Why a second generation TK Inhibitor ? The role of nilotinib in the treatment of CML

Pierre Laneuville, MD, FRCPC
Division of Hematology
McGill University Health Center
Montreal, Canada

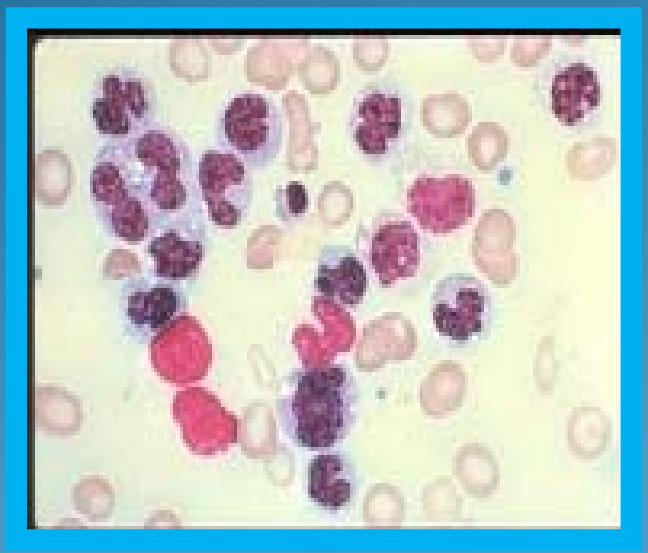
Hotel del la Bahia, La Serena, Chile, September 25 2008

Disclosures: Pierre Laneuville, MD

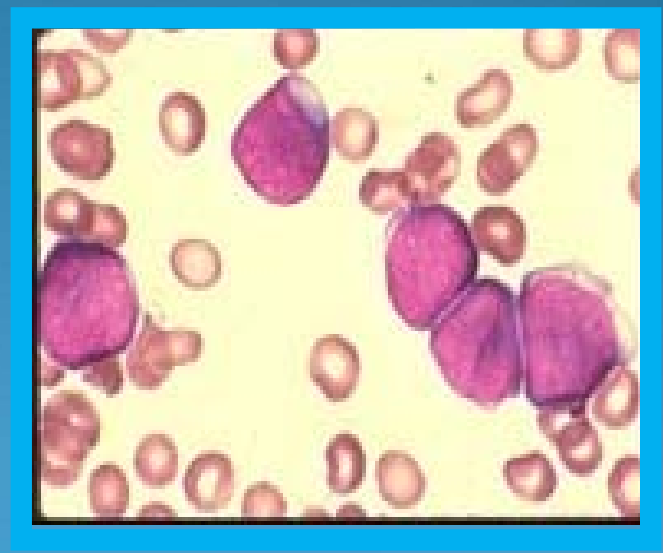
Research Support / P.I.	BMS, Novartis, Wyeth
Employee	N/A
Consultant	BMS, Novartis
Major Stockholder	N/A
Speakers Bureau	BMS, Novartis
Honoraria	BMS, Novartis
Scientific Advisory Board	BMS, Novartis, Wyeth

