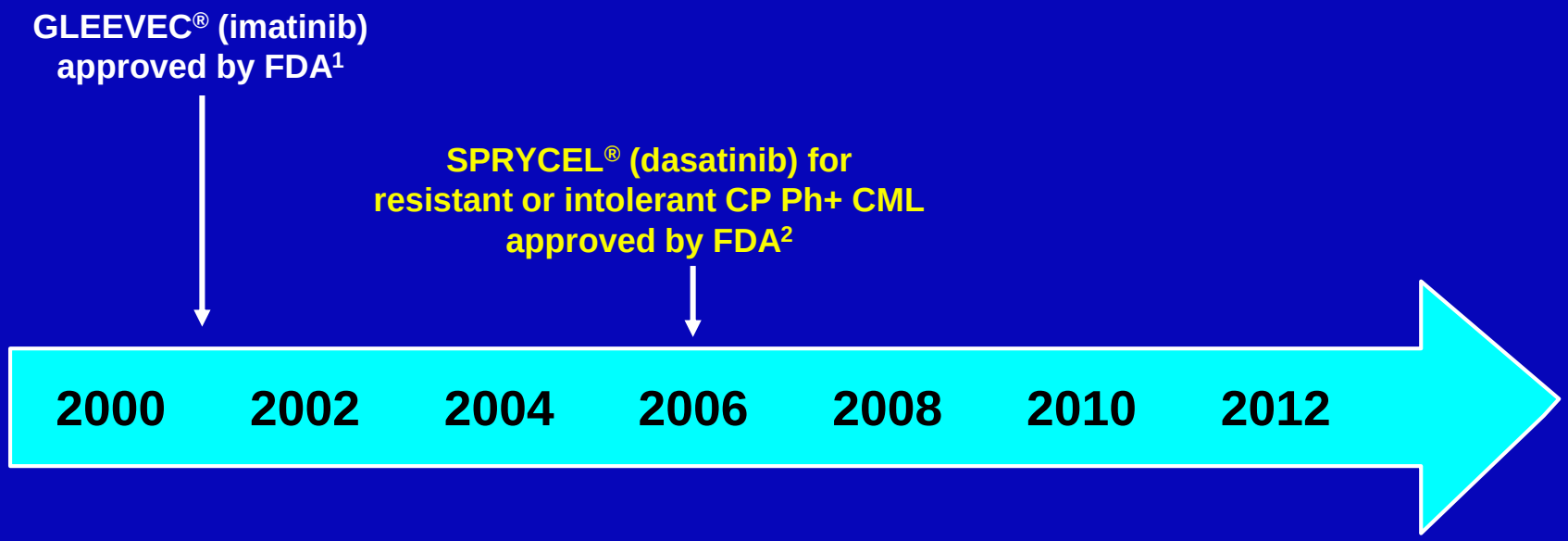
  - (unlikely)

Dasatinib for chronic phase CML patients with resistance or intolerance to imatinib



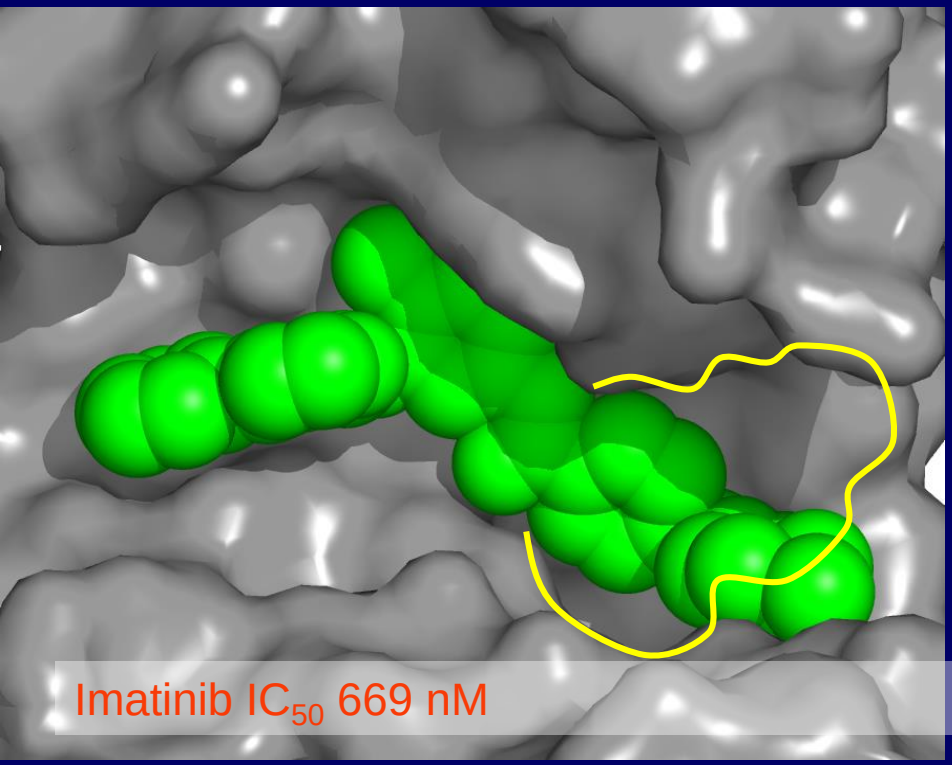
[a]CHR and CyR were last assessed at 24 months (per protocol); patients with Ph(–) BCR-ABL(+) disease (n=14) are excluded from CyR rates

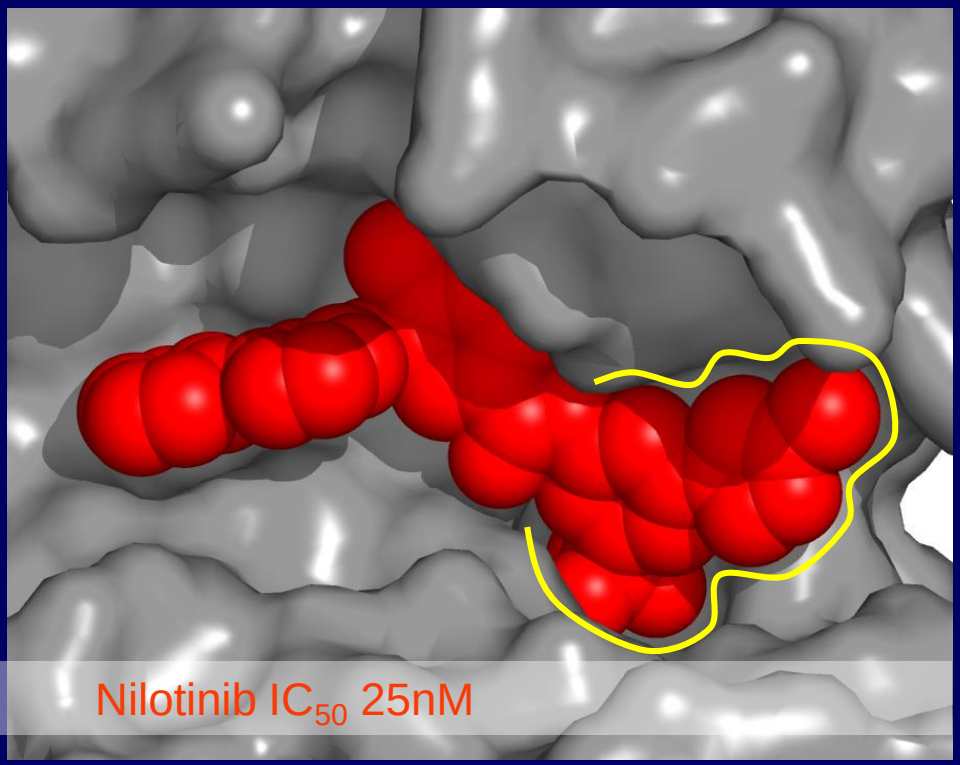
Evolving CML Treatment Landscape



Nilotinib for patients with imatinib-resistant chronic phase CML

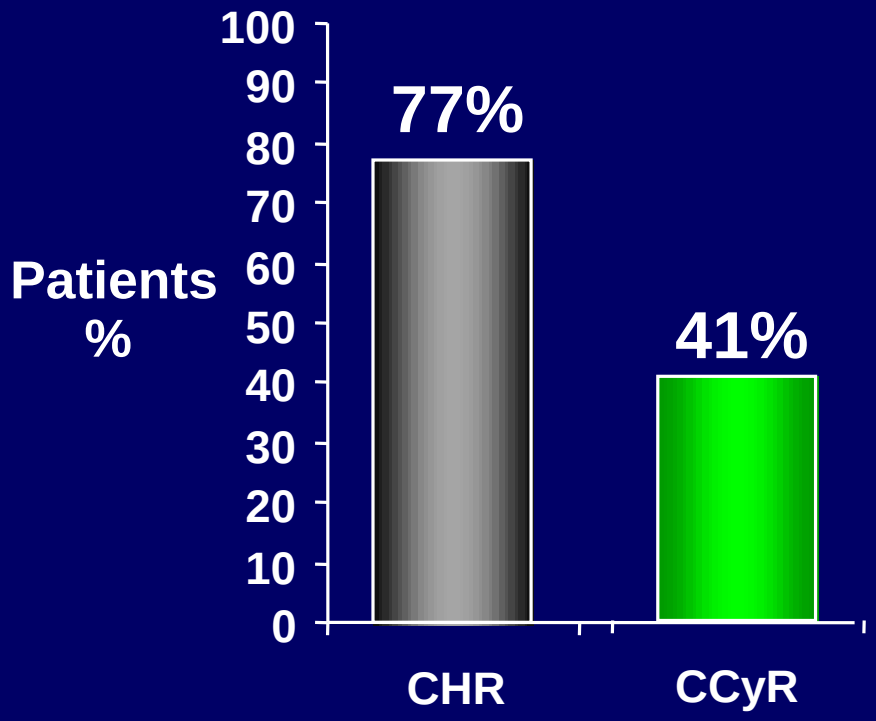
Nilotinib has a better fit to the binding pocket



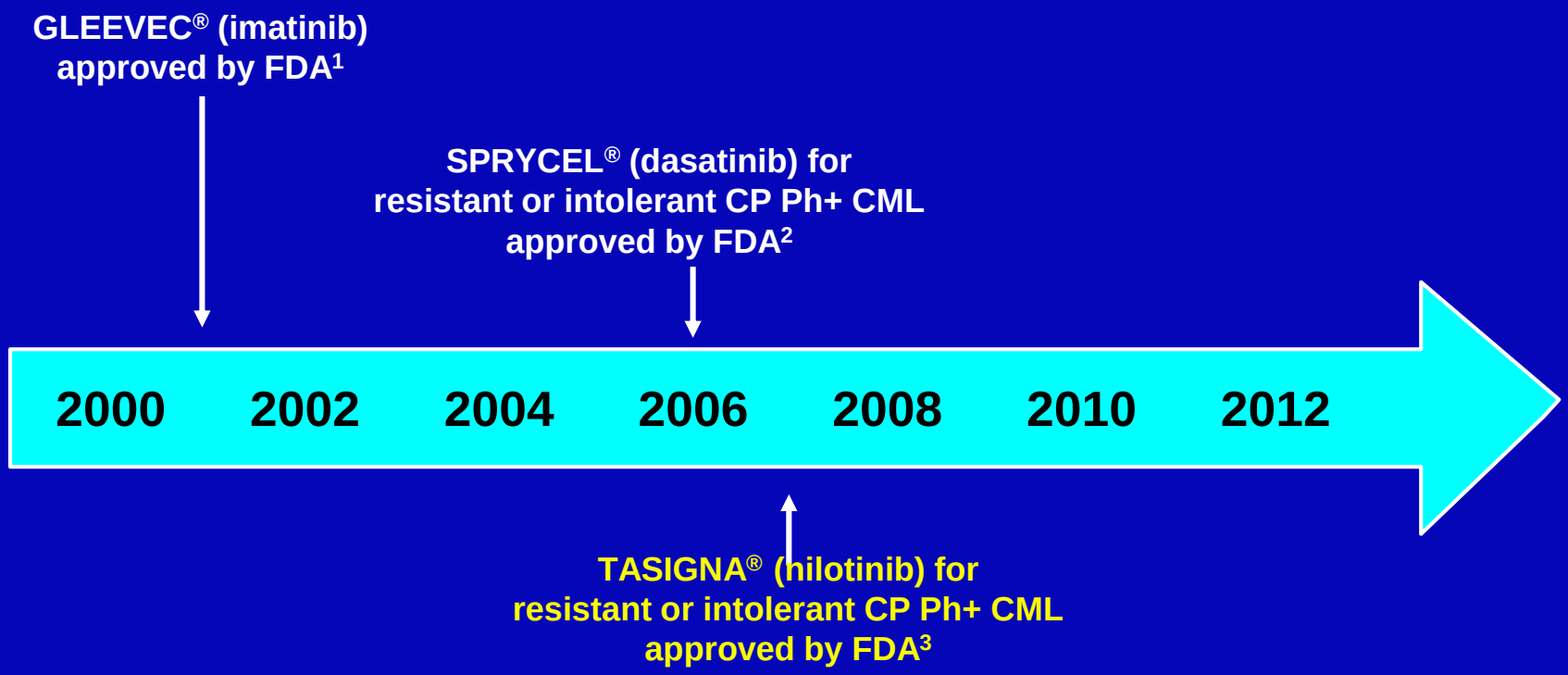


- Rationally designed highly specific inhibitor of BCR-ABL
- 30X more potent than imatinib; maintains target specificity
- No significant effect on other kinases
- (Src, FLT3, VEGFR, EGFR, InsR, RET, MET, IGFR, etc)

Nilotinib in CML-CP. Response



Evolving CML Treatment Landscape

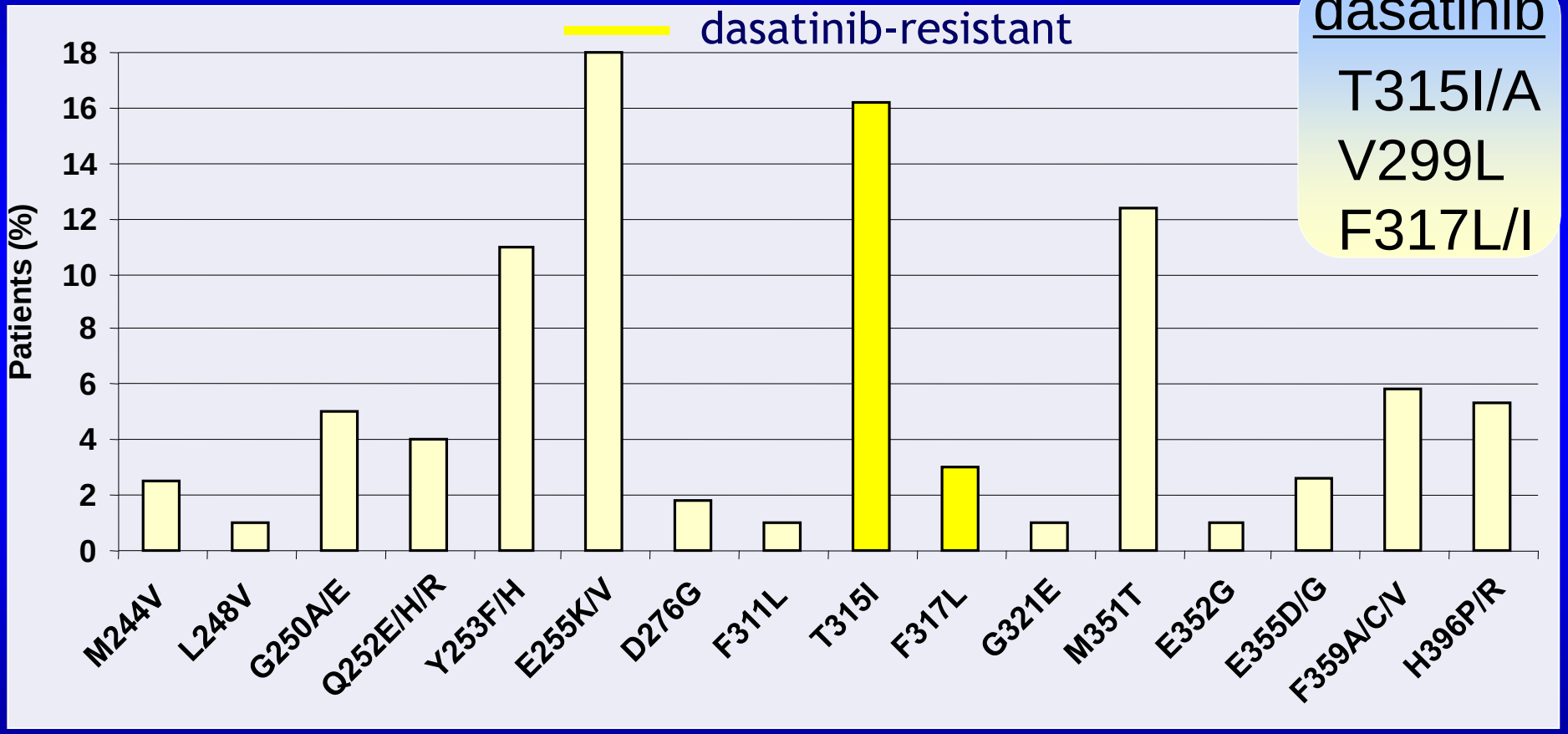


Dasatinib and Nilotinib Focus on Mutations

Clinical Resistance to Dasatinib and Nilotinib Mutations

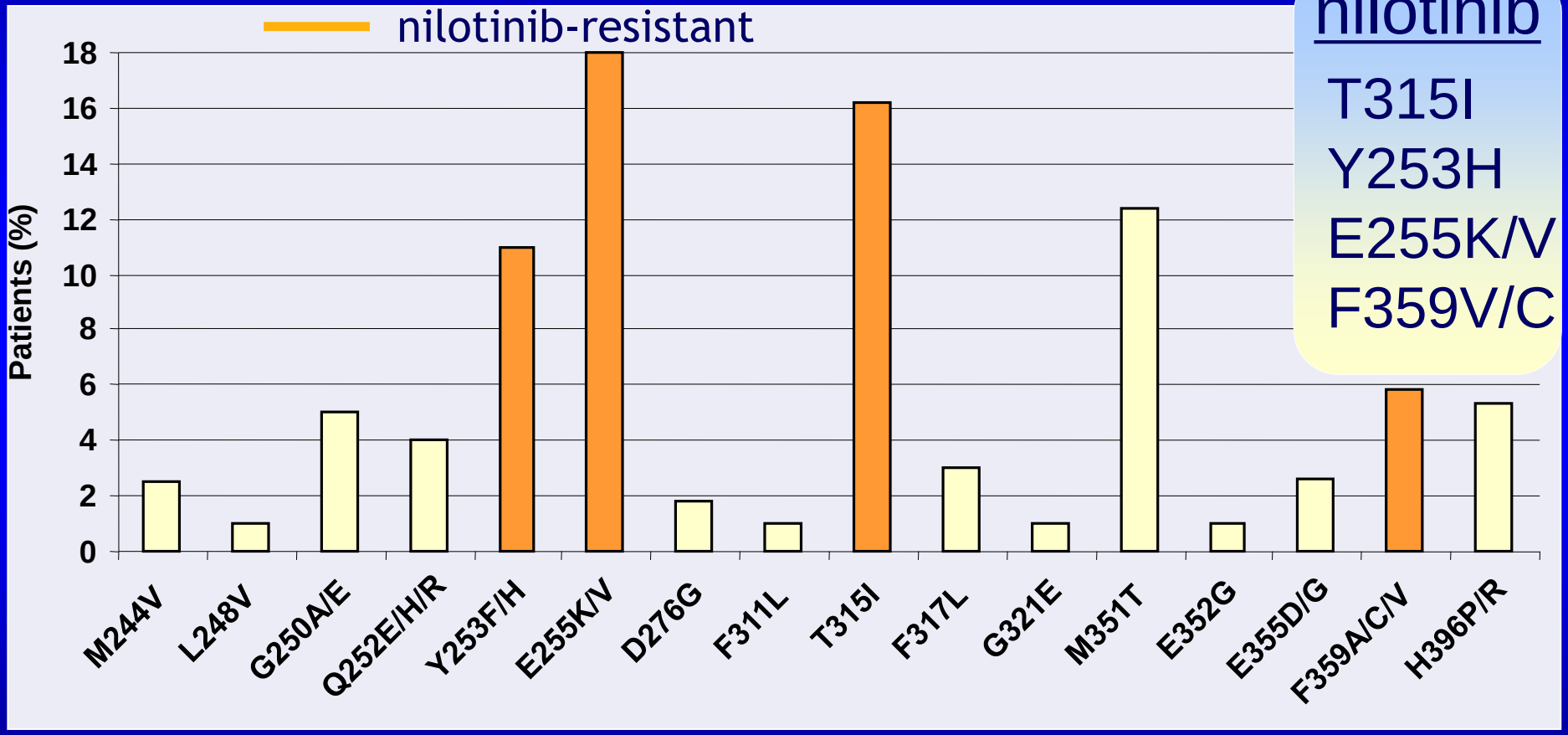
- In contrast to imatinib, which is vulnerable to >100 resistance-conferring mutations, dasatinib and nilotinib are each vulnerable to only ~ 5 resistance-conferring mutations

Frequency of Dasatinib-Resistant Mutations Following the Development of Imatinib Resistance



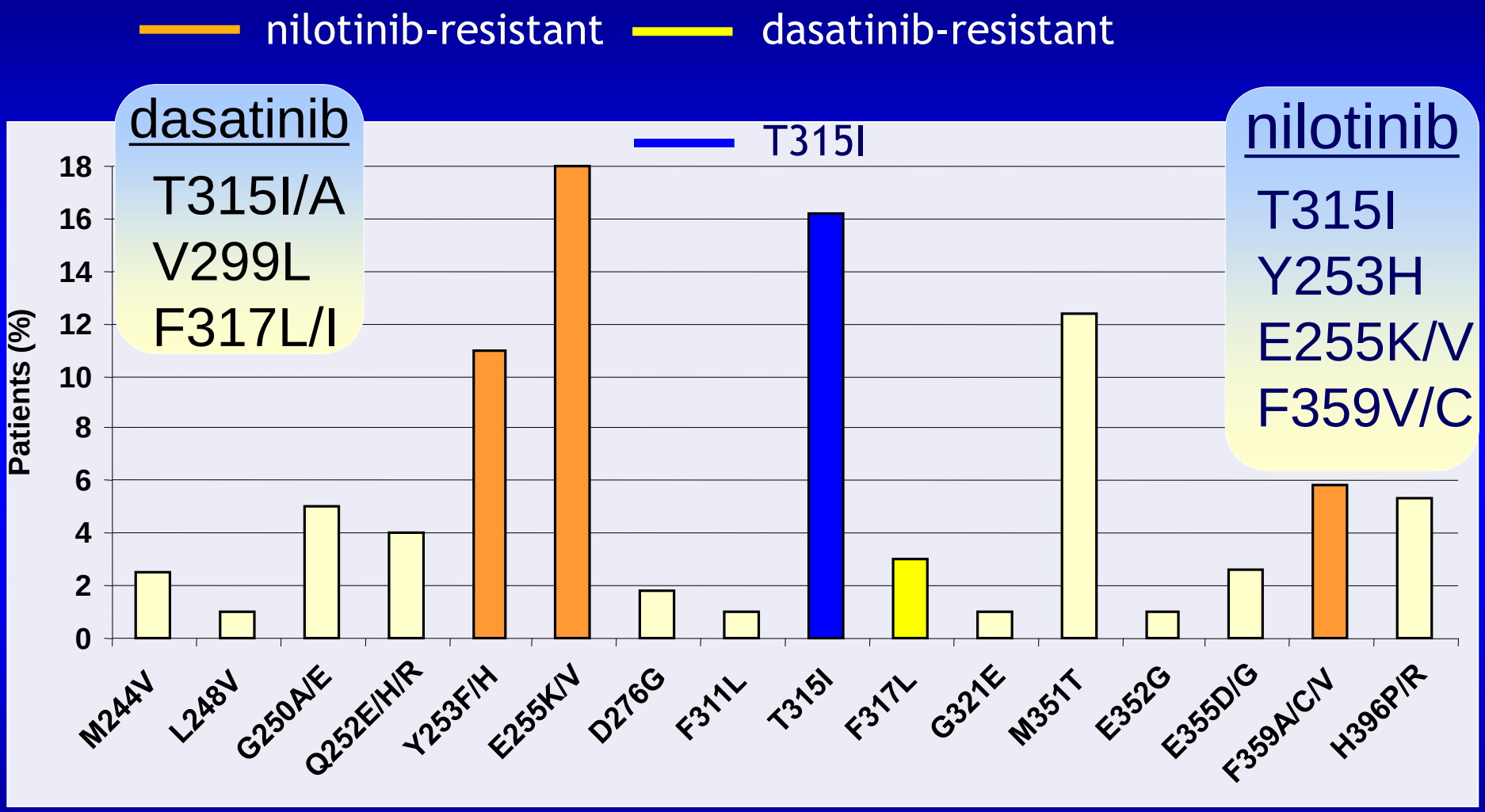
Branford S, Hematology. (Am Soc Hematol Edu Program). 2007:376-383