Evolution of CML and Genomic Instability

Chronic Phase



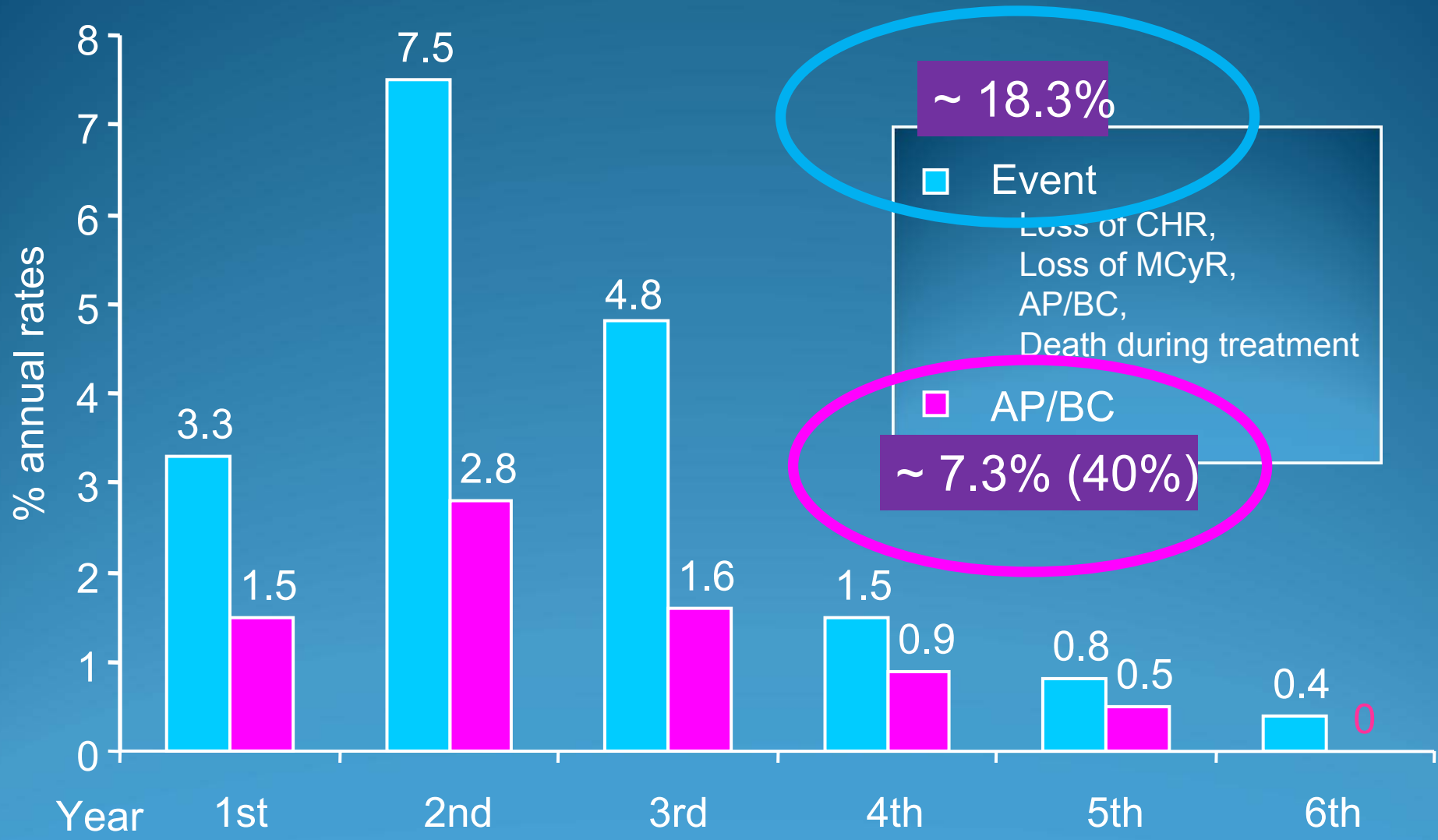
Blast Crisis



median survival ~ 4.5 years

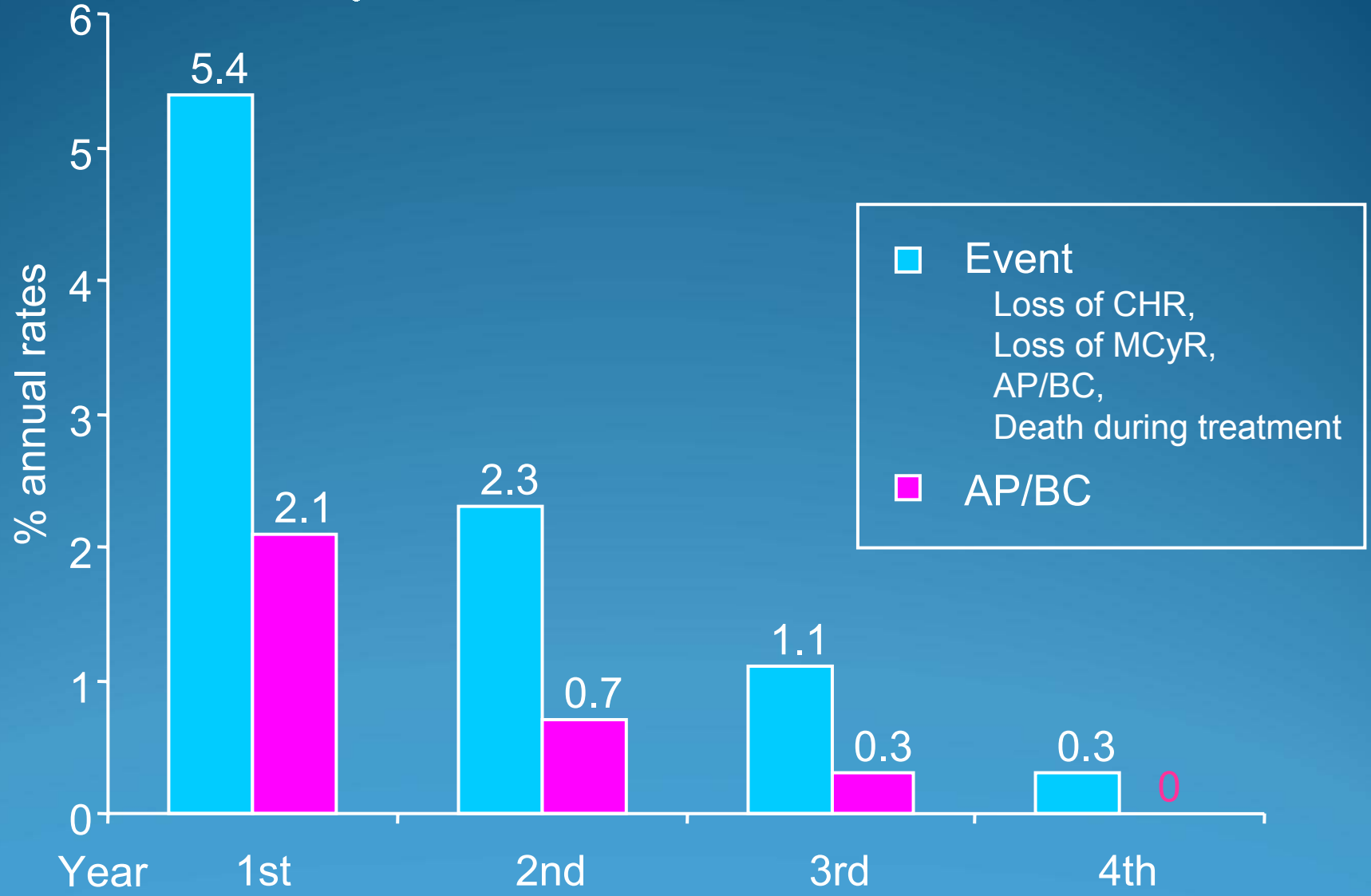
6 year OS 95%

IRIS 6 yr Update: Declining Annual Event Rates



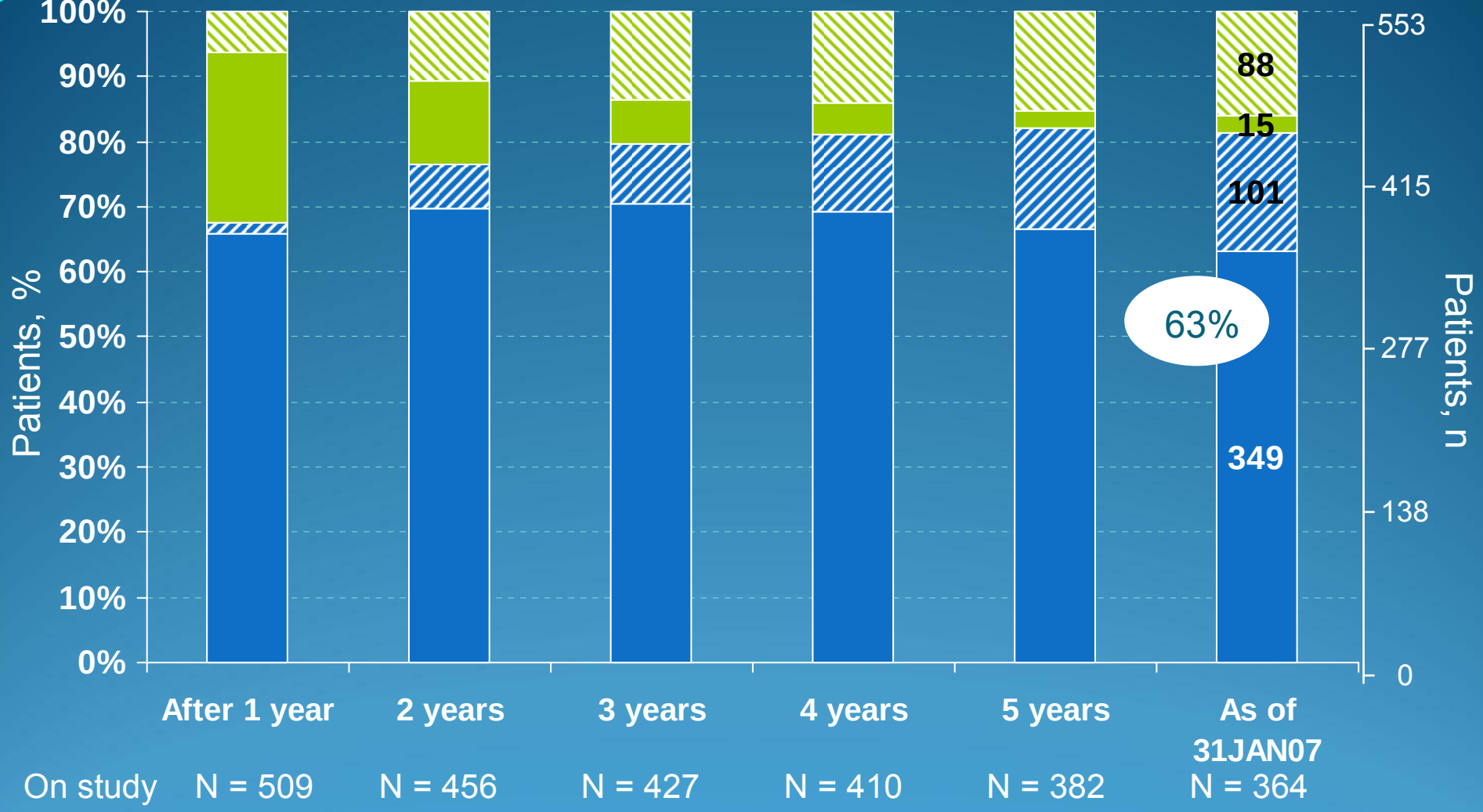
Hochhaus A. *et al*, Blood. 2007; 110, 11. Abstract 25. ASH 2007 Oral Presentation

IRIS 6 yr Update: Declining Annual Event Rates in Pts After CCyR