Frequency of Nilotinib-Resistant Mutations Following the Development of Imatinib Resistance



Branford S, Hematology. (Am Soc Hematol Edu Program). 2007:376-383

Likelihood of Having a Mutation That Confers Cross-resistance to Second-line TKIs



Branford S, Hematology. (Am Soc Hematol Edu Program). 2007:376-383

Dasatinib and Nilotinib for imatinib-resistant or -intolerant chronic phase CML

- Both drugs are active, and patients with imatinib-resistance or intolerance should be considered for treatment with one of these agents
  - Certain imatinib-resistant mutations may respond preferentially to one of these drugs
    - (F317L --> nilotinib)
    - (Y253H, E255K, E255V, F359C, F359V --> dasatinib)
  - The drugs have somewhat different side effects that can occur
    - Dasatinib: pleural effusion, pulmonary arterial hypertension
    - Nilotinib: QT prolongation, hyperglycemia, pancreatitis, peripheral arterial occlusive events
- Neither drug is active against the BCR-ABL/T315I mutation

FRONTLINE THERAPY FOR CML

Newer TKIs in newly-diagnosed CP-CML patients

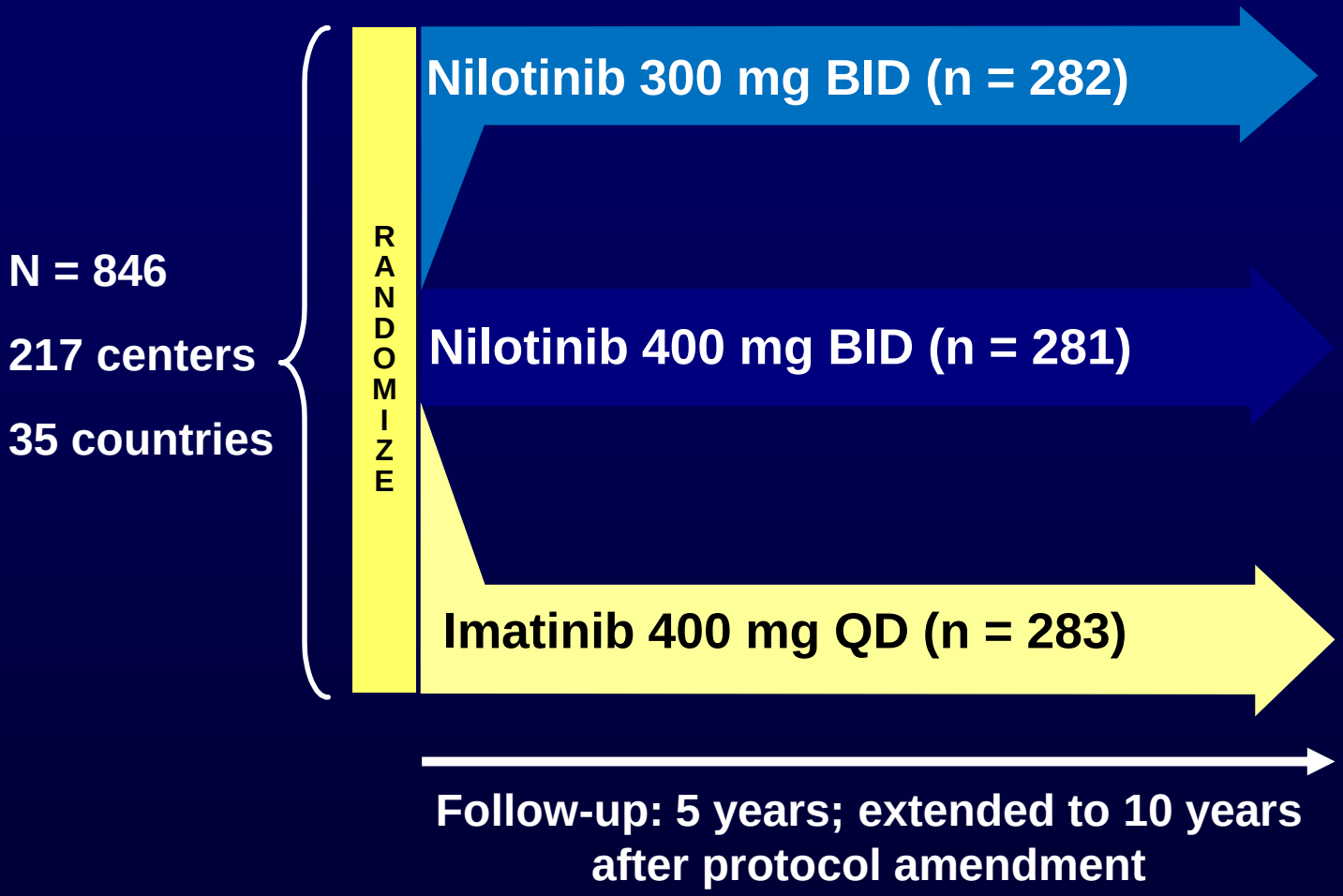
FRONTLINE THERAPY FOR CML

What is the potential role of newer agents in the frontline management of CP-CML?

ENESTnd Update: Nilotinib vs Imatinib in Patients With Newly Diagnosed CML-CP and the Impact of Early Molecular Response and Sokal Risk at Diagnosis on Long-Term Outcomes

G. Saglio, A. Hochhaus, T. P. Hughes, R. E. Clark, H. Nakamae, D.-W. Kim, S. Jootar, G. Etienne, I. W. Flinn, J. H. Lipton, R. Pasquini, B. Moiraghi, C. Kemp, X. Fan, H. D. Menssen, H. M. Kantarjian, and R. A. Larson,
on behalf of the ENESTnd Investigators

ENESTnd Study Design

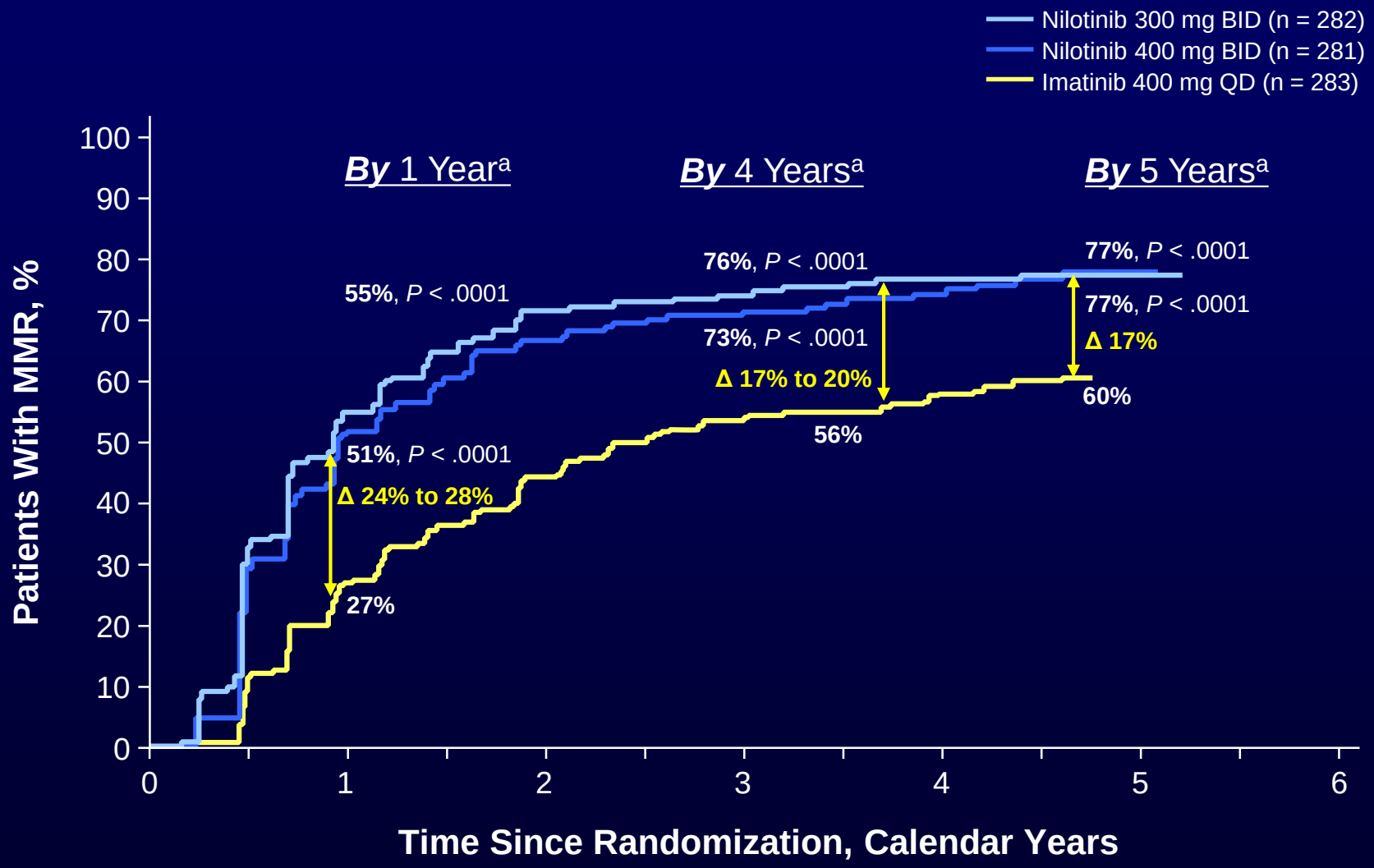


- Patients were stratified according to Sokal risk score at diagnosis

BID, twice daily; QD, once daily.

Data cutoff: May 22, 2013

Cumulative Incidence of MMR

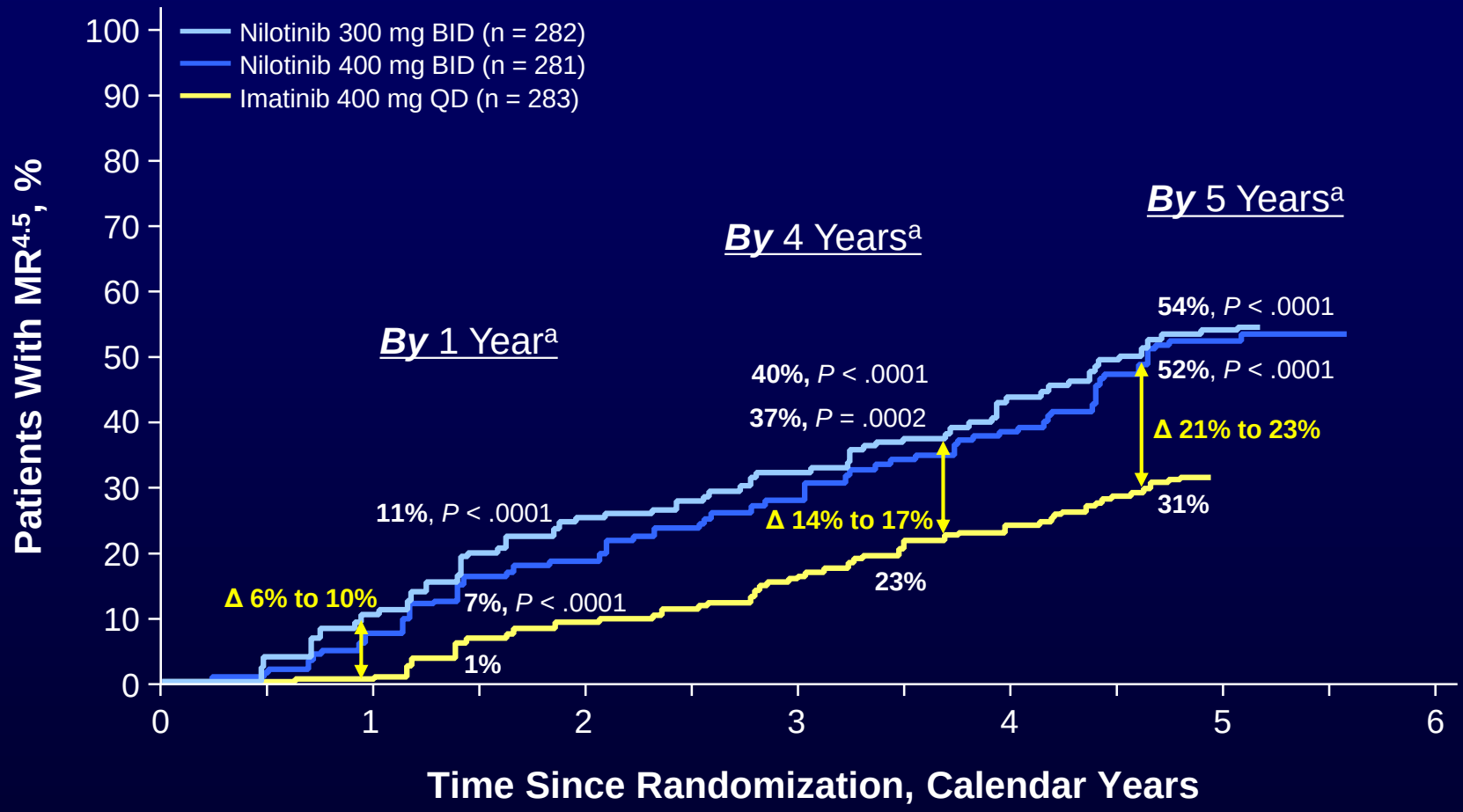


MMR, major molecular response (BCR-ABL^{IS} ≤ 0.1%).

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

Data cutoff: May 22, 2013

Cumulative Incidence of MR$^{4.5}$

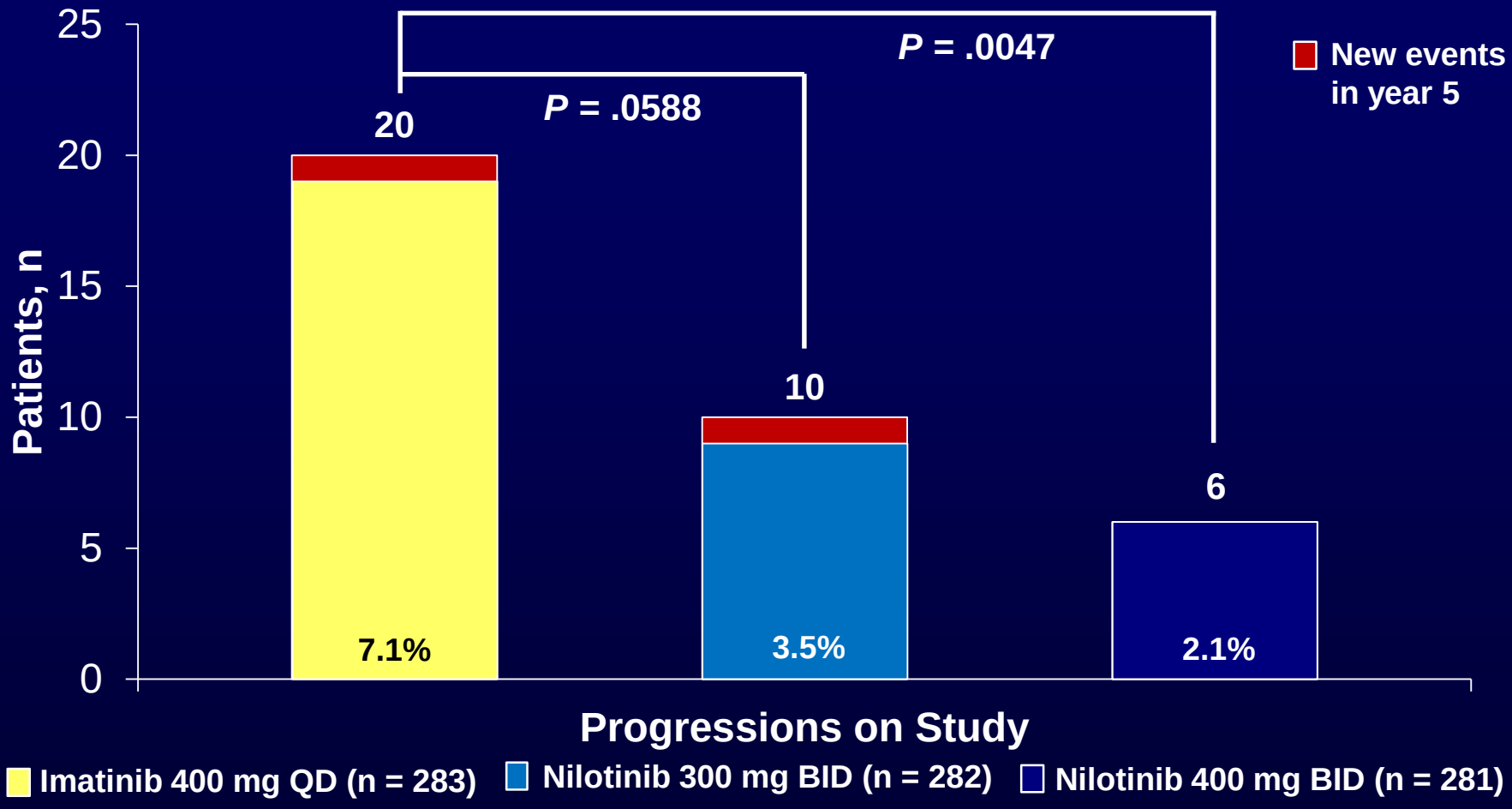


MR$^{4.5}$, molecular response ≥ 4.5-logs (BCR-ABL^{IS} ≤ 0.0032%).

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

Data cutoff: May 22, 2013

Progression to AP/BC on Study[a] (Including After Treatment Discontinuation)

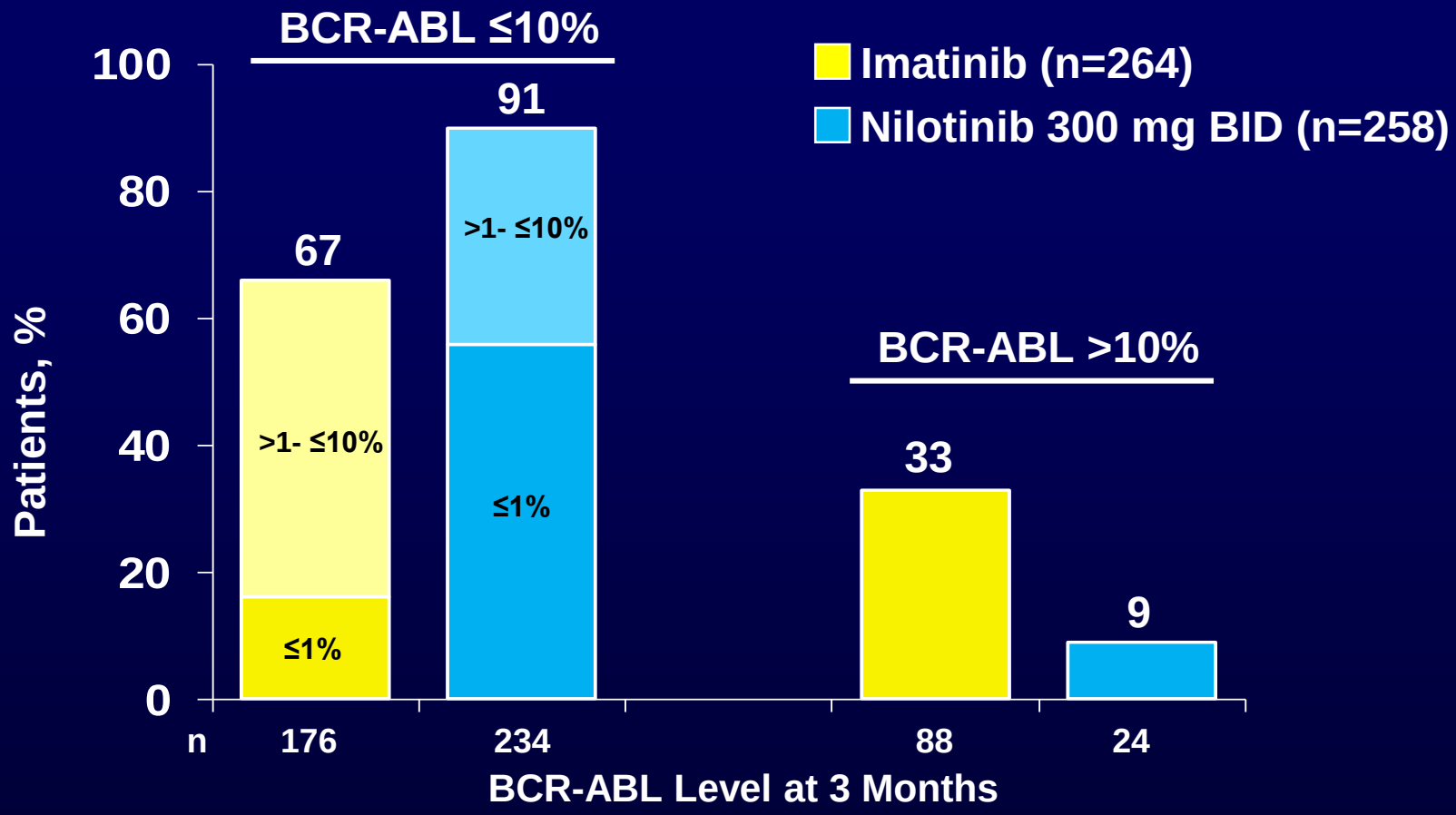


- Two new progressions on study in year 5 (1 in the nilotinib 300 mg BID arm and 1 in the imatinib arm)
- Both patients had BCR-ABL > 10% at 3 months

[a] Includes progression to AP/BC (excluding clonal evolution) or deaths in patients with advanced CML occurring on study (on core or extension treatment or during follow-up after treatment discontinuation).