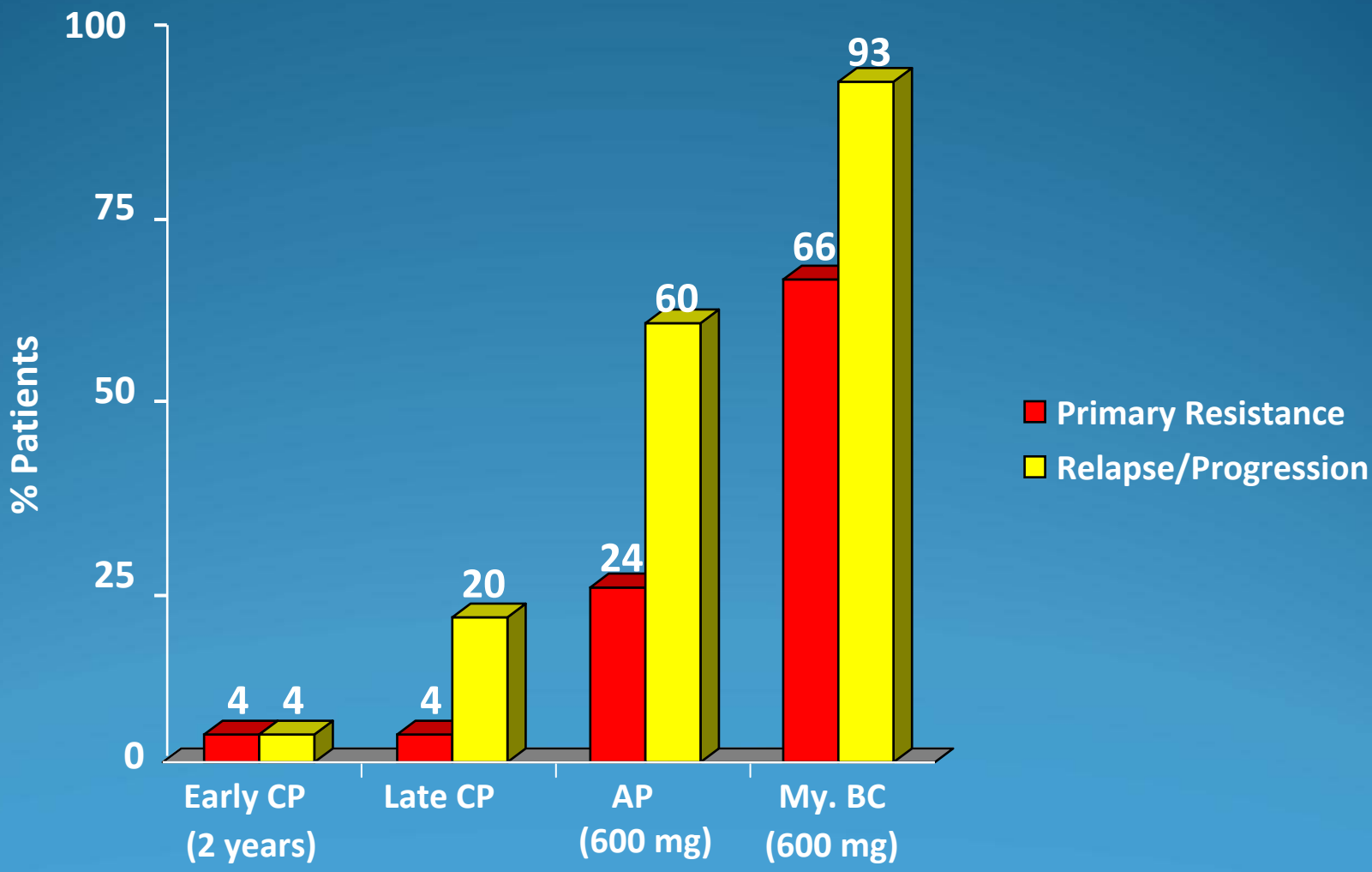
Hochhaus A. *et al*, Blood. 2007; 110, 11. Abstract 25. ASH 2007 Oral Presentation

IRIS 6 yr Update: Pts on IM Study Treatment by Year and Best Response Achieved (CCyR vs No CCyR)



Hochhaus A. *et al*, Blood. 2007; 110, 11. Abstract 25. ASH 2007 Oral Presentation

Frequency of Imatinib Resistance Within 3 Years



Hochhaus A, et al. *Leukemia* 2004;18:1321-1331.