Data cutoff: May 22, 2013

BCR-ABL Categories at 3 Months*



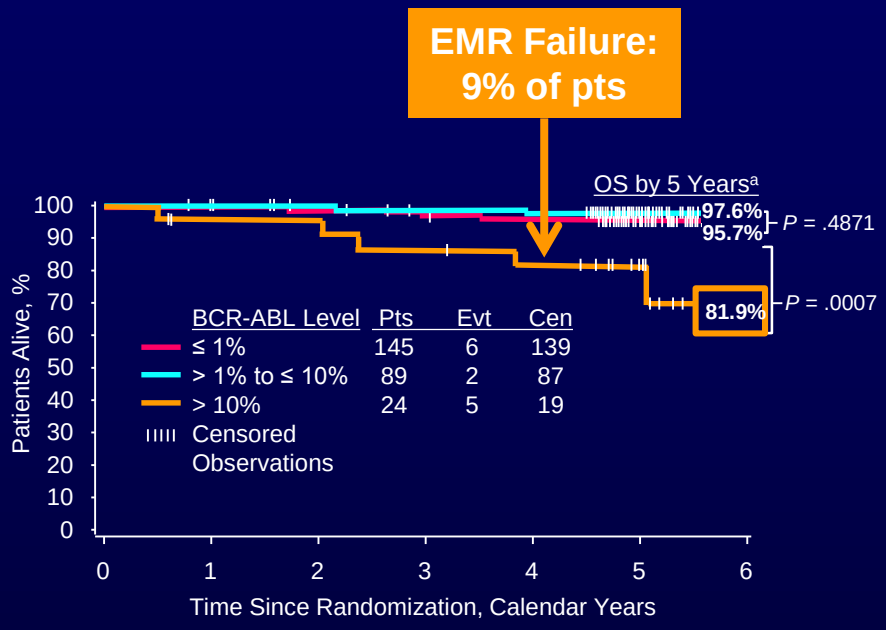
- Reasons for unevaluable samples included:
  - Atypical transcripts: 5 patients on nilotinib, 2 patients on imatinib
  - Missing samples: 4 patients on nilotinib, 5 patients on imatinib
  - Discontinuation: 15 patients (including 1 progression) on nilotinib, 12 patients (including 1 progression) on imatinib

*Calculated from total number of evaluable patients with PCR assessments at 3 months.

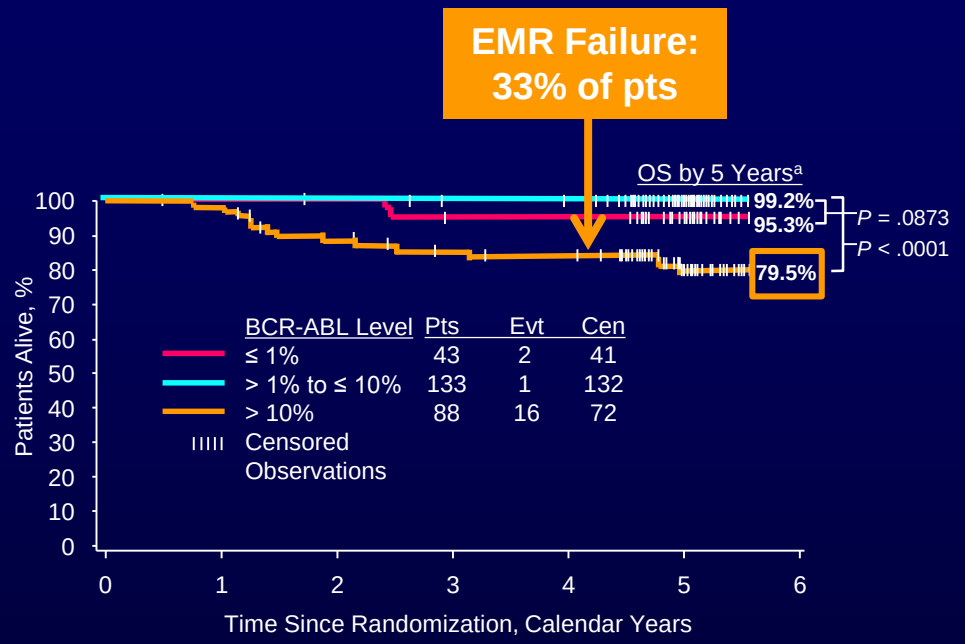
Data cutoff: May 22, 2013

OS by BCR-ABL Levels at 3 Months

Nilotinib 300 mg BID



Imatinib 400 mg QD



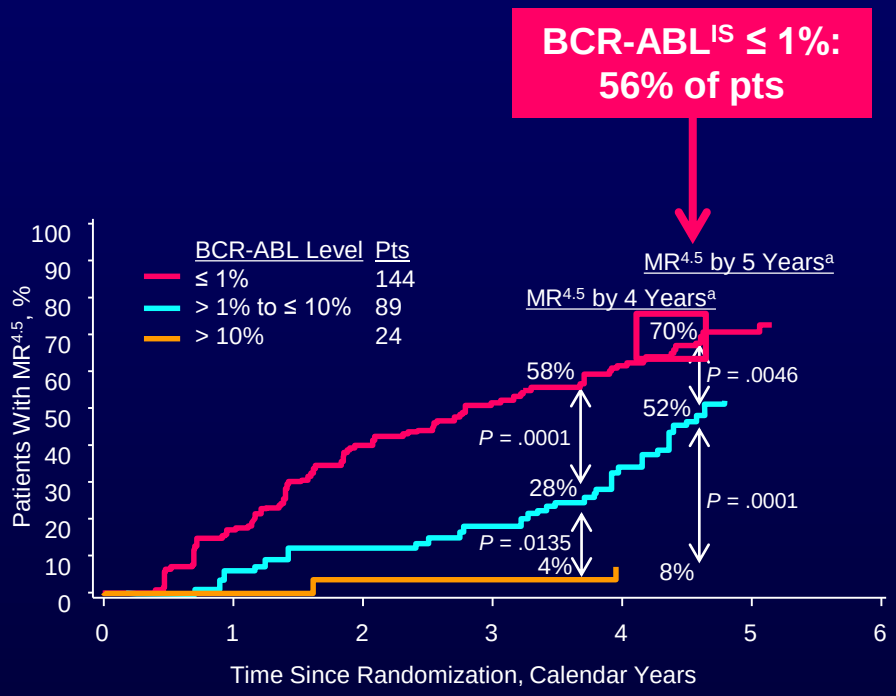
- Patients with EMR failure (BCR-ABL > 10% at 3 months) have significantly worse 5-year OS
- Rates of EMR failure are lower on nilotinib 300 mg BID vs imatinib

Cen, censored; EMR, early molecular response; Evt, events; Pts, patients.
[a] OS rates reported consider each year to consist of twelve 28-day cycles.

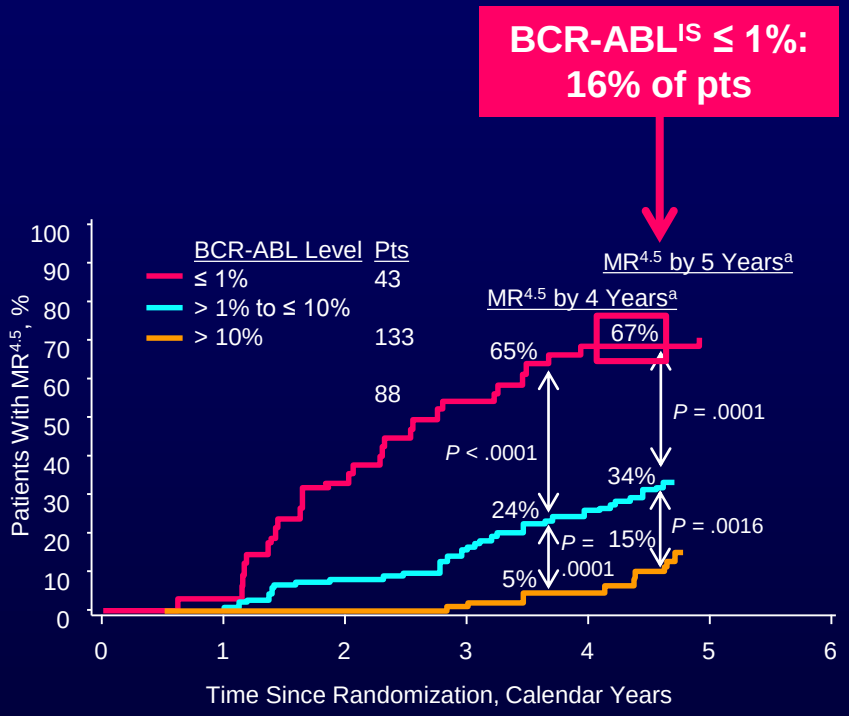
Data cutoff: May 22, 2013

Proportion of Patients With $MR^{4.5}$ by BCR-ABL Levels at 3 Months

Nilotinib 300 mg BID



Imatinib 400 mg QD



- Patients with BCR-ABL ≤ 1% at 3 months have significantly higher rates of $MR^{4.5}$ by 5 years
- More patients achieve BCR-ABL ≤ 1% at 3 months on nilotinib 300 mg BID vs imatinib

[a] Cumulative response rates reported consider each year to consist of twelve 28-day cycles.

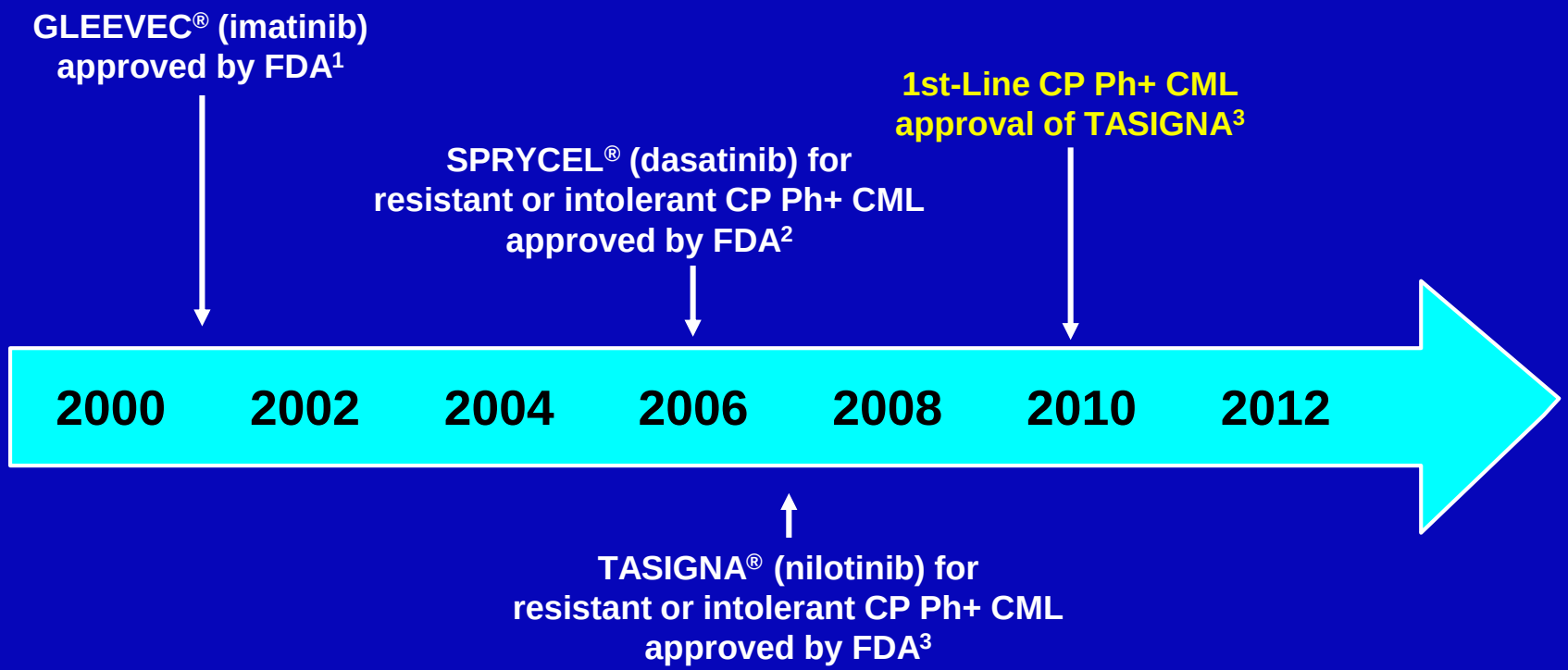
Data cutoff: May 22, 2013

Conclusions

- At 5 years of follow-up, rates of event-free survival, progression-free survival, and overall survival were higher in patients treated with nilotinib than imatinib
- Nilotinib demonstrated higher rates of early and deeper molecular response, including $MR^{4.5}$, and a reduced risk of progression
- By 5 years, more than half of nilotinib-treated patients had achieved $MR^{4.5}$, a key eligibility criterion for many treatment-free remission studies
- Side effects that appear unique to nilotinib include pancreatitis, hyperglycemia, EKG changes and peripheral arterial occlusive events.

Data cutoff: May 22, 2013

Evolving CML Treatment Landscape



Final Study Results of the Phase 3 Dasatinib Versus Imatinib in Newly Diagnosed Chronic Myeloid Leukemia in Chronic Phase (CML-CP) Trial (DASISION, CA180-056)

J. Cortes,[1] G. Saglio,[2] M. Baccarani,[3] H. Kantarjian,[1] J. Mayer,[4] C. Boqué,[5] N.P. Shah,[6] C. Chuah,[7] L. Casanova,[8] G. Narayanan,[9] B. Bradley-Garelik,[10] G. Manos,[10] A. Hochhaus[11]

[1]University of Texas M.D. Anderson Cancer Center, Houston, TX, USA; [2]University of Turin, Turin, Italy; [3]Department of Hematology "L. and A. Seràgnoli", S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy; [4]University Hospital Brno and Central European Institute of Technology Masaryk University Brno, Czech Republic; [5]Hematology Service, Institut Català d'Oncologia, Hospital Duran i Reynals, L'Hospitalet, Barcelona, Spain; [6]UCSF School of Medicine, San Francisco, CA, USA; [7]Singapore General Hospital and Duke-National University of Singapore Graduate Medical School, Singapore; [8]Instituto Nacional de Enfermedades Neoplásicas, Lima, Peru; [9]Regional Cancer Centre, Medical College, Thiruvananthapuram, Kerala, India; [10]Bristol-Myers Squibb, Wallingford, CT, USA; [11]Universitätsklinikum Jena, Jena, Germany

DASISION (CA180-056) Study Design

- Treatment-naïve CML-CP patients (N=519)
- 108 centers
- 26 countries
- Enrollment: September 2007–December 2008

Randomized [a]

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

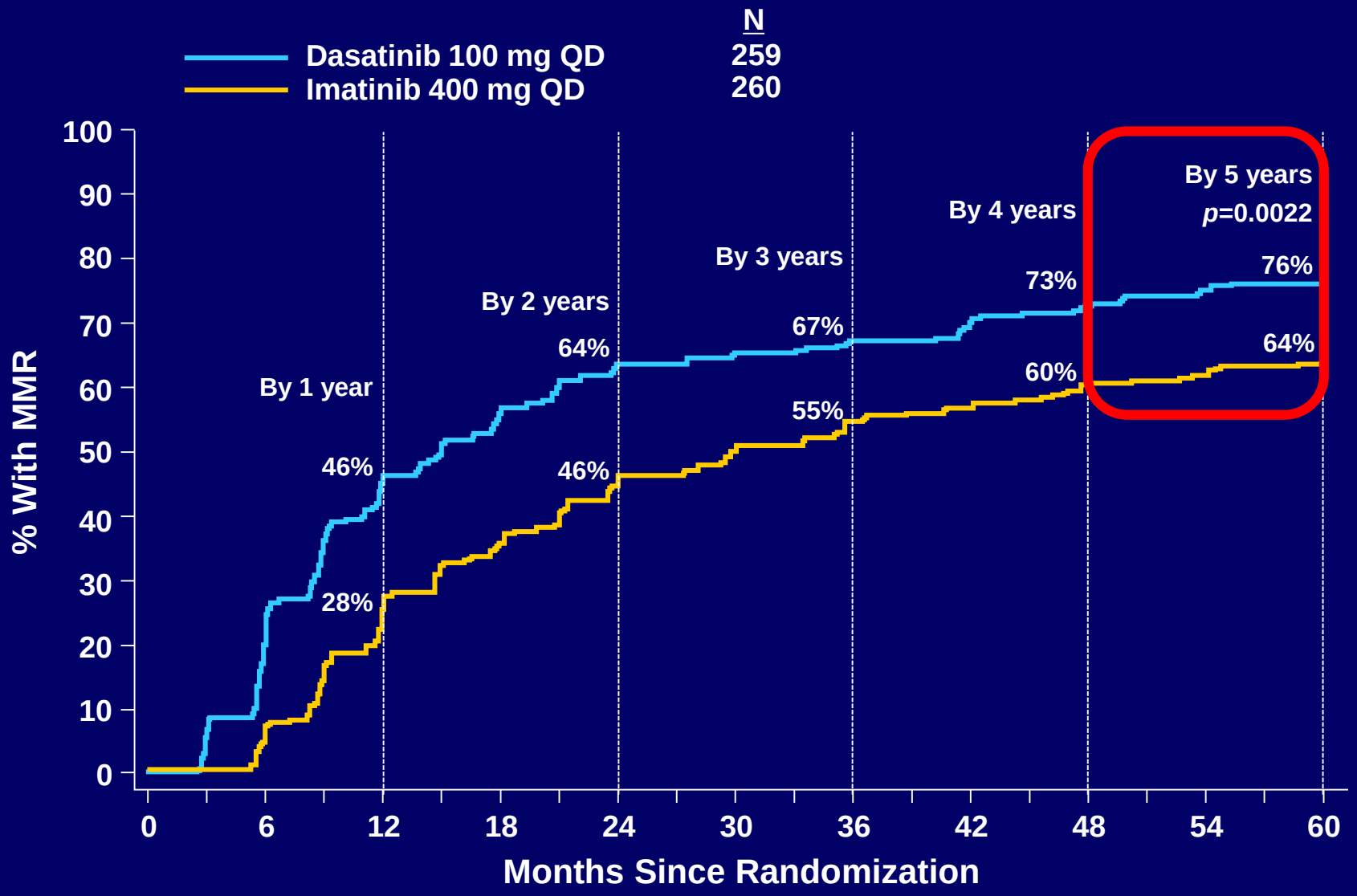
5-year final results

- Database lock of 24-Mar-2014
- Primary end point: confirmed CCyR by 12 months
  - 77% dasatinib vs. 66% imatinib (*P*=0.007)[1]

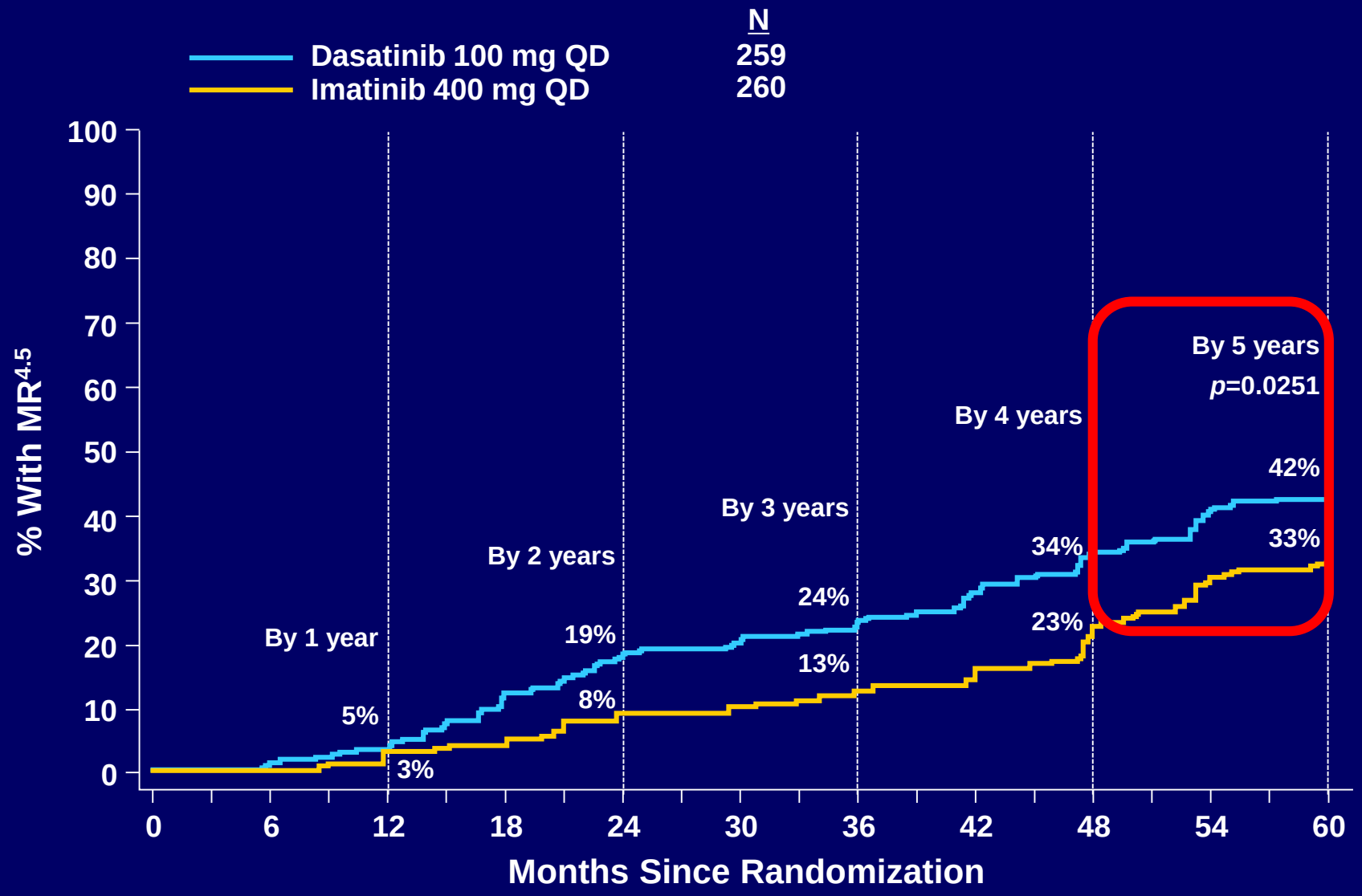
[a] Stratified by EURO (Hasford) risk score.

1. Kantarjian H et al. *N Engl J Med* 2010;362:2260–70.

Cumulative MMR Rates Over Time



Cumulative MR$^{4.5}$ Rates Over Time



MR$^{4.5}$, BCR-ABL (IS) ≤0.0032% (for subjects with B2a2 and B3A2 transcripts).

Best 5-Year Responses by Molecular Response at 3 Months

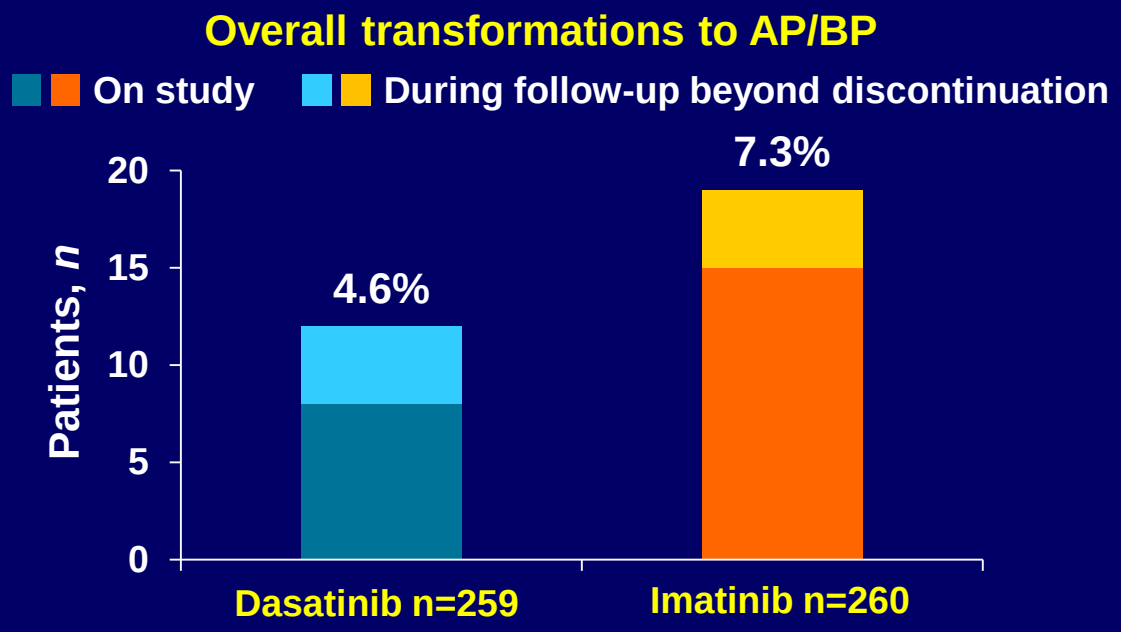
	Dasatinib 100 mg QD (n=259)		Imatinib 400 mg QD (n=260)	
BCR-ABL at 3 Months	≤10% (84%)	>10% (16%)	≤10% (64%)	>10% (36%)
CCyR, %	94	41	92	59
MMR, %	87	38	81	41
$MR^{4.5}$, %	54	5	48	12

5-Year Outcomes by Molecular Response at 3 Months

	Dasatinib 100 mg QD (n=259)			Imatinib 400 mg QD (n=260)		
BCR-ABL at 3 Months	≤10% (84%)	>10% (16%)	*P* value	≤10% (64%)	>10% (36%)	*P* value
Estimated 5-year OS, %	94	81	0.0028	95	81	0.0003
Estimated 5-year PFS, %	89	72	0.0014	93	72	<0.0001
Estimated 5-year TFS, %	97	83	0.0004	97	80	<0.0001

On-study treatment and in follow-up after discontinuation of randomized treatment.
TFS, transformation-free survival.

Transformation to AP/BP CML by 5 Years



	Dasatinib 100 mg QD (n=259)		Imatinib 400 mg QD (n=260)	
BCR-ABL at 3 Months [a]	≤10% n=198	>10% n=37	≤10% n=154	>10% n=85
Transformation to AP/BP [b], n (%)	6 (3)	5 (14)	5 (3)	13 (15)

- One imatinib patient and no dasatinib patients transformed between 4 and 5 years

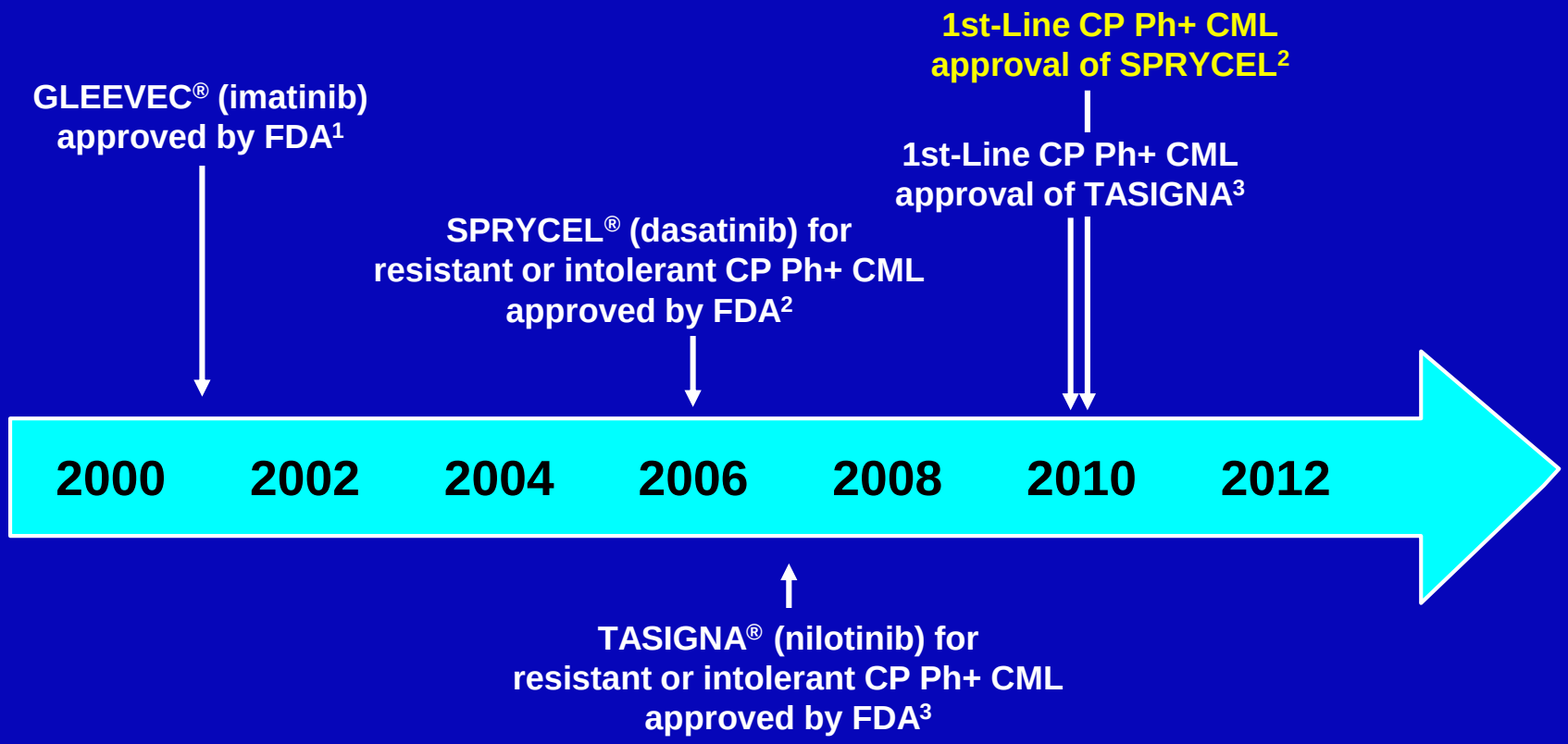
[a] One dasatinib and one imatinib patient transformed but did not have 3-month molecular assessments.

[b] Including follow-up beyond discontinuation (intent to treat).

Conclusions

- 5-Year follow-up demonstrates:
  - Deeper molecular responses with dasatinib versus imatinib
  - More optimal molecular responses with dasatinib versus imatinib
  - Fewer transformations to AP/BP
- Achievement of BCR-ABL ≤10% at 3 months is associated with significantly higher PFS and OS by 5 years
  - BCR-ABL ≤10% at 3 months: dasatinib 84% versus imatinib 64%
- By 5 years, 42% of dasatinib-treated patients had achieved $MR^{4.5}$, a key eligibility criterion for many treatment-free remission studies
- Side effects that appear unique to dasatinib include pleural effusion and pulmonary arterial hypertension.

Evolving CML Treatment Landscape



Dasatinib and Nilotinib in Previously Untreated Chronic Phase CML Patients
Concluding Thoughts

- Nilotinib and dasatinib are superior to imatinib at achieving deep responses
- Tolerability of these agents appears comparable to imatinib
- Patients and physicians now have three approved TKI treatment options for newly diagnosed chronic phase CML

The First of Many Great Curveballs of 2016

- In February 2016, generic imatinib became available in the USA
  - In February, with one generic manufacturer, the annual cost of generic imatinib was $142,000 (compared with $145,750)
  - In August, additional generic formulations were permitted to be introduced into the marketplace, but even with 4-5 generic manufacturers, the annual price is currently about $131,000
- Some insurance plans are refusing to authorize prescriptions for dasatinib or nilotinib until a patient has first tried imatinib

Is Generic Imatinib Equivalent to Brand-Name Drug?

- "Imatinib Generics in Treatment of CML: A Prospective Observation in Large Cohort of Patients from Polish Imatinib Generics Registry" (abstract 629)
  - Found that rates of response in newly diagnosed CML patients with generic imatinib were as expected from historical experience with brand-name imatinib, and that response was typically maintained in patients who switched from brand-name to generic imatinib.
- "Generic Imatinib in CML: Survival of the Cheapest" (abstract 630)
  - Found comparable efficacy and safety between generic and brand-name imatinib in India

IMATINIB-RESISTANT ACCELERATED AND BLAST PHASE CML

Summary of efficacy in accelerated phase CML

Dasatinib CCyR rate imatinib-resistant and -intolerant patients[1]:

- 24% (n=107)

Nilotinib CCyR rate imatinib-resistant and -intolerant patients[2]:

- 16% (n=119)

[1]Guilhot et al, Blood 109:4143-50.

[2]le Coutre et al, Blood 111:1834-9.

Summary of efficacy in blast phase CML

Induction chemotherapy achieves morphologic CRs in approximately 10-15% of MBC patients

Dasatinib CCyR rate imatinib-resistant and -intolerant patients[1]:

-MBC: 27% (n=109)

-LBC: 48% (n=46)

-Documented CNS disease clearance

Nilotinib CCyR rate imatinib-resistant and -intolerant patients[2]:

-MBC: 29% (n=105)

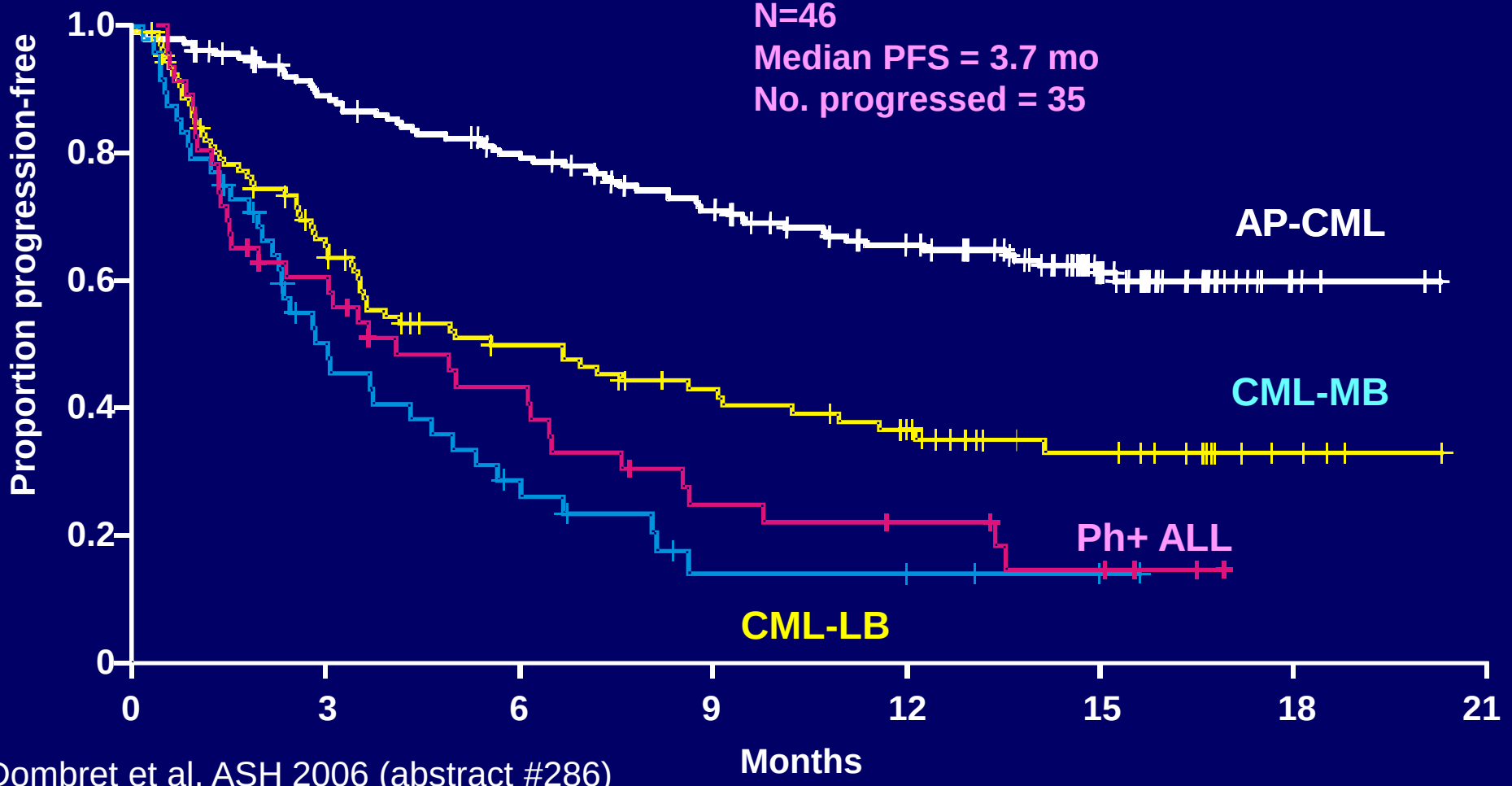
-LBC: 32% (n=31)

-Not currently approved for blast phase CML

[1]Gambacorti-Passerini et al, ASH 2007

[2]Giles et al, ASH 2007

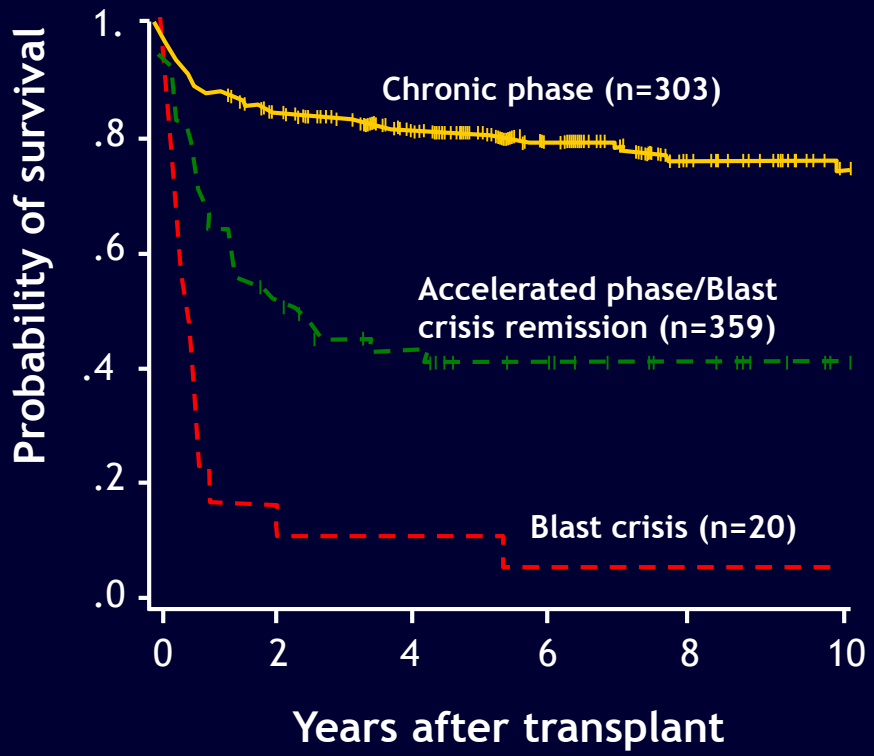
Dasatinib in advanced CML and Ph+ ALL
Progression-free survival

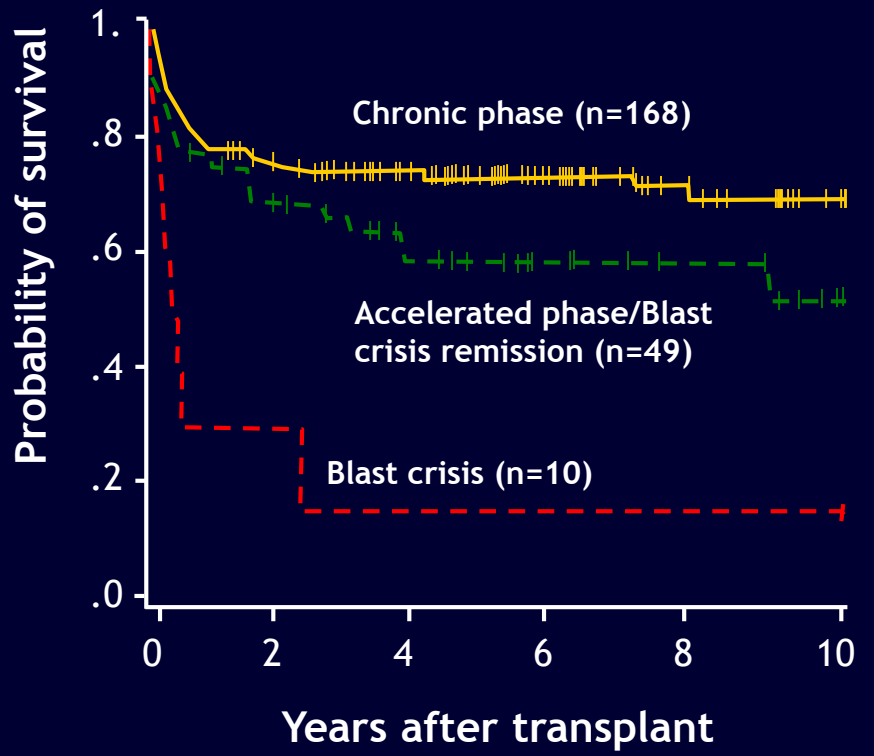


Dombret et al, ASH 2006 (abstract #286)

Cortes et al, ASH 2006 (abstract #2160); Martinelli et al, ASH 2006 (abstract #745)

Related and Unrelated Transplants, FHCRC ≥ 1992





Courtesy of Dr Ted Gooley and Jerald Radich; provided and used with permission.

Newer Agents

Efficacy and Safety of Bosutinib (SKI-606) Among Patients with Chronic Phase Ph+ Chronic Myelogenous Leukemia (CML)

J. Cortes, T.H. Brümmendorf, H. Kantarjian, J. Khoury, G. Rosti, T. Fischer, L. Tornaghi, B. Hewes, E.C. Martin, C. Gambacorti-Passerini

Bosutinib in CP CML
Response (Imatinib Resistant or Intolerant*)

Response (N=115)	N / N evaluable (%)
Hematologic	
Complete	34 / 38 (89)
Cytogenetic	
Major	23 / 56 (41)
Complete	17 / 56 (30)
Molecular	
Major	19 / 58 (33)
Complete	11 / 58 (19)

*Patients had no prior exposure to kinase inhibitors other than imatinib.

Bosutinib in CP CML
Response (Prior Dasatinib or Nilotinib)

Response (N=37)	N / N evaluable (%)
Hematologic	
Complete	10 / 13 (77)
Cytogenetic	
Major	2 / 10 (20)
Molecular	
Major	4 / 25 (16)
Complete	2 / 25 (8)

Bosutinib in CP CML
Non-Hematologic Adverse Events (N=152)

Event	N (%)	
	All Grades	Grade 3/4
Diarrhea	104 (68)	10 (7)
Nausea	65 (43)	1 (1)
Vomiting	42 (28)	4 (3)
Abdominal pain	41 (27)	1 (1)
Rash	37 (24)	10 (7)
Other pain	27 (18)	0
Fatigue	26 (17)	2 (1)
Any fluid retention	17 (11)	1(1)

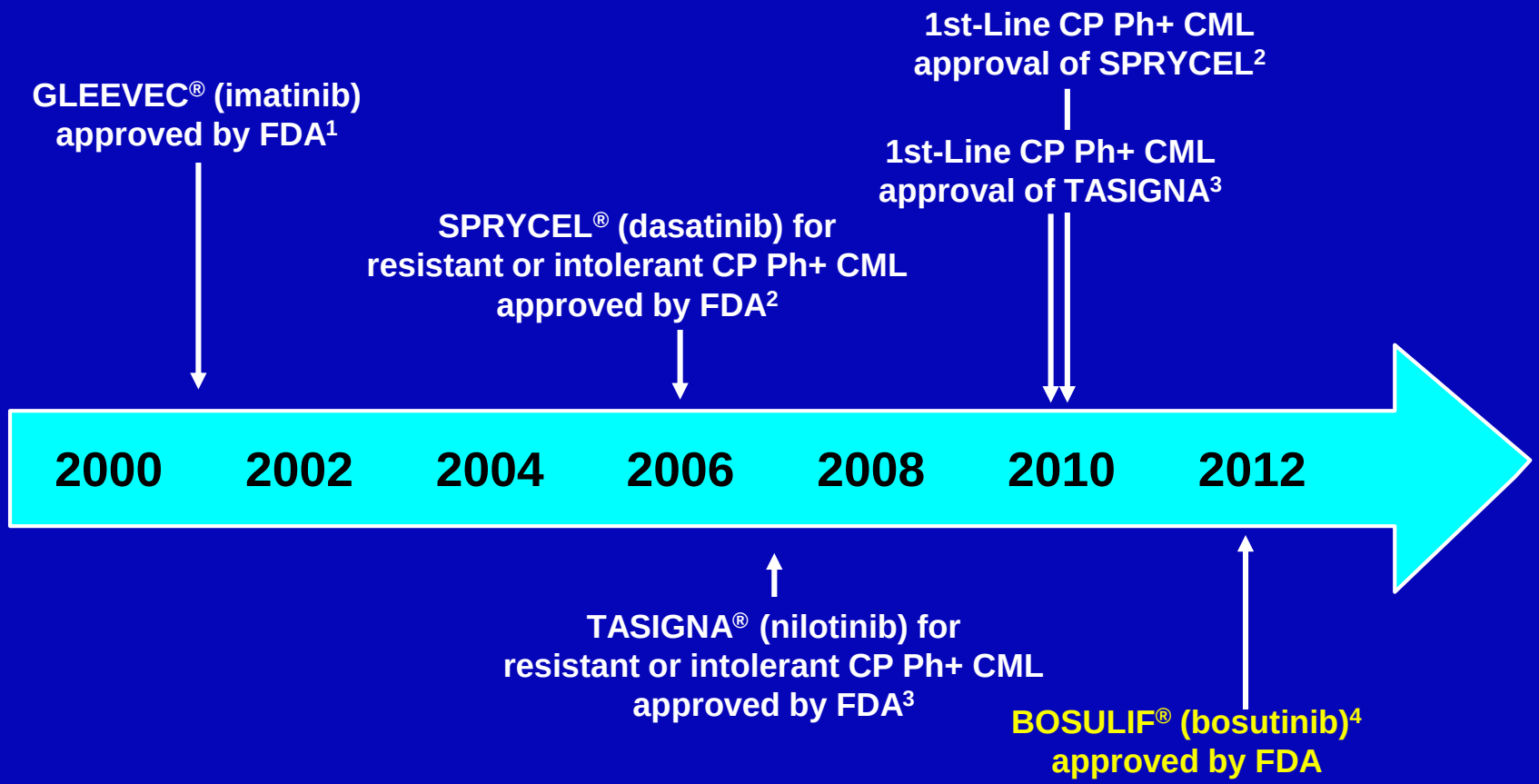
Bosutinib in CP CML
Other Laboratory Abnormalities