Imatinib Resistance

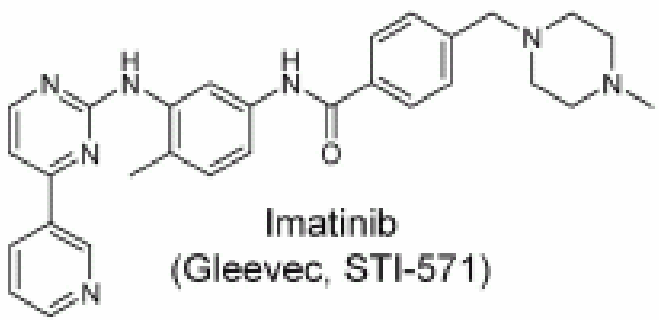
- Resistance (CML CP)
  - Primary: Failure to meet “milestones”
    - 3M CHR, 6M mCR, 12M MCR, 18M CCR
  - Secondary: Progression after initial response
    - Molecular, cytogenetic, hematological

- Mechanisms
  - ~ 50% Abl KD mutations
  - ~ 15% gene amplification
  - metabolic/compliance (therapeutic monitoring)
  - cellular drug influx/efflux
  - other ?

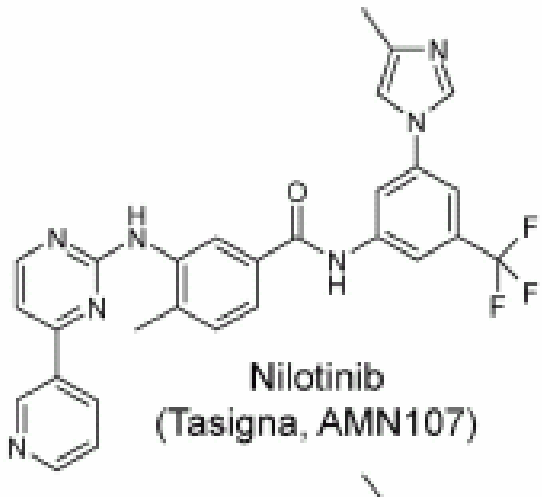
Intolerance

- Recurrent grade 3 toxicity
- Persistant grade 2 toxicity

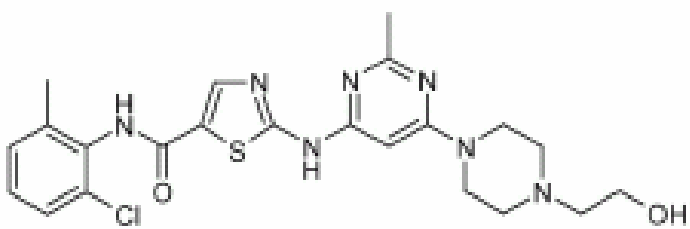
BCR/ABL Inhibitors
Imatinib, Nilotinib, Dasatinib, Bosutinib



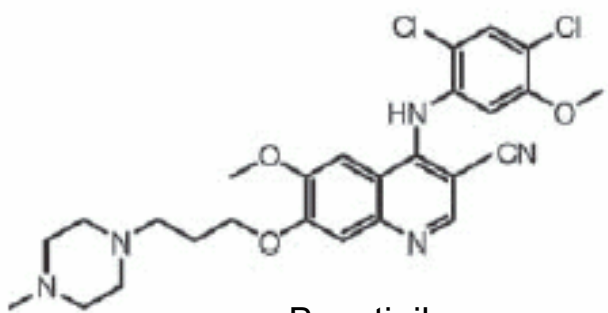
Imatinib
(Gleevec, STI-571)



Nilotinib
(Tasigna, AMN107)



Dasatinib
(Sprycel, BMS-354825)



Bosutinib
(SK-606)