Abnormality	No. (%) Grade 3/4
Hypophosphatemia	11 (7)
Elevated ALT	10 (7)
Elevated lipase	6 (4)
Elevated glucose	4 (3)
Elevated INR	4 (3)
Elevated AST	2 (1)
Elevated creatinine	2 (1)
Hypocalcemia	2 (1)

Bosutinib in CP CML Conclusions

- Clinical efficacy in CP CML resistant or intolerant to imatinib (and other TKIs)
- Responses across a wide range of mutations, but not T315I
- Acceptable toxicity profile
  - Self-limiting diarrhea, liver function test abnormalities
  - Low hematologic toxicity

Evolving CML Treatment Landscape



Ponatinib in Patients with CML and Ph+ ALL Resistant or Intolerant to Dasatinib or Nilotinib, or with the T315I BCR-ABL Mutation: 2-Year Follow-up of the PACE Trial

ASH 2013 Abstract 650

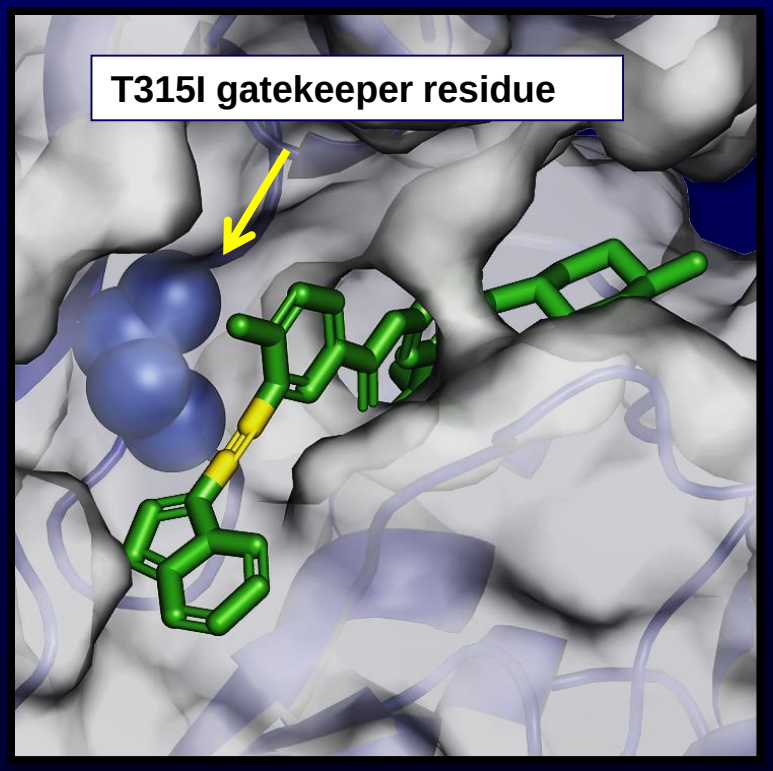
JE Cortes, D-W Kim, J Pinilla-Ibarz, PD le Coutre, R Paquette, C Chuah, FE Nicolini, JF Apperley, HJ Khoury, M Talpaz, JF DiPersio, DJ DeAngelo, E Abruzzese, D Rea, M Baccarani, MC Müller, C Gambacorti-Passerini, S Lustgarten, VM Rivera, T Clackson, CD Turner, FG Haluska, F Guilhot, MW Deininger, A Hochhaus, TP Hughes, JM Goldman, NP Shah, and HM Kantarjian

On behalf of the PACE Study Group

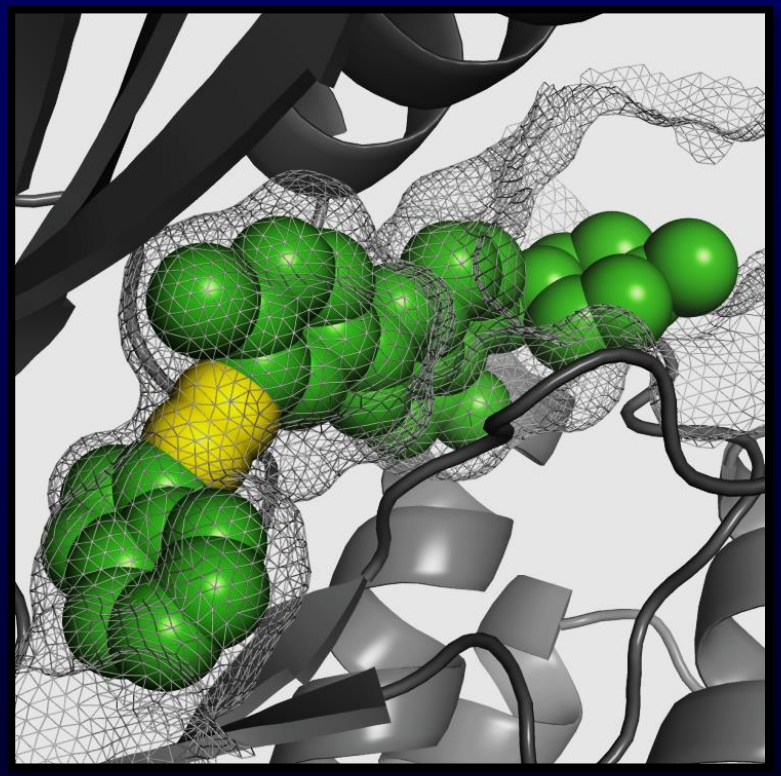
PACE
PONATINIB Ph+ ALL AND CML EVALUATION

Ponatinib

- **Oral pan-BCR ABL TKI with potent activity against native and mutated BCR-ABL and other kinases**



Triple bond (yellow) unique structural feature evades the T315I gatekeeper mutation (blue)



Extensive network of molecular contacts for optimal fit to the binding cavity of ABL

Ponatinib Phase 2 Study Patient Population

	CP-CML N=270*	AP-CML N=85*	BP-CML N=62	Ph+ ALL N=32
Median age, yrs [range]	60 [18–94]	60 [23–82]	53 [18–74]	62 [20–80]
Median time since diagnosis, yrs [range]	7 [0.5–27]	7 [0.3–28]	4 [0.5–27]	1 [0.5–8]
≥ 2 prior TKIs[#]	252 (93)	80 (94)	60 (97)	26 (81)
≥ 3 prior TKIs[#]	161 (60)	51 (60)	37 (60)	13 (41)
No Mutation	138 (51)	40 (47)	17 (27)	3 (9)
Any Mutation	132 (49)	43 (51)	43 (69)	28 (88)
T315I	64 (24)	18 (21)	24 (39)	22 (69)

*Includes 5 patients (3 CP-CML, 2 AP-CML) who were non-cohort assigned (post-imatinib, non-T315I), but treated

[#]Includes approved and investigational agents

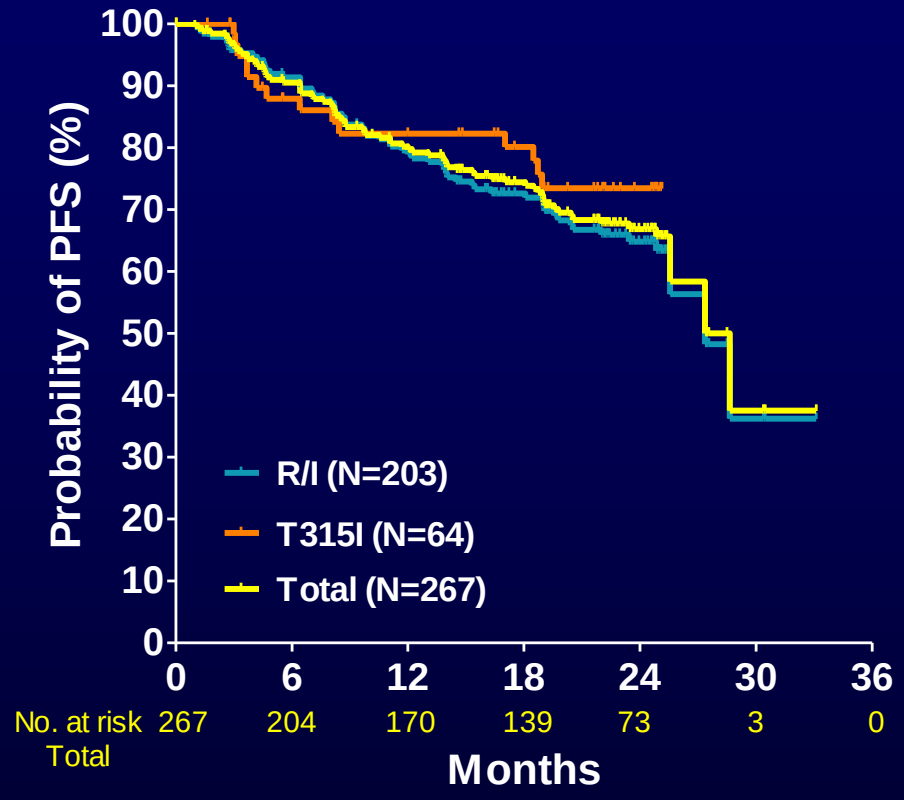
Ponatinib Phase 2 Study Responses at Any Time

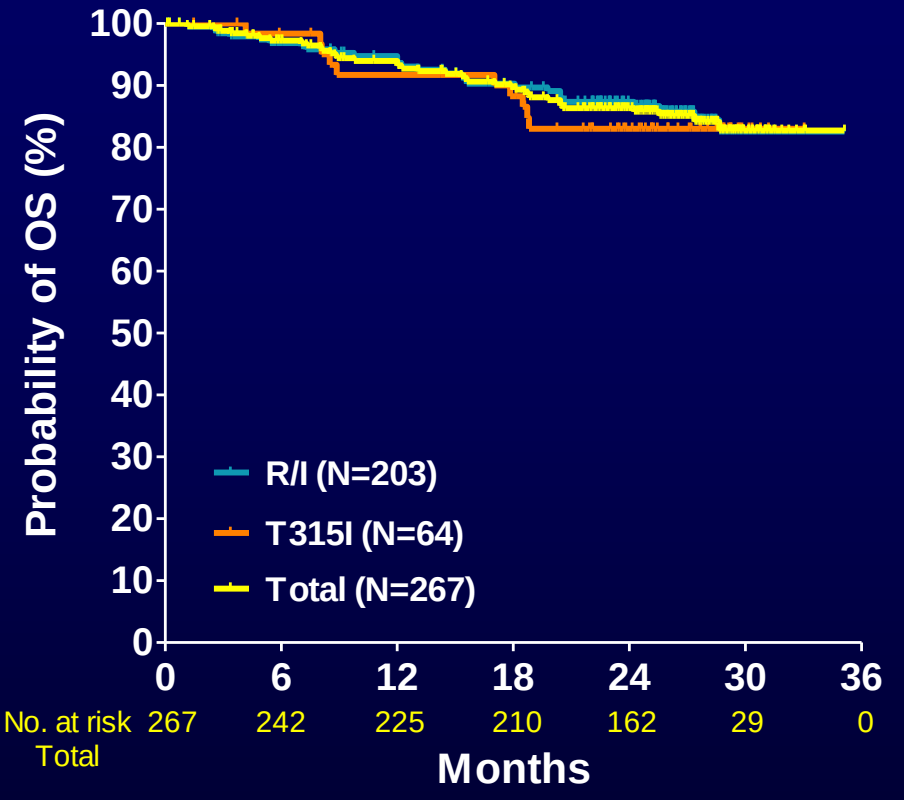
	CP-CML			AP-CML	BP-CML	Ph+ ALL
	MCyR	CCyR	MMR	MaHR*	MaHR	MaHR
R/I to das/nil	56%	48%	31%	62%	32%	50%
T315I	72%	70%	58%	61%	29%	36%
Total**	60%	54%	38%	61%	31%	41%
Median time to response, months						
	2.8	2.9	5.5	0.7	1.0	0.7

*14 AP-CML patients with baseline MaHR and 1 AP-CML patient with no baseline MaHR assessment counted as non-responders

**Total comprises all eligible patients treated with ponatinib. It excludes 5 patients (3 CP-CML, 2 AP-CML) who were non-cohort assigned (post-imatinib, non-T315I), but treated; all 5 achieved MCyR

Ponatinib Phase 2 Study
PFS and OS in CP-CML

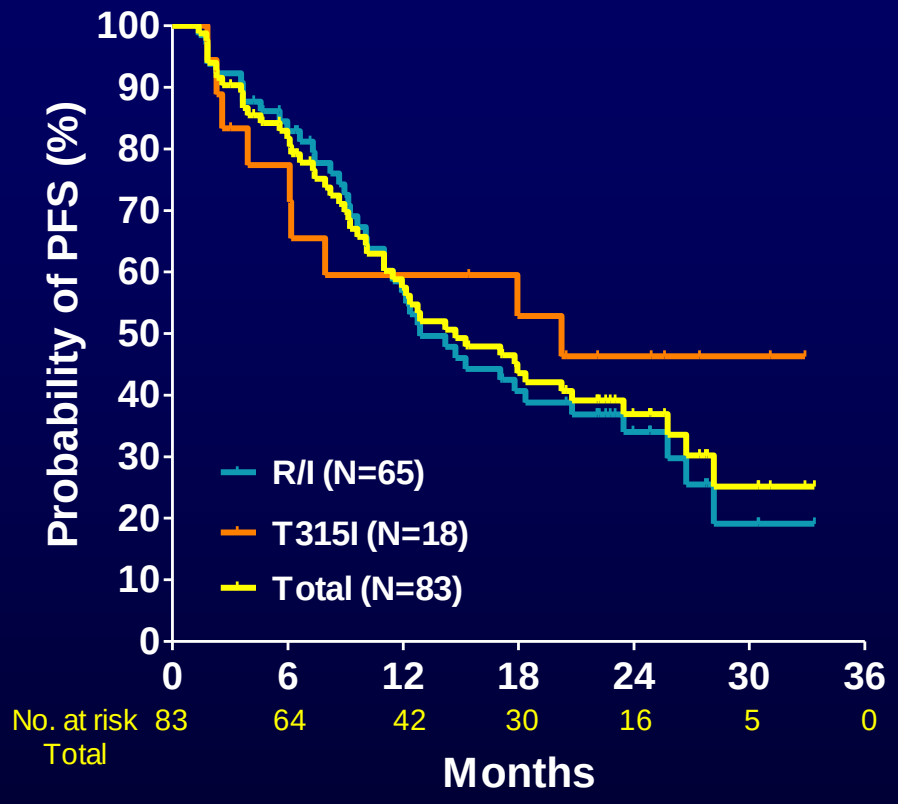


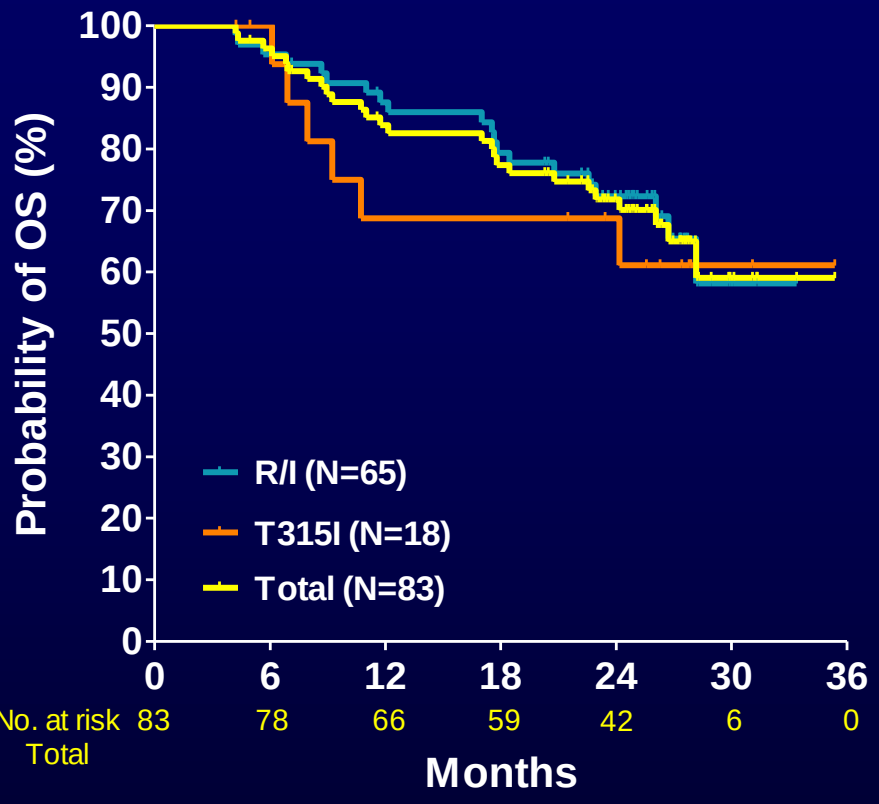


- **PFS at 2 years: 67% (median 29 months)**
- **OS at 2 years: 86% (median not reached)**

Criteria for progression in CP: death, development of AP or BP, confirmed loss of CHR in absence of CyR, loss of MCyR, or confirmed doubling (to >20K) of WBC w/o CHR

Ponatinib Phase 2 Study PFS and OS in AP-CML

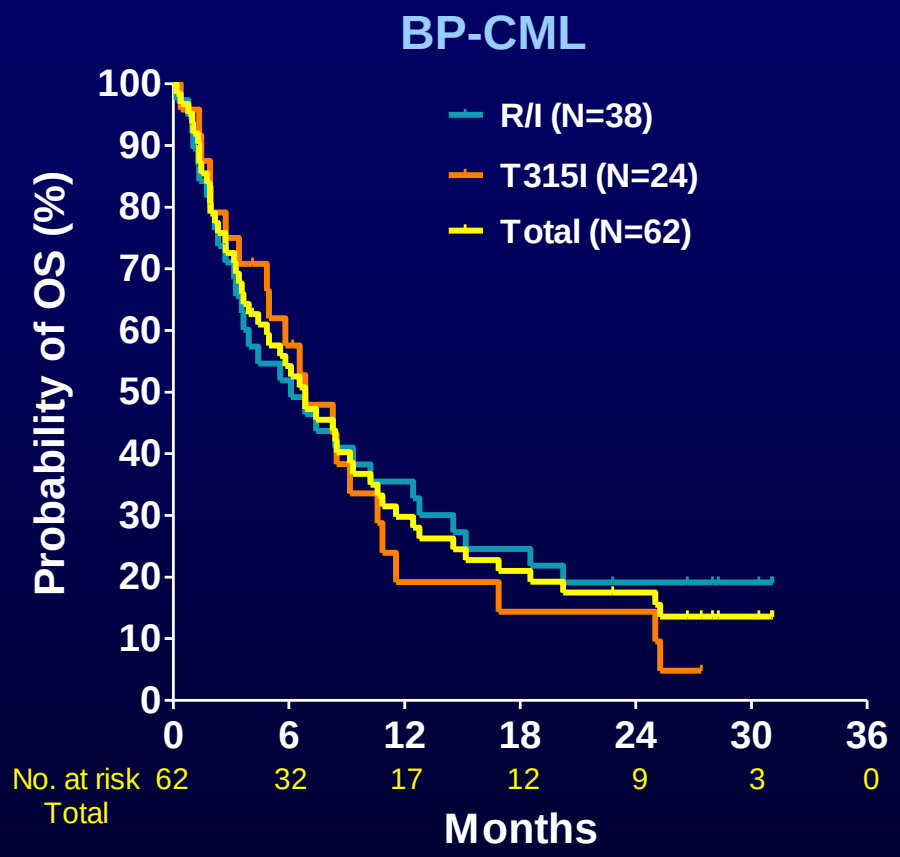


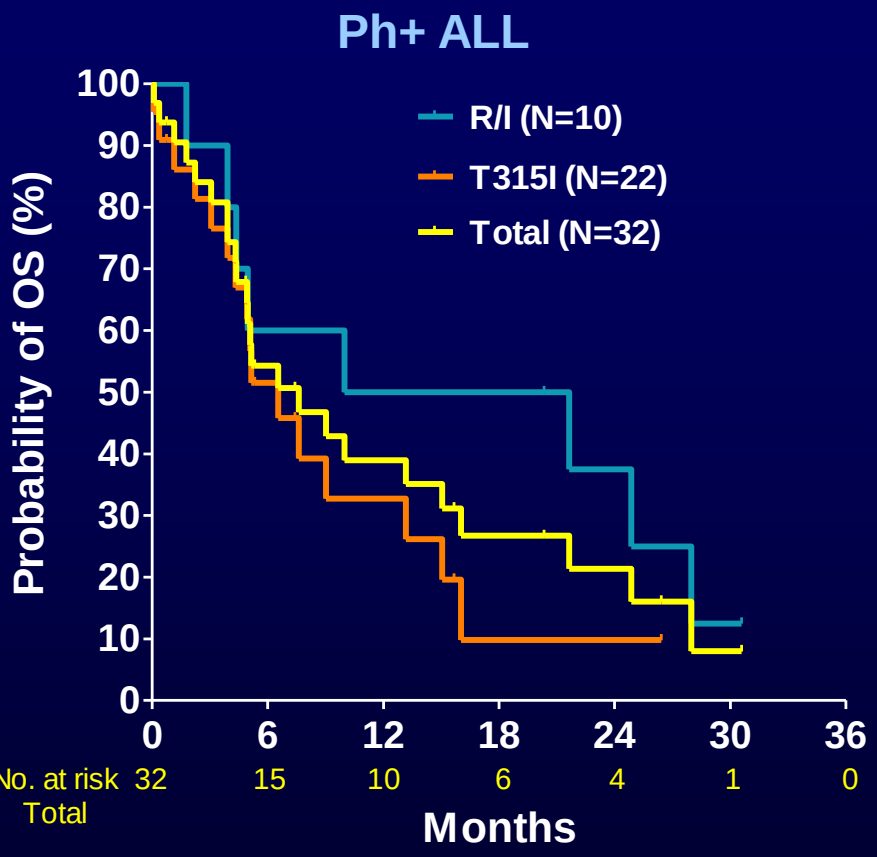


- **PFS at 2 years: 37% (median 15 months)**
- **OS at 2 years: 72% (median not reached)**

Criteria for progression in AP: death, development of BP, loss of hematologic response over 2 wks, or no reduction from baseline in % blasts on all assessments over 4 wks

Ponatinib Phase 2 Study
OS in BP-CML and Ph+ ALL





- **OS at 2 years in BP-CML: 18% (median 7 months)**
- **OS at 2 years in Ph+ ALL: 21% (median 8 months)**