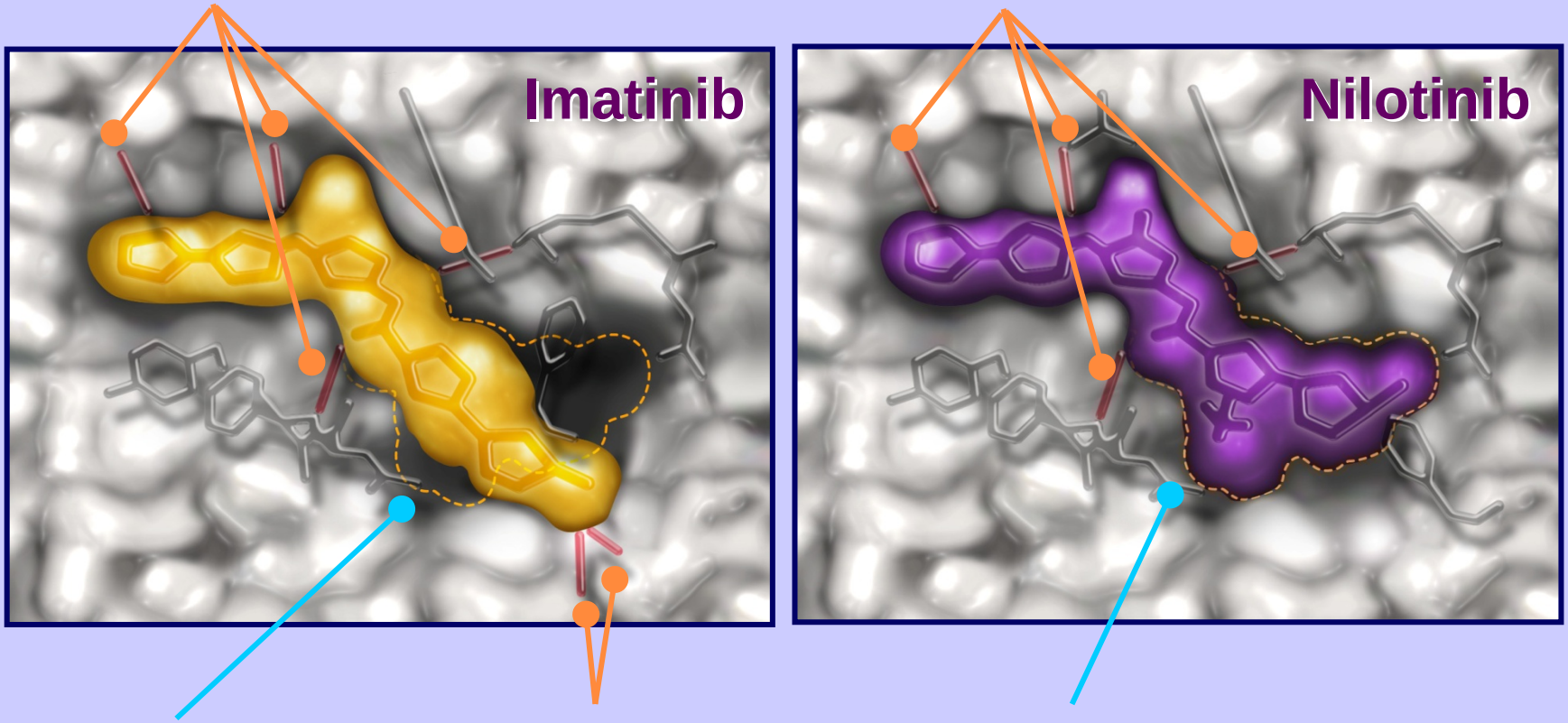
Comparison of Kinase Inhibitors

	Imatinib (STI571) Gleevec*	Nilotinib (AMN 107) Tasigna*	Dasatinib (BMS354825) Sprycel*	Bosutinib (SK606)
Route	Oral	Oral	Oral	Oral
Potency	1	~25	~300	~ 200
t½ (hours)	20	15	5½	24
Dose	400 mg QD	400 mg BID	100 mg QD	500 mg QD
Metabolism	CYP4A4 CYP2D6	CYP3A4 CYP2C8 CYP2C9 CYP2D6	CYP3A4 FMO3 CYP2C8	CYP3A4
Abl KD	Inactive	Inactive	Inactive & Active	Inactive & Active

Nilotinib is Rationally Designed for More Effective Binding to the Inactive Conformation of the ABL Kinase Domain

Hydrogen bonds form with specific amino acids lining the binding site

Only maintains 4 hydrogen-bonds



Auxiliary binding pocket

Hydrogen bonds with Ile360 & His361

Improved fit to auxiliary pocket, via lipophilic interactions, making it less susceptible to point mutations

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

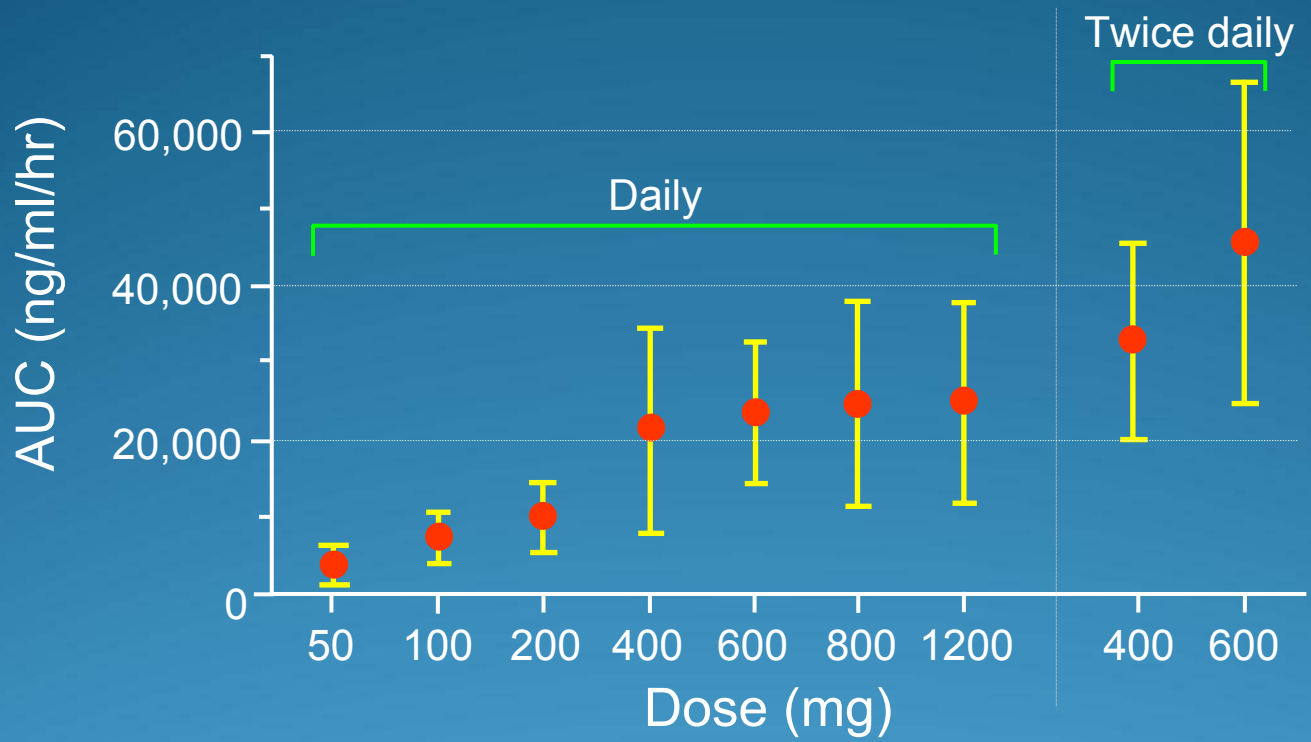
Preferential Binding of Tyrosine Kinases

Imatinib	**PDGFR > KIT > ABL**
Nilotinib	**ABL > PDGFR > KIT**
Dasatinib	**SRC > ABL > PDGFR > KIT**
Bosutinib	**SRC ~ ABL >> PDGFR > KIT**

- **The balance between preferential targeting and potency for *BCR-ABL1* may prove to be beneficial in providing activity against point mutations and retaining a favourable tolerability profile.**
- **Nilotinib has no significant effect on other kinases evaluated (including SRC, FLT3, VEGFR, EGFR, InsR, RET, MET, IGFR, etc.) at concentration <3000 nM**

1. Mestan J et al. *Blood.* 2004;104(546a):Abstract 1978. 2, Weisberg E et al. *Cancer Cell.* 2005;7:129.
3. Bantscheff M et al. Nat Biotech 2007:25:1035. 4. Puttini M et al. Cancer Res 2006:66:11314.

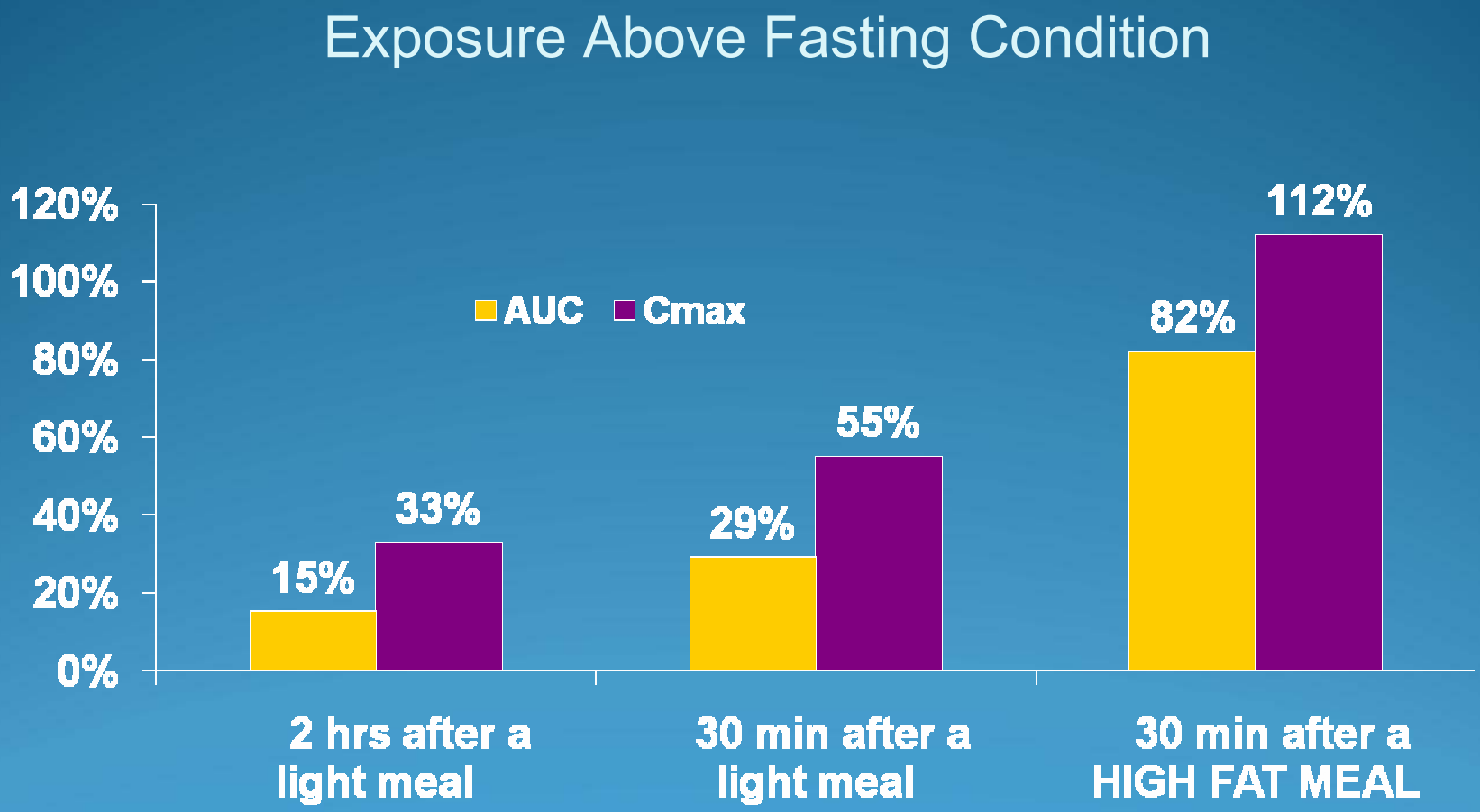
Phase I Study Pharmacokinetics



- Median time to peak concentrations 3 hours post dose
- Mean apparent half-life = 15 hours
- Steady state by day 8 in both QD and BID regimens
- All trough levels > IC50 for cellular Bcr-Abl phosphorylation
- PK parameters dose proportional to 400 mg QD
- Exposure is greatest in the 600 mg BID group

Kantarjian*, Giles* et al. N Engl J Med. 2006;354:2542.
*Indicates co-first author.

Nilotinib-Food Interaction



Data on File: NDA submission. Sep-2007.

Comparison of Kinase Inhibitors

	Imatinib (STI571) Gleevec*	Nilotinib (AMN 107) Tasigna*	Dasatinib (BMS354825) Sprycel*	Bosutinib (SK606)
Influx	Oct-1	Not Oct-1	Not Oct-1	?
Efflux	P-gp/ABCB1 BCRP/ABCG2	Not ? P-gp/ABCB1	P-gp/ABCB1	?
Resistant Mutations	T315I > 90 mutations	T315I Y253H E255K/V F359C/V	T315I/A F317L/I/S/V V299L	T315I E255K V299L