Criteria for progression in BP or Ph+ ALL: death, increasing blasts over 4 wks

Ponatinib Phase 2 Study Hypertension

Baseline BP (mm Hg), NCI CTCAE	Increase in BP on study (single measurement)[a]		
	Grade 1	Grade 2	Grade 3
Normal (<120/<80), N=70	36%	30%	23%
Grade 1 (120-139)/(80-89), N=167	-	53%	34%
Grade 2 (140-159)/(90-99), N=157	-	-	60%
Grade 3 (≥160/≥100), N=55	-	-	-

- 379/449 (84%) patients had elevated BP at baseline (≥140/90, 47%)
- 301/449 (67%) patients experienced any increase in BP[a] on study
- AEs of hypertension were reported in 109/449 (24%) patients (SAEs in 8/449 [2%])

[a]Any shift to higher grade (NCI CTCAE v.4.0), based on single BP measurements

Ponatinib Phase 2 Study
Incidence of Arterial Thrombotic Events Over Time

	N=449 n (%)			
Data as of:	23 July 2012 (USPI)		03 Sep 2013	
Median Follow-up [exposure]	12 months [340 patient-yrs]		24 months [578 patient-yrs]	
Category	SAE	AE	SAE	AE
Cardiovascular	21 (5)	29 (6)	28 (6)	41 (9)
Cerebrovascular	8 (2)	13 (3)	18 (4)	25 (6)
Peripheral vascular	7 (2)	17 (4)	16 (4)	28 (6)
Total Arterial Thrombosis	34 (8)	51 (11)	53 (12)	77 (17)

- 1.7-fold increase in exposure over additional 13 mos of follow-up
- Incidence of serious AEs increased from 8% to 12%
- Median time to onset: 215 days (range 3-887 days)

SAE = AE reported as serious by the investigator, per standard criteria

Ponatinib Phase 2 Study
Incidence of Vascular Occlusive Events Over Time

	N=449 n (%)			
Data as of:	23 July 2012 (USPI)		03 Sep 2013	
Median Follow-up [exposure]	12 months [340 patient-yrs]		24 months [578 patient-yrs]	
Category	SAE	AE	SAE	AE
Cardiovascular	21 (5)	29 (6)	28 (6)	41 (9)
Cerebrovascular	8 (2)	13 (3)	18 (4)	25 (6)
Peripheral vascular	7 (2)	17 (4)	16 (4)	28 (6)
Total Arterial Thrombosis	34 (8)	51 (11)	53 (12)	77 (17)
Venous Thromboembolism	10 (2)	15 (3)	13 (3)	23 (5)

- In October 2013, inclusion of venous thromboembolism events (3 SAEs in intervening months) to create Vascular Occlusion category

 SAE = AE reported as serious by the investigator, per standard criteria

Ponatinib Phase 2 Study Impact of Dose Modification on Response

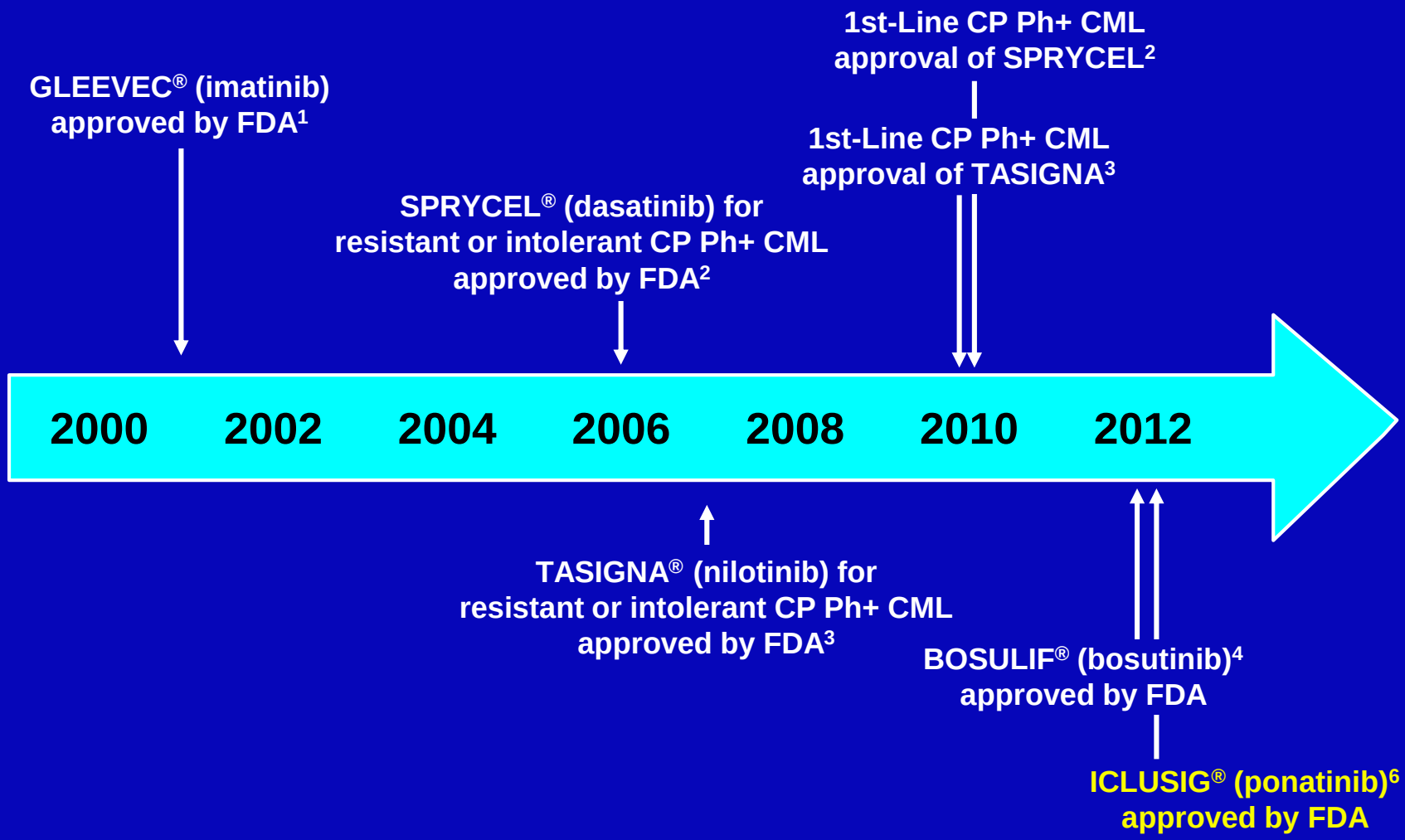
- 149 CP-CML patients achieved MCyR by 12 mos
- Among patients who dose reduced after achieving response
  - 97% (62/64) maintained MCyR
  - 96% (51/53) maintained CCyR
  - 92% (34/37) maintained MMR

For additional information, see Poster 4007, Monday Dec. 9, 6-8pm

Ponatinib Phase 2 Study - PACE
2 Year Follow-up Summary

- Confirmed substantial clinical activity in heavily pretreated patients with BCR-ABL+ leukemias
- Early, deep, and durable responses were observed; 89% maintained MCyR for at least 2 yrs in CP-CML
- Arterial thrombotic events occurred; higher dose intensity, older age, presence of other risk factors at baseline associated with higher likelihood of event
- Ponatinib is an important treatment for patients in whom the need and potential benefit outweigh the potential risk

Evolving CML Treatment Landscape



Omacetaxine is a Recently Approved Protein Synthesis Inhibitor

Table 3. Response rates in chronic-phase CML patients treated with omacetaxine

Response	Patients treated, n (%), N = 62
Hematologic response categories	
Complete hematologic response	48 (77%; 95% LCL, 65%)
No response	12 (19)
Unevaluable	2 (3)
Cytogenetic response categories	
Major	14 (23%; 95% LCL, 13%)
Complete: 0% Ph^+ cells*	10 (16)
Partial: > 0%-35% Ph^+ cells*	4 (6)
Minor	3 (5)
Minimal	10 (16)
No response	23 (37)
Unevaluable†	12 (19)

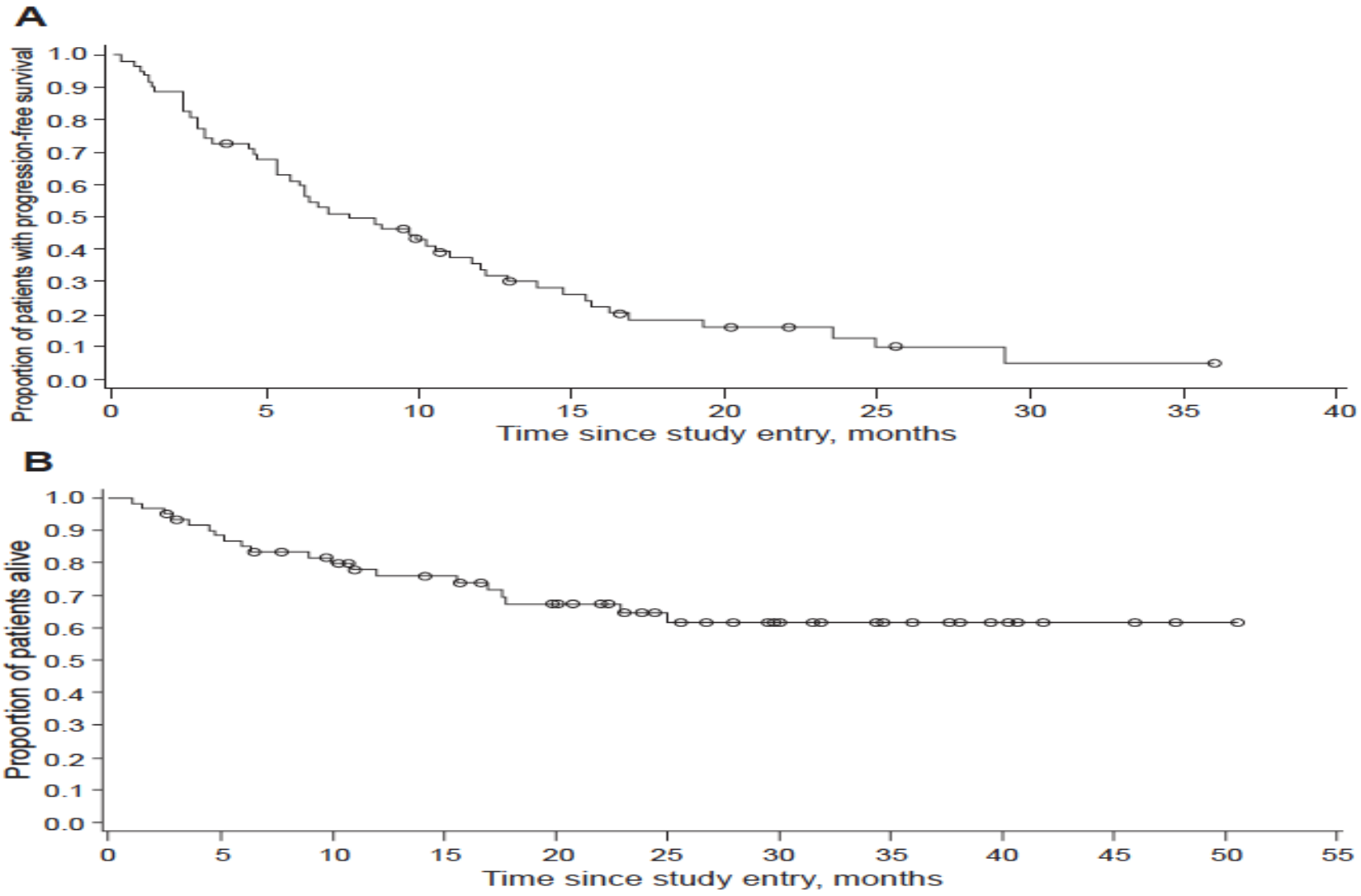
CML indicates chronic myeloid leukemia; and LCL, lower confidence limit.

*Includes both confirmed and unconfirmed response. Unconfirmed response is based on a single bone marrow cytogenetic evaluation for patients where a confirmatory evaluation is not available.

†Patients with unevaluable cytogenetic responses are those with no postbaseline bone marrow assessment.

Cortes et al, Blood 2012.

Omacetaxine for CP-CML Patients with the T315I Mutation



Cortes et al, Blood 2012.

Omacetaxine in CP-CML: Adverse Events

Table 6. Most frequent (> 10%) adverse events associated with omacetaxine

Adverse event	Patients, n (%)		
	All grades	Grade 3/4	Grade 5
Hematologic			
Thrombocytopenia	49 (79)	47 (76)	0
Anemia	41 (66)	24 (39)	0
Neutropenia	31 (50)	27 (44)	0
Pancytopenia	16 (26)	13 (21)	1 (2)
Leukopenia	13 (21)	11 (18)	0
Lymphopenia	11 (18)	10 (16)	0
Nonhematologic			
Infection*	26 (42)	5 (8)	1 (2)
Diarrhea	25 (40)	1 (2)	0
Nausea	21 (34)	1 (2)	0
Pyrexia	18 (29)	1 (2)	0
Fatigue	18 (29)	3 (5)	0
Asthenia	17 (27)	0	0
Arthralgia	14 (23)	1 (2)	0
Injection site erythema	13 (21)	0	0
Alopecia	11 (18)	0	0
Constipation	11 (18)	0	0
Headache	11 (18)	0	0
Cough	11 (18)	0	0
Upper abdominal pain	10 (16)	0	0
Epistaxis	9 (15)	1 (2)	0
Insomnia	8 (13)	0	0
Peripheral edema	8 (13)	0	0
Back pain	7 (11)	1 (2)	0
Extremity pain	7 (11)	0	0
Rash	7 (11)	0	0
Myalgia	7 (11)	1 (2)	0

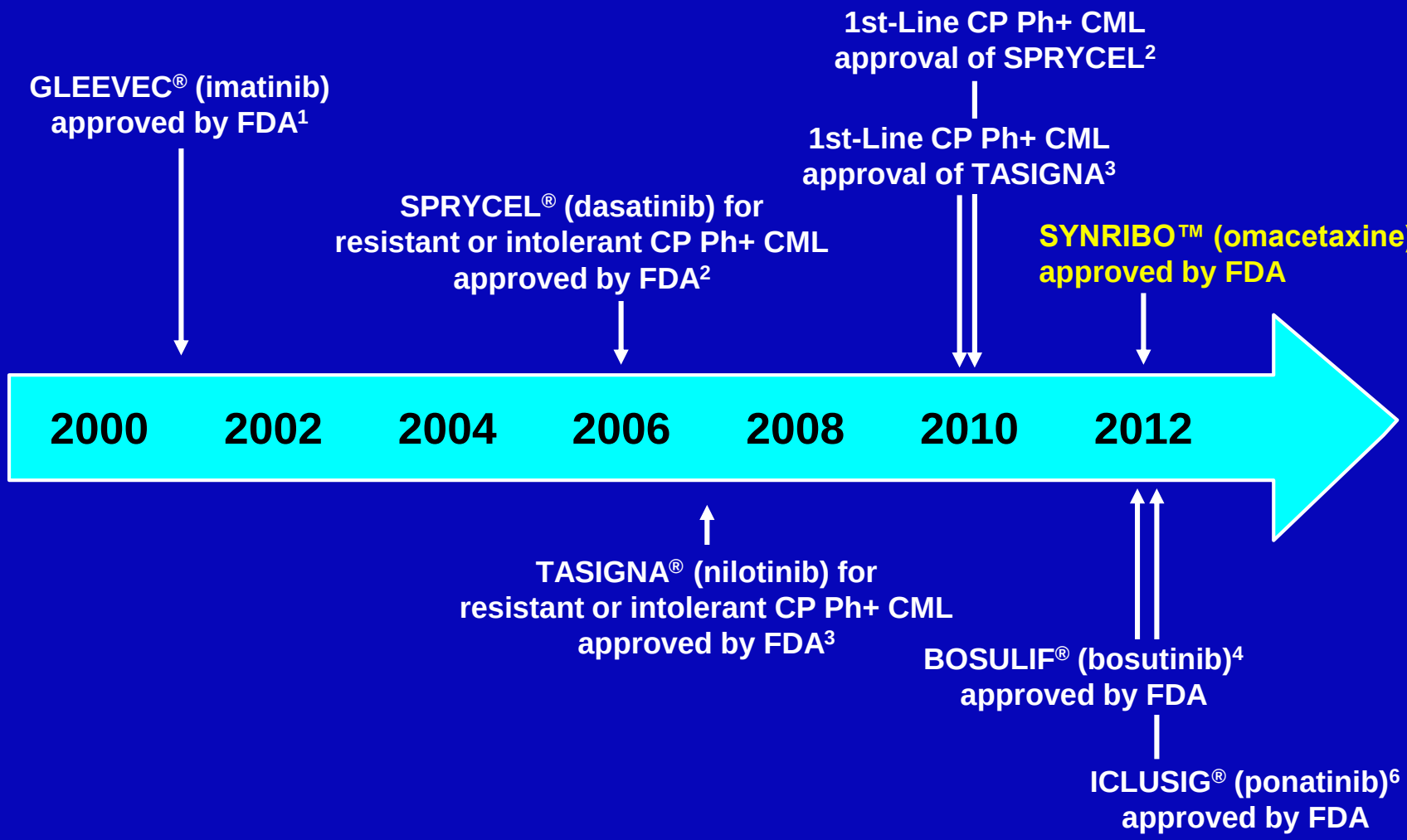
*Includes all preferred terms in system organ class "Infections and Infestations."

Cortes et al, Blood 2012.

Omacetaxine Conclusions

- Omacetaxine is a first-in-class protein synthesis inhibitor with modest activity in highly pretreated CP-CML and accelerated phase patients, including those with the BCR-ABL T315I mutation
- Response duration appears to be modest
  - Nine of 108 patients remain on treatment after ~5 years
- Grade 3/4 myelosuppression is common
- Non-hematologic grade 3/4 toxicities are uncommon
- Omacetaxine was approved by the US FDA in October 2012 for the treatment of imatinib-resistant chronic and accelerated phase CML.

Evolving CML Treatment Landscape



PROMISING AGENTS UNDERGOING CLINICAL INVESTIGATION

Expanded Phase I Study of ABL001, a Potent, Allosteric Inhibitor of BCR-ABL1, Reveals Significant and Durable Responses in Patients With CML-Chronic Phase With Failure of Prior TKI Therapy

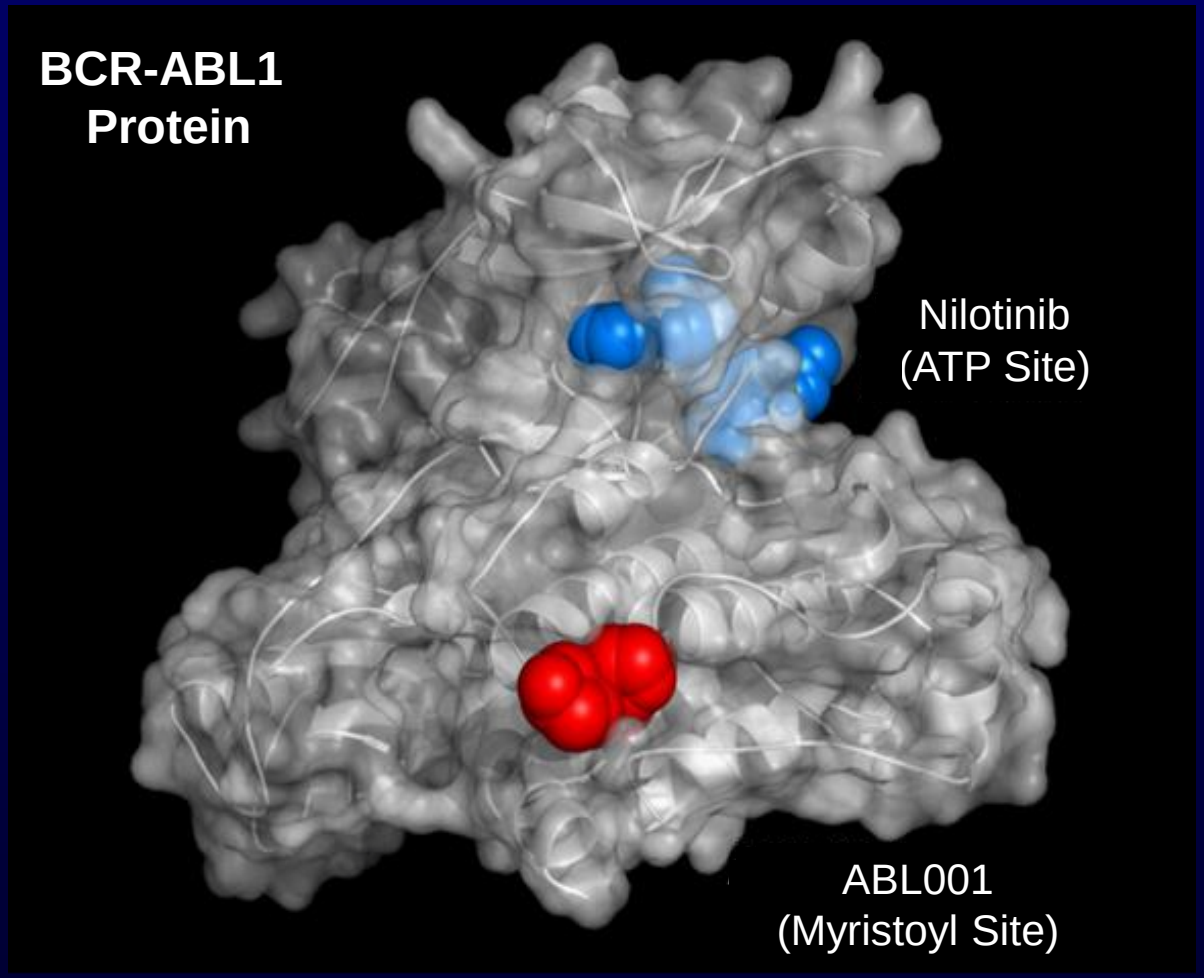
Timothy P. Hughes, Yeow-Tee Goh, Oliver Ottmann, Hironobu Minami, Delphine Rea, Fabian Lang, Michael Mauro, Daniel J. DeAngelo, Moshe Talpaz, Andreas Hochhaus, Massimo Breccia, Jorge Cortes, Michael Heinrich, Jeroen Janssen, Juan-Luis Steegmann, François-Xavier Mahon, Ally He, Varsha Iyer, David Hynds, Gary J. Vanasse, Dong-Wook Kim