Comparison of Kinase Inhibitors: Toxicity

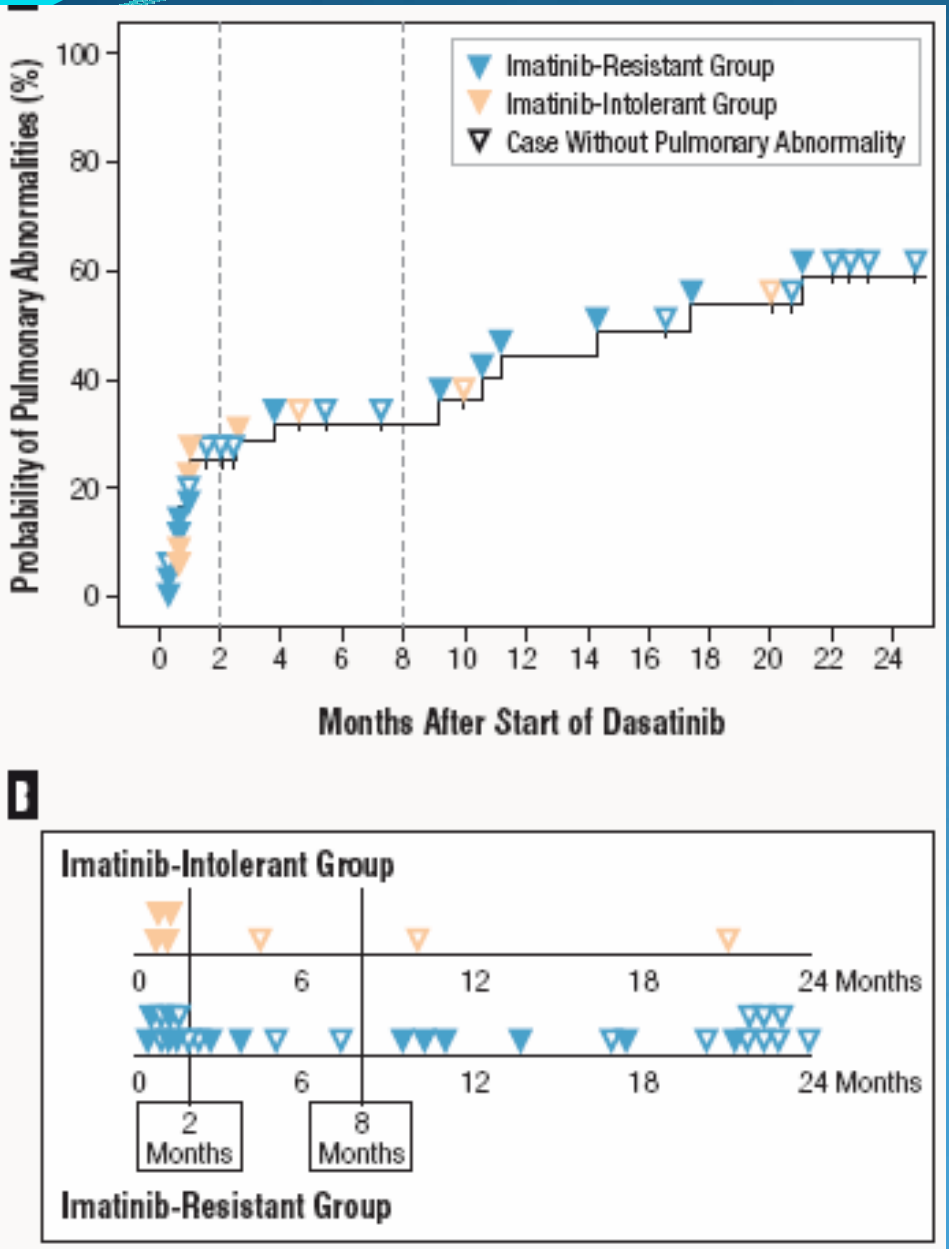
	Imatinib (STI571) Gleevec*	Nilotinib (AMN 107) Tasigna*	Dasatinib (BMS354825) Sprycel*	Bosutinib (SK606)
Hematologic	++	++	+++	+
Pleural Effusions	-	-	+++	+
Hepatic	+	++	+	+
Pancreatitis	-	+	-	-
GI Bleeding	-	-	+	-
Platelet Function	-	-	+	?
Immune	-	-	++	?
Diarrhea	+	+	+	+++
Q-Tc	-	++	++	+?

Dasatinib Dose and Schedule Optimization in CML-CP

Side Effect	All grades/Grades 3-4 (%)				
	100 mg qd	50 mg bid	140 mg qd	70 mg bid	P-value*
Pleural effusion	7/1	11/2	16/3	18/2	0.015/0.824
Pericardial effusion	1/0	1/1	3/1	1/1	NA
Pulmonary edema	1/0	1/0	0/0	1/1	NA
Congestive heart failure	1/1	1/1	3/2	5/4	NA
Pulmonary hypertension	0/0	0/0	0/0	2/1	NA
Peripheral edema	11/0	7/0	9/1	12/0	NA

*P value associated with Fisher's exact test for comparing rates for 4 treatment arms

Cumulative Incidence Pulmonary Abnormalities

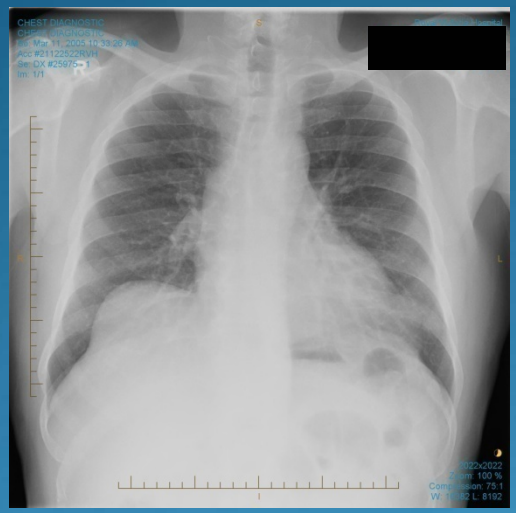


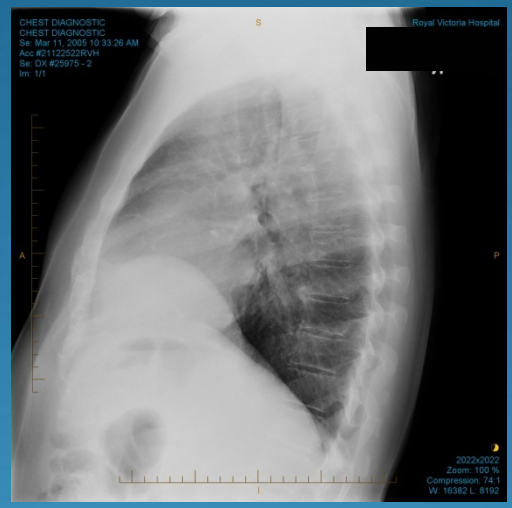
- median exposure 95 weeks (3-124)
- pulmonary abn 17/38 (45%)
  - 16 – pleural effusion
    - gr 1 = 1, gr2 = 11, gr3 = 4
  - 1 - gr 3 lung parenchimal
- total 51 events
- actuarial risk 45%±9% at 1 year
- median time to onset 4 weeks (2-90)
- dose dasatinib at 1st event
  - n=15 70 mg bid
  - n=1 140 mg qd
  - n=1 90 mg bid
- 13/17 (76%) PE bilateral
- disease/phase
  - 9/22 (41%) CP
  - 3/8 (38%) AP
  - 3/5 (60%) MBC
  - 2/3 (67%) LBC/Ph+ALL

Kim DH *et al* Clin Leuk **2**:55-63 (2008)