American Society of Hematology
Annual Meeting 2016

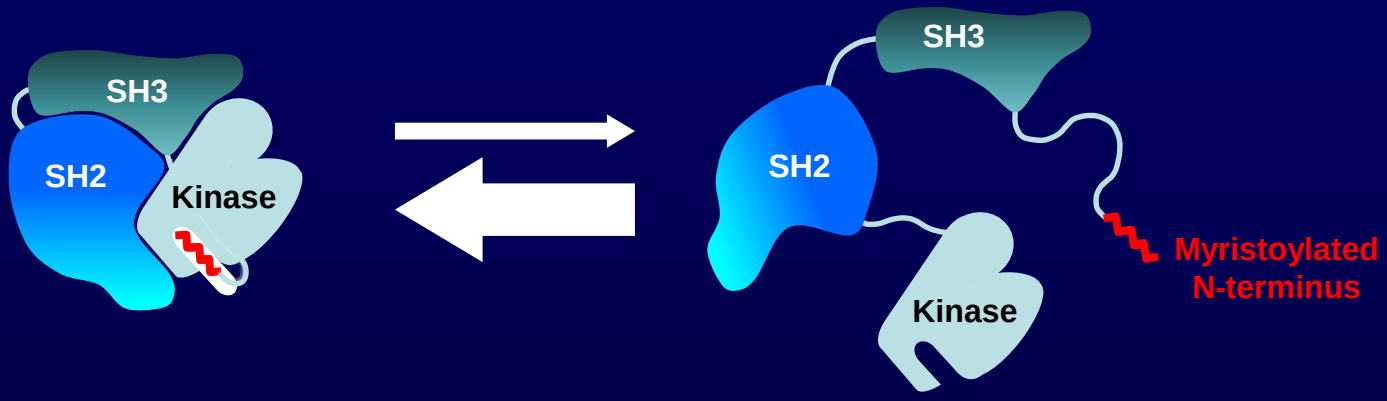
Abstract # 625

ABL001 Is a Potent, Specific Inhibitor of BCR-ABL1 With a Distinct Allosteric Mechanism of Action

- Developed to gain greater BCR-ABL1 inhibition, with activity against BCR-ABL1 mutations conferring resistance to TKIs
- Potential to combine with TKIs for greater pharmacological control of BCR-ABL1



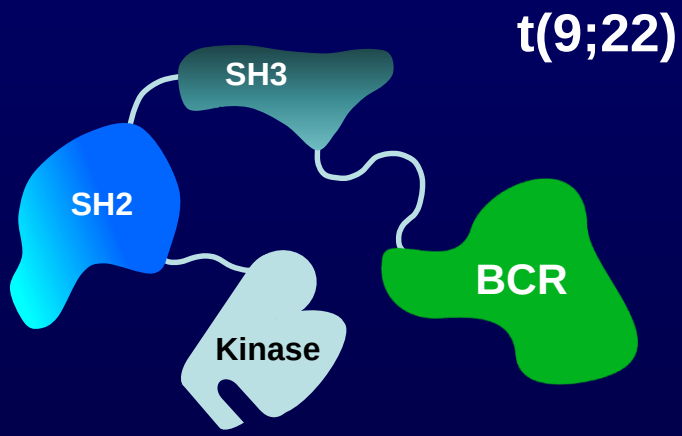
Autoinhibition of ABL1 By Engagement of Myristoyl Binding Site



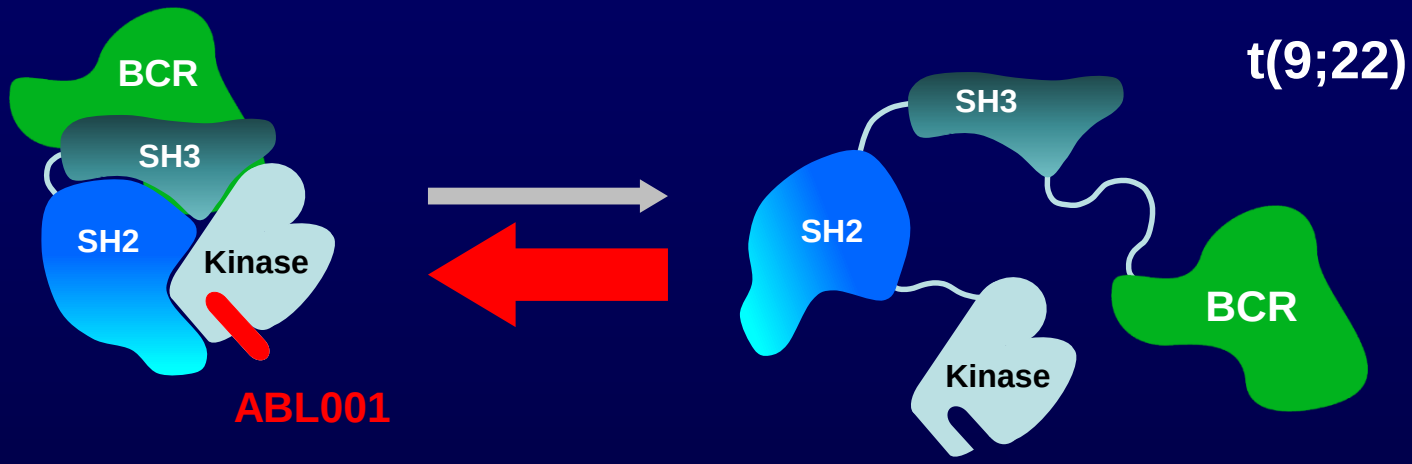
INACTIVE

ACTIVE

Loss of ABL1 Autoinhibition Due to BCR-ABL1 Translocation



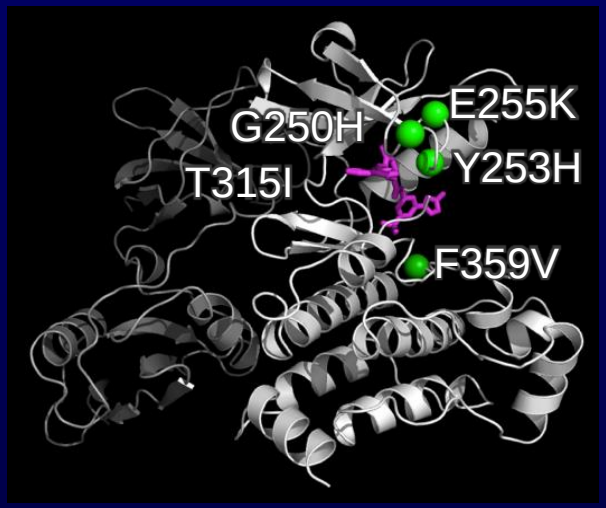
ABL001 Allosterically Inhibits BCR-ABL1 Kinase Activity



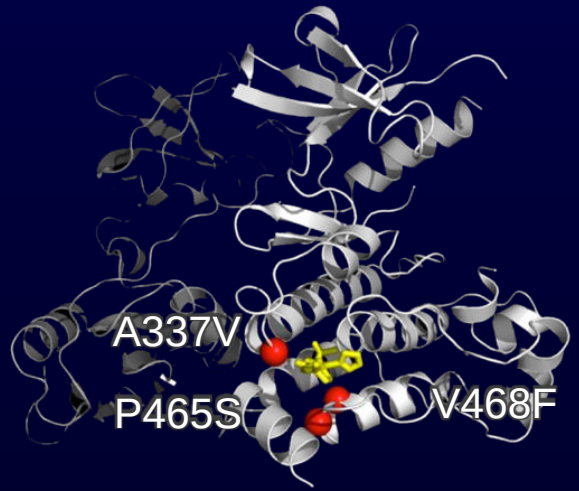
ABL001

ABL001 and Classical TKIs Exhibit Complementary Mutation Profiles

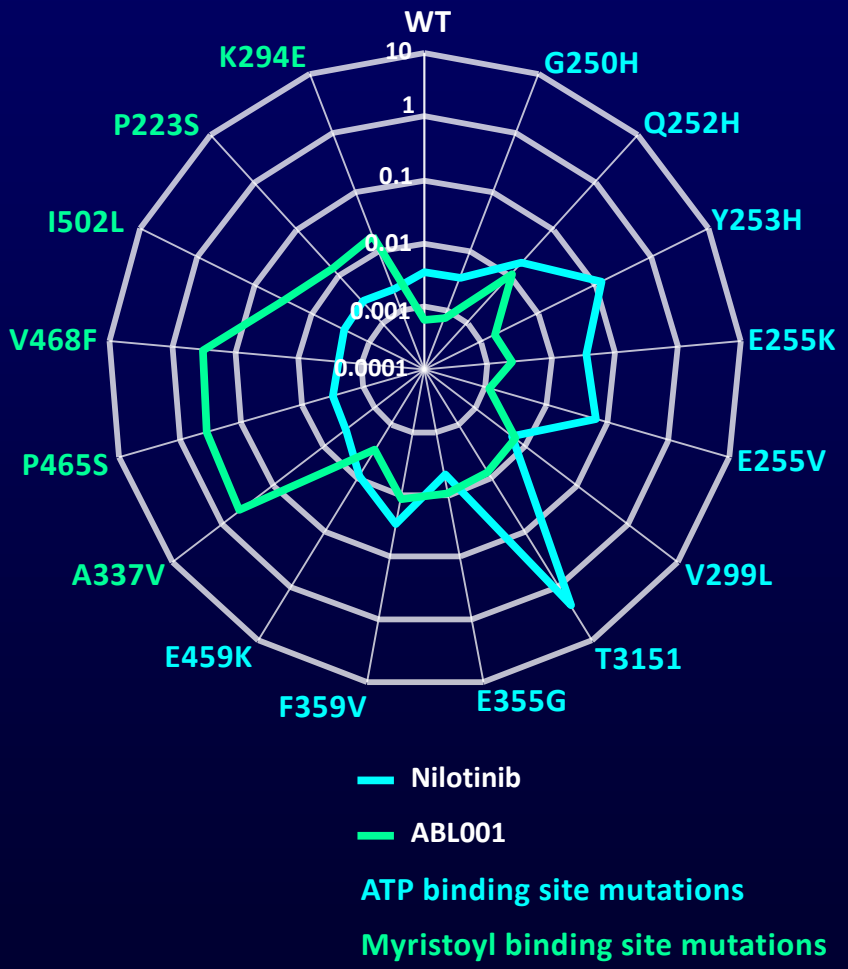
ATP Binding Site Mutations



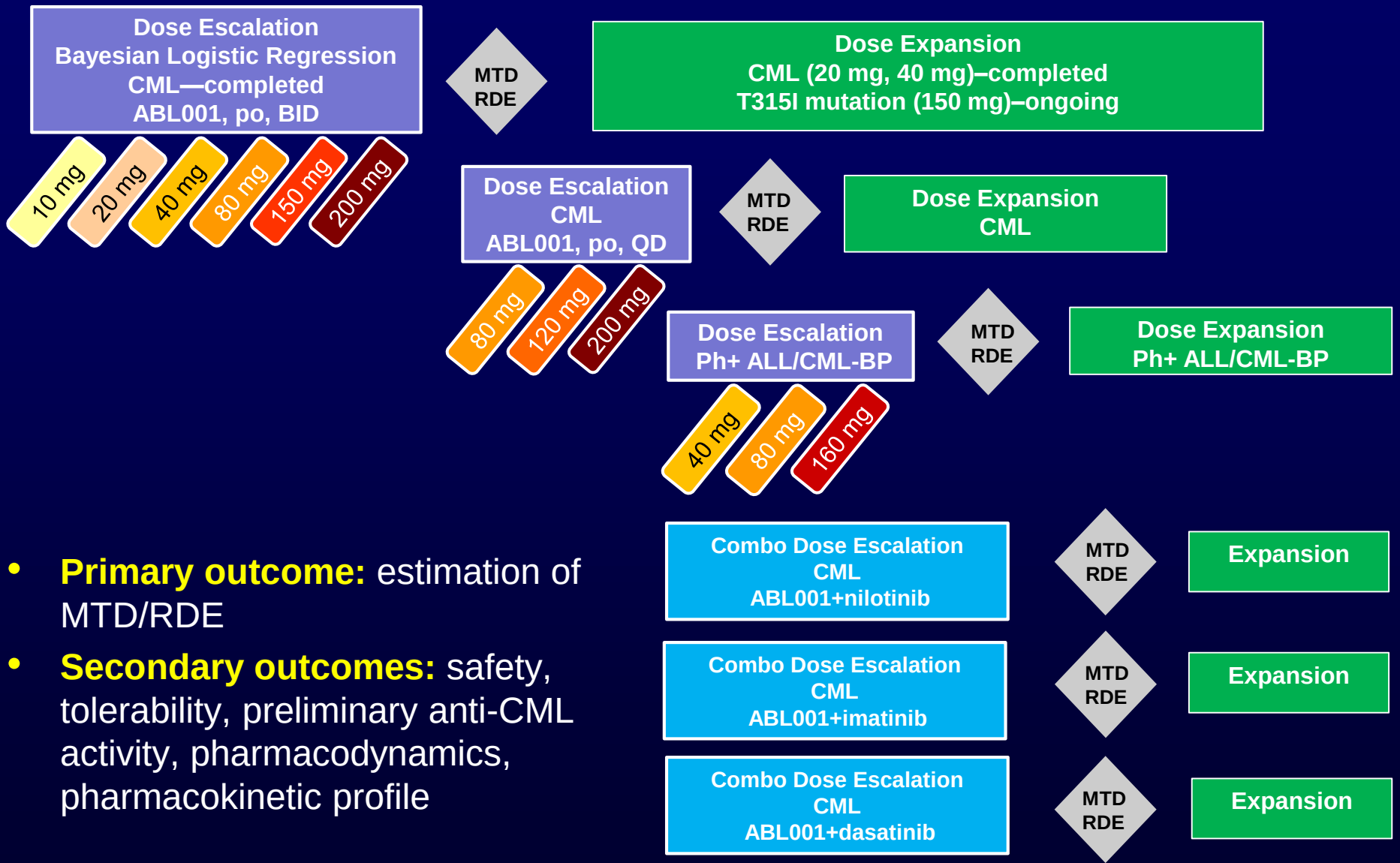
Myristoyl Binding Site Mutations



Proliferation IC_{50} Profiles in Ba/F3 *BCR-ABL1*–Mutant Lines



ABL001X2101: Study Design
A multicenter, phase 1, first-in-human study



- **Primary outcome:** estimation of MTD/RDE
- **Secondary outcomes:** safety, tolerability, preliminary anti-CML activity, pharmacodynamics, pharmacokinetic profile

ALL, acute lymphocytic leukemia; BID, twice daily; BP, blast phase; CML, chronic myeloid leukemia; MTD, maximum tolerated dose; Ph+, Philadelphia chromosome–positive; po, peroral; QD, once daily; RDE, recommended dose for expansion.

Patient Disposition—Single-Agent ABL001 in CML

	ABL BID						ABL QD			Total
mg	10	20	40	80	150	200	80	120	200	
N	1	14	35	12	10	5	6	10	6	99
Median duration of exposure, weeks	49	37.6	29.6	81.0	52.6	69.4	16.8	51.6	53.6	37.6
Ongoing, n (%)	0	14 (100)	30 (86)	9 (75)	7 (70)	3 (60)	6 (100)	10 (100)	5 (83)	84 (85)
Discontinued, n (%)	1 (100)	0	5 (14)	3 (25)	3 (30)	2 (40)	0	0	1 (17)	15 (15)
Reason for discontinuation, n (%)										
AE	0	0	2 (6)	1 (8)	2 (20)	1 (20)	0	0	0	6 (6)
Disease progression[a]	0	0	2 (6)	0	1 (10)	0	0	0	1 (17)	4 (4)
Patient/guardian decision	1 (100)	0	1 (3)	1 (8)	0	1 (20)	0	0	0	4 (4)
Death	0	0	0	1 (8)	0	0	0	0	0	1 (1)

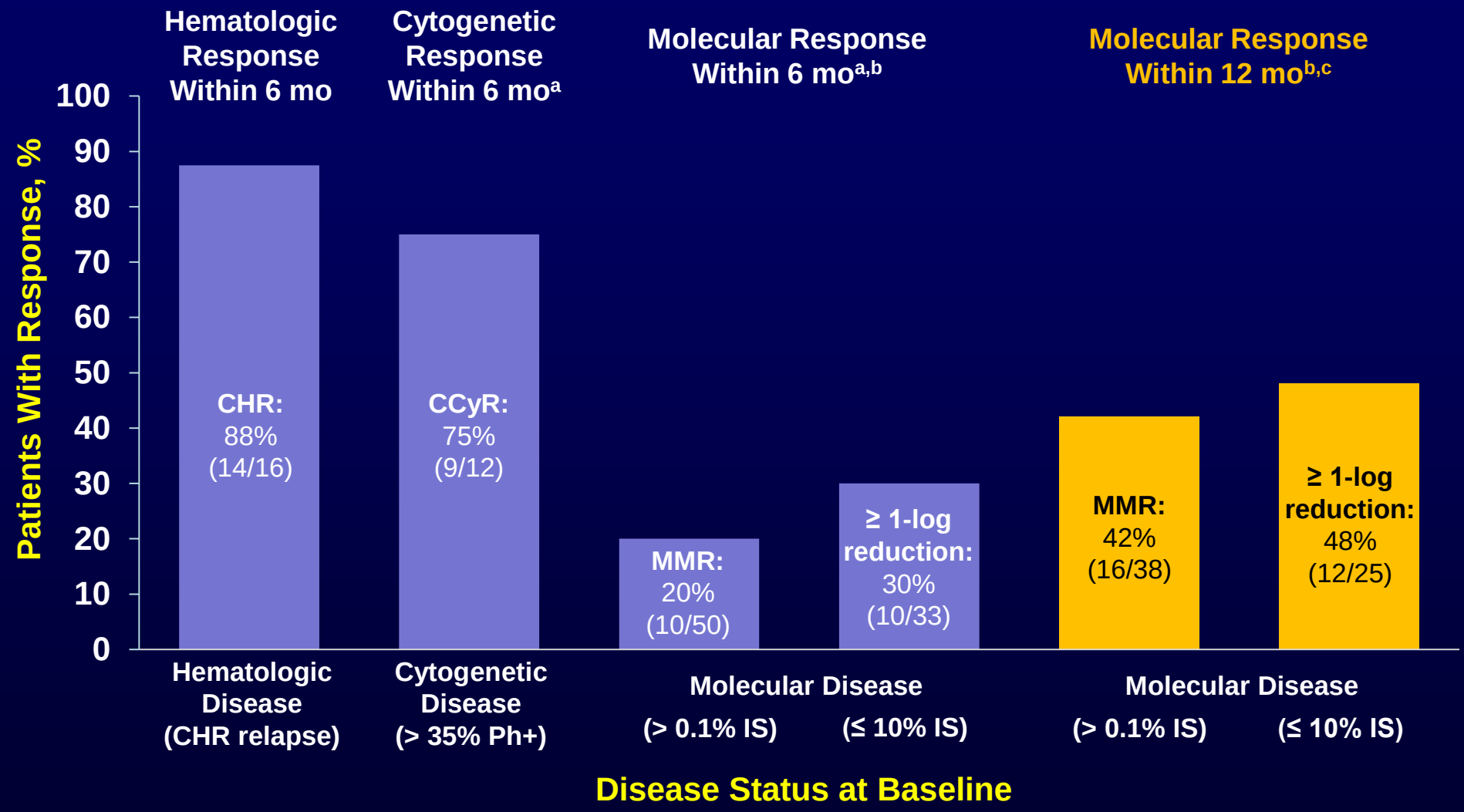
[a] Only 1 of 8 patients with relapsed or progressive disease had detectable myristoyl binding pocket mutations (V468H, I502L)

AE, adverse event.

Safety: AEs Suspected of Being Related to Study Drug Occurring in ≥ 5% of Patients (n = 123)

Adverse Event	**All Grades, n (%)**	**Grade 3/4, n (%)**
Lipase increase	26 (21)	12 (10)
Rash	19 (15)	0
Thrombocytopenia	16 (13)	7 (6)
Fatigue	15 (12)	1 (1)
Nausea	14 (11)	0
Arthralgia	13 (11)	0
Amylase increased	12 (10)	1 (1)
Headache	12 (10)	0
Pruritus	11 (9)	1 (1)
Anemia	9 (7)	5 (4)
Diarrhea	9 (7)	0
Myalgia	9 (7)	1 (1)
Vomiting	9 (7)	0
Hypophosphatemia	7 (6)	1 (1)
Neutropenia	7 (6)	5 (4)

Responses in Patients With CML Treated With Single-Agent BID ABL001 With ≥ 3 Months Exposure on Study



CCyR, complete cytogenetic response; CHR, complete hematologic response; IS, International Scale; MMR, major molecular response.

[a] Patients had ≥ 6 months of treatment exposure or achieved response within 6 months.

[b] *BCR-ABL1*^{IS} reduction achieved.

[c] Patients had ≥ 12 months of treatment exposure or achieved response within 12 months.

Responses in CML Patients Resistant to Last TKI

- 47 of 77 (61%)[a] patients with CML treated with single-agent ABL001 BID were resistant to their last TKI[b]
- Responses in all TKI-resistant patients treated with single-agent ABL001 BID
  - 13.3% and 37.5% achieved MMR by 6 and 12 months, respectively
  - 29.4% and 42.9% achieved ≥ 1-log reduction by 6 and 12 months, respectively
  - 8 of 10 (80%) patients > 35% Ph+ achieved CCyR by 6 months

[a] % calculated based on number of evaluable patients for each endpoint and by each time point.
[b] Includes imatinib, nilotinib, dasatinib, bosutinib, radotinib, ponatinib.

Responses in CML Patients with T315I Mutation

- 11 of 77 (14%) CML patients treated with BID ABL001 had T315I mutations at baseline; 10 had 3 months' follow-up
  - 4 of 10 patients > 35% Ph+ achieved CCyR by 6 mo
  - 6 patients have maintained stable disease without achieving CCyR or MMR
  - No patients have progressed to blast crisis
  - 1 patient has maintained baseline MMR for > 1 year
- Dose escalation for T315I-mutant patients is ongoing to explore whether higher doses can achieve deeper molecular responses

Conclusions

- ABL001 was generally well tolerated in heavily pretreated patients with CML resistant to or intolerant of prior TKIs
- Clinical activity seen in patients with nonmutant BCR-ABL1 as well as across multiple TKI-resistant mutations
  - Only 1 patient with relapsed or progressive disease had detectable mutations (both kinase and myristoyl domain mutations)
- Recommended dose of 40 mg BID declared for patients with CML-CP without T315I mutations
- Phase I enrollment is ongoing for other cohorts
- These findings support further evaluation in phase 2/3 clinical trials

Newer Treatment Options
Concluding Thoughts

- Bosutinib and ponatinib are approved for patients with resistance or intolerance to a prior TKI
- Omacetaxine is approved for patients with disease that is resistant or intolerant to two or more TKIs
- There is now an effective tyrosine kinase inhibitor option for every known imatinib-resistant BCR-ABL kinase domain mutation
- ABL001 binds to a distinct region of BCR-ABL and may therefore retain clinical activity against many TKI-resistant mutations. Clinical trials are ongoing to define an optimal dose for patients with the T315I mutation.

IMATINIB DISCONTINUATION STUDIES

Can imatinib be safely stopped in patients with deep molecular responses?

Long-term Follow-up of the French Stop Imatinib Study (STIM1) in Chronic Myeloid Leukemia Patients*

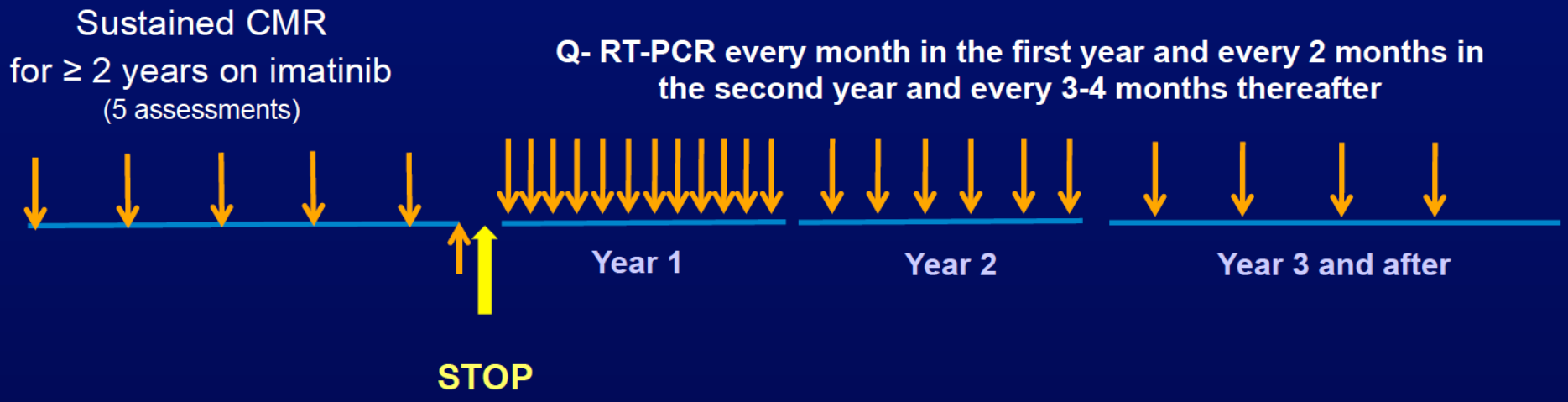
Gabriel Etienne, Delphine Réa, Joëlle Guilhot, François Guilhot, Françoise Huguet, Laurence Legros, Franck Nicolini Aude Charbonnier, Agnès Guerci, Bruno Varet, Philippe Rousselot, François-Xavier Mahon on behalf of the Intergroupe Français des Leucémies Myéloïdes Chroniques (FILMC) on behalf of the STIM Investigators

*This study is registered with ClinicalTrials.gov, number NCT00478985

Orlando, ASH 2015, abstract 85121

STIM study design*

N=100



Molecular recurrence: positivity of *BCR–ABL* transcript confirmed by *a* second consecutive analysis point indicating a increase of one log or loss of MMR at one point.

Molecular recurrence → Imatinib rechallenge

* *Mahon FX et al. The Lancet Oncology, 2010;11(11): 1029-1035.*

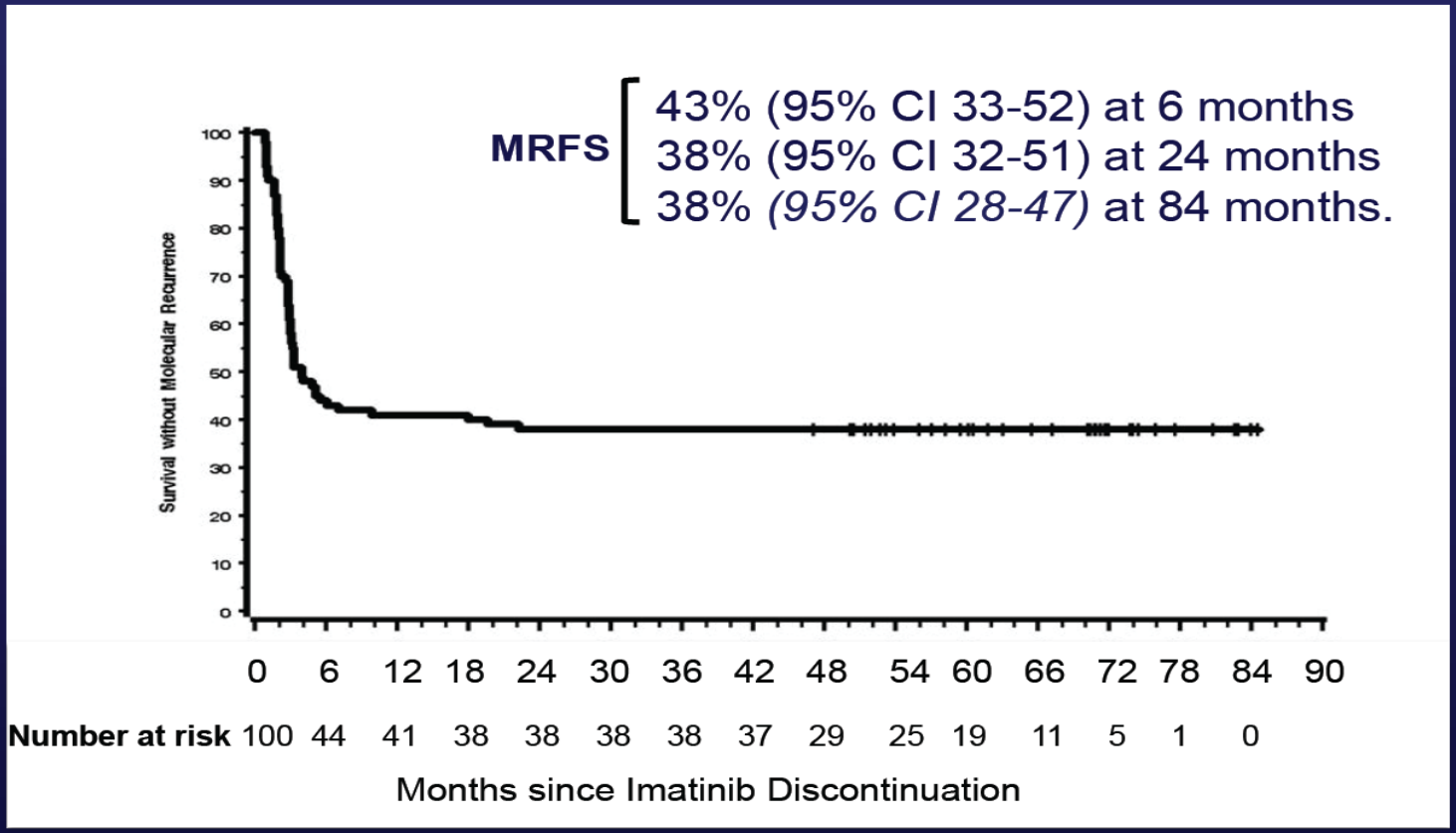
Characteristics of patients included in the STIM Study

A prospective, multicentre, non-randomized study with 19 participating institutions in France:

- 100 patients enrolled between July 2007 and Dec 2009
- Median age (range): 59 years (29–81)
- Gender distribution: 48 males, 52 females
- Patients with previous IFN treatment: 50
- *De novo* CML patients: 50
- Median follow up: 65 months

Molecular Recurrence-free Survival (MRFS)

MRFS after imatinib discontinuation – Median Follow-up = 65 mo.
accounting for competing events (death in complete molecular remission without any relapse, n=1)



Imatinib was restarted in 57 patients, and 55 re-achieved their initial level of response

Five patients died of causes unrelated to CML

No patient experienced CML progression

Conclusion

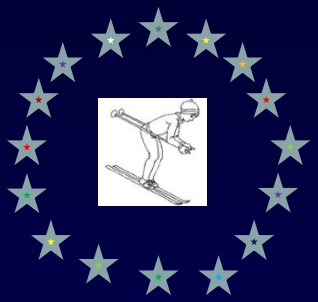
With a longer follow-up (65 mo.) after imatinib discontinuation

- No CML event progression have been reported
- Most if not all relapsing patients have achieved a second deep molecular response after TKI resumption
- Molecular recurrence was very rare after 6 months and no molecular recurrence was reported after 2 years

Imatinib discontinuation is safe provided that:

- A deep sustained molecular response have been achieved before discontinuation
- A close molecular monitoring is available after treatment cessation

EURO-SKI Study Design

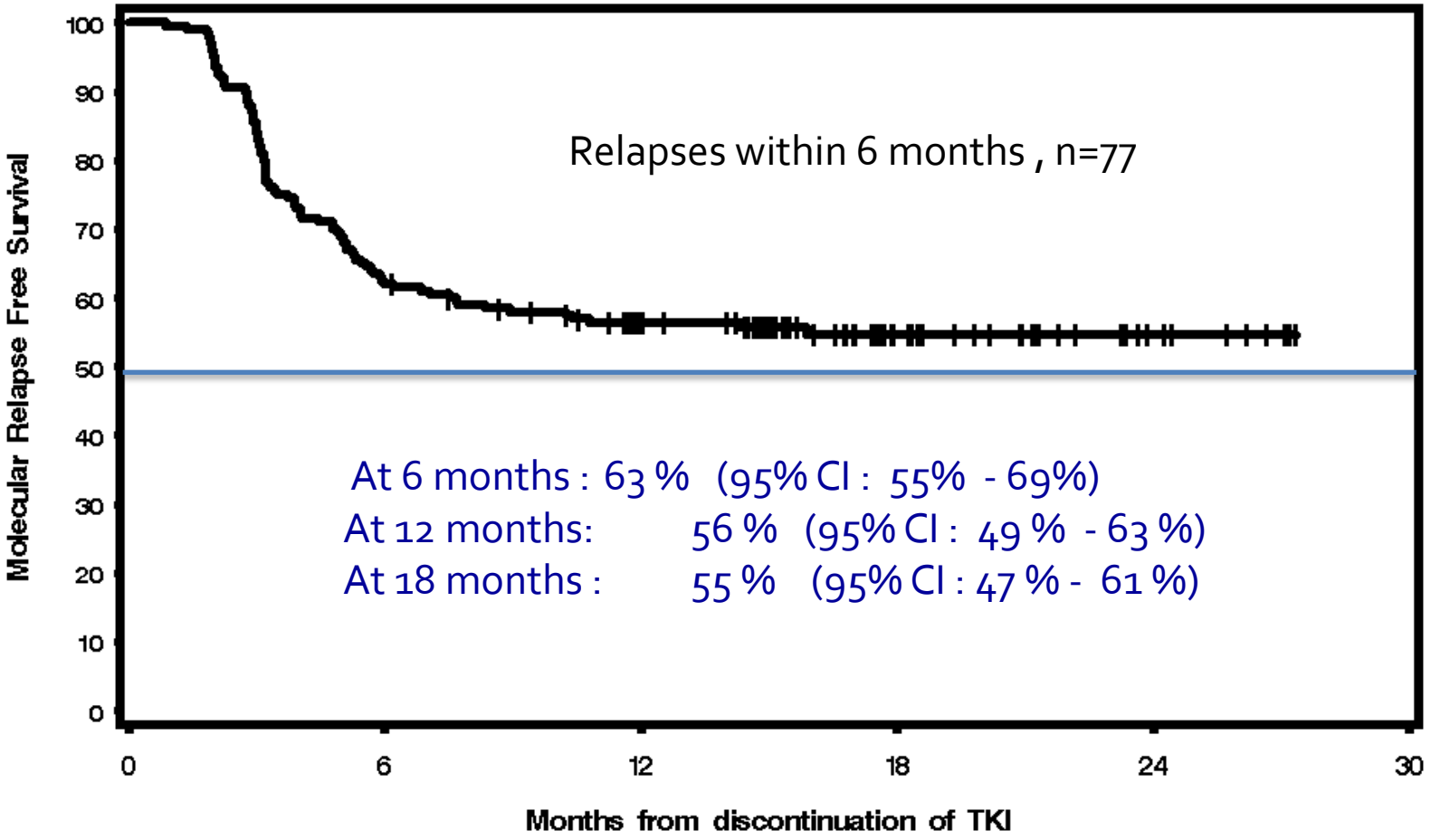


Relapse defined as BCR-ABL > 0.1% (loss of MMR) on the IS at one time point

Courtesy of ELN

EURO-SKI: Molecular Relapse Free Survival

200 interim patients – overtime, loss MMR=89

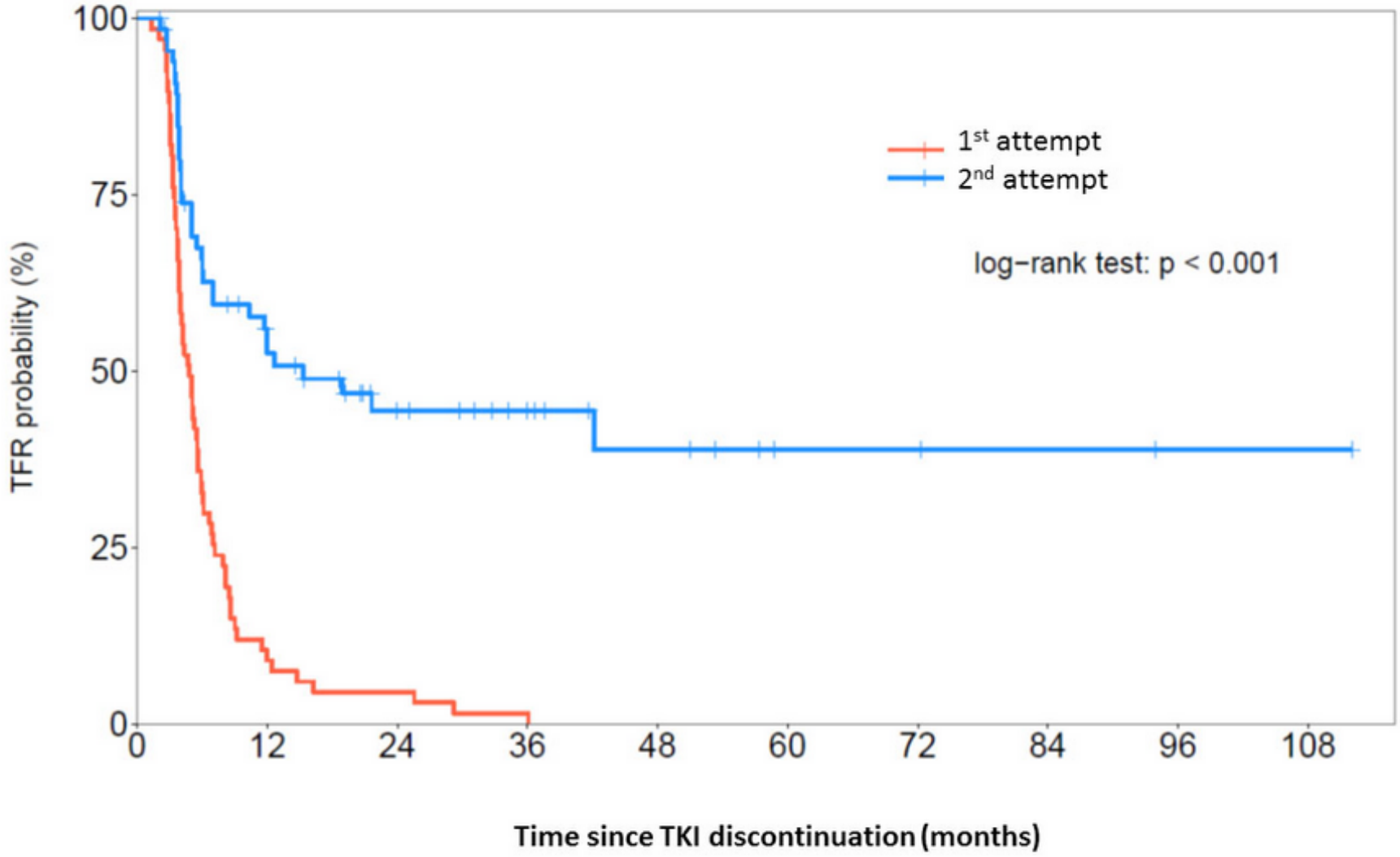


Mahon FX et al, Blood 2014 124:151

IMATINIB DISCONTINUATION STUDIES

Can patients whose disease relapses off treatment successfully discontinue in the future?

Second TKI Discontinuation in CML Patients Who Regained Deep Molecular Response Following TKI Rechallenge



TKI DISCONTINUATION

Is it possible for more patients to achieve a deep remission so that they may ultimately try stopping treatment?

Clinical Trials Aimed at Deepening Molecular Response

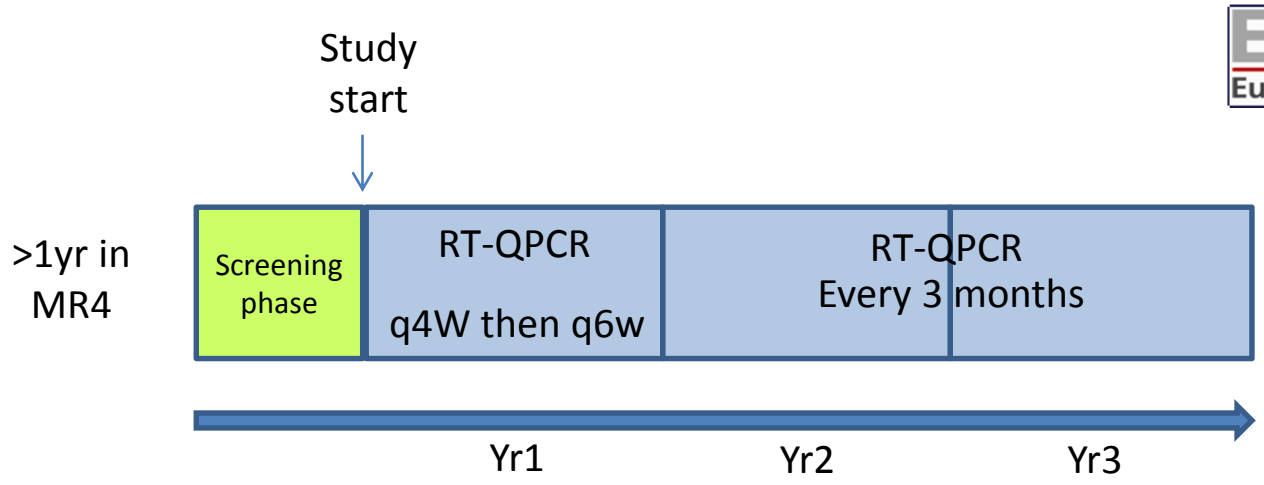
- TKI + Smo inhibitors (failed)
- TKI + hydroxychloroquine (unknown status)
- TKI + ruxolitinib (ongoing)
- TKI + inteferon (ongoing)
- TKI + pioglitazone (ongoing)

TKI DISCONTINUATION

Is it possible that symptoms may develop with treatment interruption?

Context

- **Richter et al. first reported a "tyrosine kinase inhibitors withdrawal" syndrome consisting in musculoskeletal pain after stopping imatinib in CML patients included in the Euroski trial.** (*Richter et al.*, JCO, 2014).



- **Beside the Euroski trial, we are currently running the STIM-2 study in France and prospectively recording all events from the time of TKI discontinuation.**

STIM2 & French EUROSKI cohorts: Prevalence of WS

Patients	Without WS	With WS
Total cohort : % (N)	76.2 (326)	**23.8** (102)
STIM2 (n(%))	86.2 (193)	**13.8** (31)
EUROSKI (n(%))	65.2 (133)	**34.8** (71)

Withdrawal syndrome: clinical characteristics

WS characteristics (n=40)	values
Time from discontinuation (days, median)	21
Duration (months, median (range))	7 (3 - 30)
Location	
Shoulder and spine	67 %
Others	33 %
Intensity	
Grade 1 - 2	62.5 %
Grade 3 - 4	37.5 %
Evolution after TKI resumption (n=19)	
Disappearance	52.6 %
Median duration of TKI (weeks)	3

STIM2 & French EUROSKI cohort: Risk factors for WS

All patients	Without WS	With WS	*p-value*
Sex (H/F (ratio))	158/168 (51.5)	50/52 (51.0)	*0.92*
Age (median; range)	61.9 ± 14.4	63.1 ± 9.5	*0.33*
Sokal, n (%) Low Intermediate High	 115 (40.6) 129 (45.6) 39 (13.8)	 49 (49.5) 34 (34.3) 16 (16.2)	*0.15*
CML duration (months, mean ± SEM)	8.7 ± 3.1	9.7 ± 3.8	*0.02*
Time on TKI (months, median [IQR])	**81.2 [61.2 – 108.0]**	**97.3 [73.7 – 122.9]**	*<0.001*
TKI, n (%) DAS IMA NIL	 1 (0.3) 323 (99.1) 2 (0.6)	 0 (0.0) 100 (98.0) 2 (2.0)	*0.42*
Previous history of osteo articular symptoms (n (%))	**28 (9.8)**	**19 (22.9)**	*0.002*

Discussion - 1

- **The TKI withdrawal syndrome occurred in 23% of French patients included in the Euroski and STIM-2 discontinuation trials**

- **For patients having to restart TKIs, WS disappeared in 50% of the case after a median of 3 weeks**

Study	Prevalence	Onset	TKI	Location	Duration
Richter *et al*. 2014 (n = 50)	30%	< 1 month	Imatinib	Shoulders Hips	A few weeks to several months
This study (n= 428)	24%	21 days	Imatinib and nilotinib (n=2)	Shoulders Spine	A few weeks to several months

Treatment Cessation: Conclusions

- With longer follow-up:
  - Approximately 40-60 percent of patients in stable deep molecular response are able to discontinue imatinib without suffering molecular relapse
    - Second attempts at treatment discontinuation in patients who have suffered molecular relapse can be successful

- Many ongoing trials have been performed to assess the safety and efficacy of TKI cessation in sustained molecular remission. Under proper supervision, it is now possible for select patients treated in the community to try discontinuing treatment.

- Significant long-term follow-up (decades) of patients enrolled in ongoing cessation studies is necessary to affirm CML cure.

- Some patients may experience a “TKI withdrawal syndrome” upon stopping treatment.

Conclusions - I

- Imatinib is favorably impacting survival in patients with chronic phase CML
  - ~65% are estimated to be on imatinib in CCyR after 7 years
  - ~25% of patients meet the definitions of resistance within the first 18 months of therapy
- Dasatinib, nilotinib, bosutinib and ponatinib are effective in cases of imatinib -resistant and -intolerant chronic and accelerated phase of CML
- Nilotinib and dasatinib are approved for the treatment of newly diagnosed chronic phase CML patients
- Achieving a reduction in BCR-ABL transcript level to ≤10% after 3 months of TKI treatment is associated with superior outcomes. The slope of decline may be as important.

Conclusions - II

- Loss of response to dasatinib, nilotinib and bosutinib is most often due to a small number of BCR-ABL kinase domain mutations (~5), commonly the T315I mutation
  - In cases where the T315I mutation is not the cause of resistance, it is reasonable to try treatment with another of these drugs
  - Ponatinib may be effective against all single BCR-ABL mutants, but there are some safety concerns that limit its use
- ABL001 is an investigational agent that is showing signs of efficacy in early experience, including in some cases that have the T315I mutation
- Adequate monitoring of disease burden in CML patients is essential, and CML patients are encouraged to consult with a CML expert to ensure their disease is being optimally managed
- Some patients with sustained deep molecular responses can stop treatment for at least several years. Monitoring is essential.

Conclusions - III

- In 2017, the remaining frontiers for the management of CML remain
  - Improving outcomes in advanced phase CML patients
  - Understanding and treating mechanisms of BCR-ABL-independent resistance to TKIs
  - Determining why some patients are able to successfully discontinue treatment but others are not
  - Eliminating the small proportion of CML cells that remain in most patients with deep responses so that they may be able to discontinue therapy altogether (“true cure”)
    - Studies with investigational agents are currently ongoing
- The continued participation of CML patients in clinical trials is essential to further improve treatment outcomes

Thank you for your attention and your support of the LLS

To Schedule an Appointment
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