Patient FW

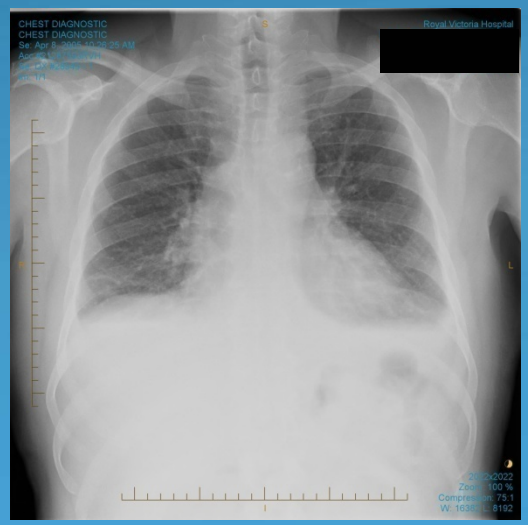
Baseline

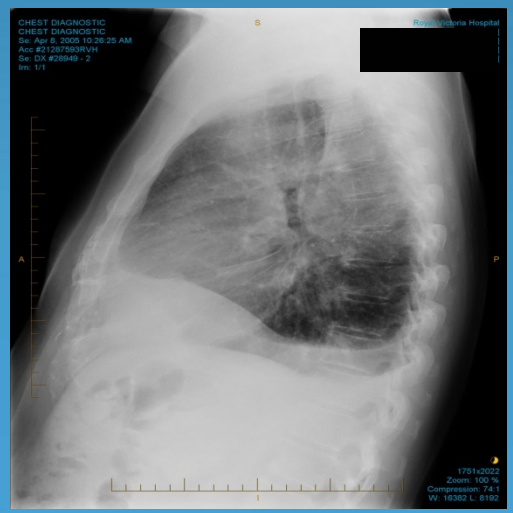


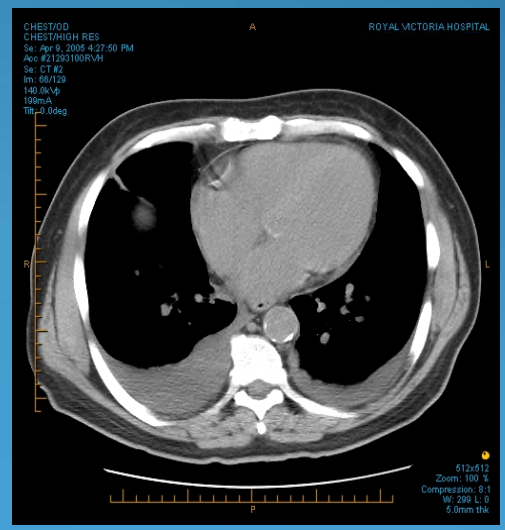


-62 yo male
- remote asthma
- Hydrea – necrosis
- IFNα – anaphylaxis
- IM -> F317C
- DA -> Gr 2 PE
- Nilotinib

Dasatinib
70 mg bid
D+26







Patient FW

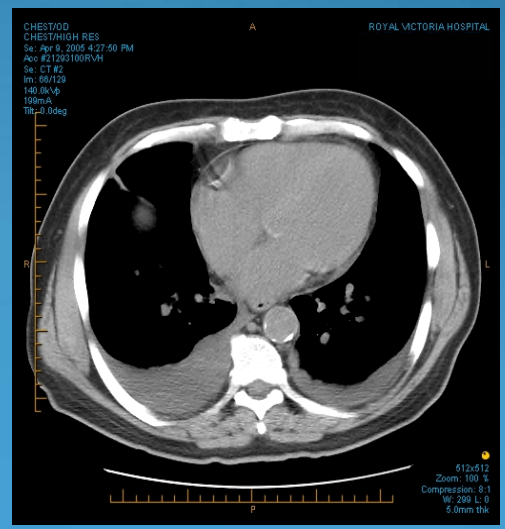
Biochemistry

	TP (g/L)	LDH U/ml
Effusion	45	149
Serum	67	205
Ratio %	67.2%	72.7%

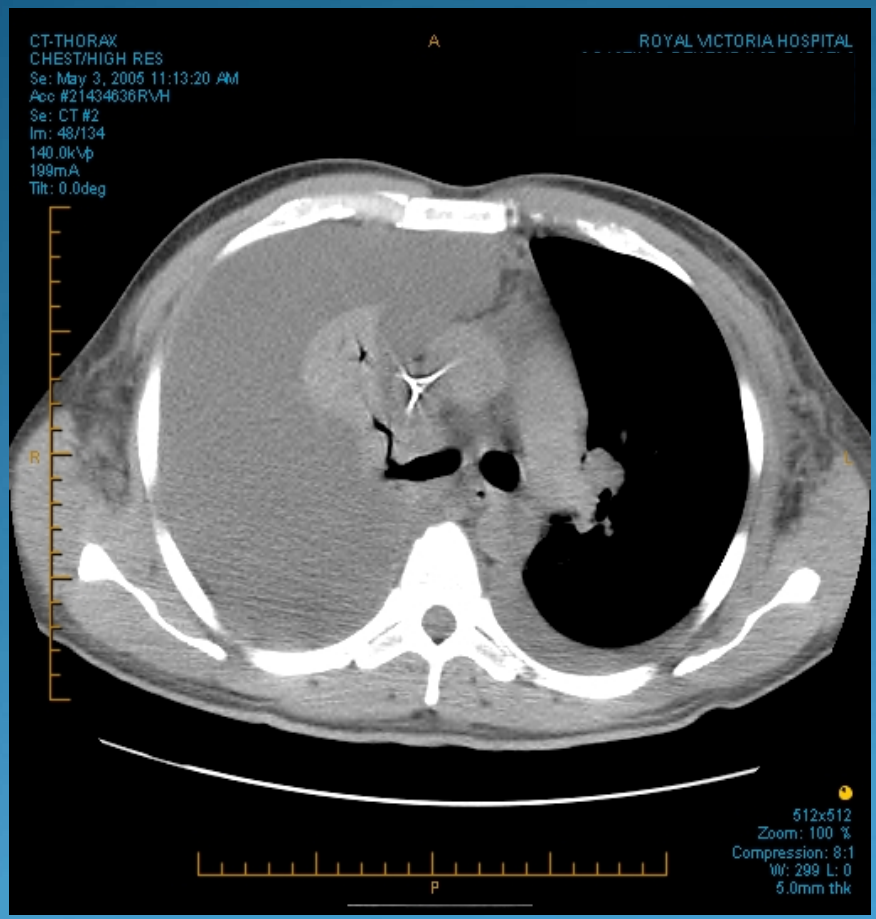
-62 yo male
- remote asthma
- Hydrea – necrosis
- IFNα – anaphylaxis
- IM -> F317C
- DA -> Gr 2 PE
- Nilotinib

Cell Count and Flow Cytometry

RBC x10⁹/L	WBC x10⁹/L	CD5	CD3	CD4	CD8	CD56
< 0.01	0.94	81%	78%	60%	16%	1%



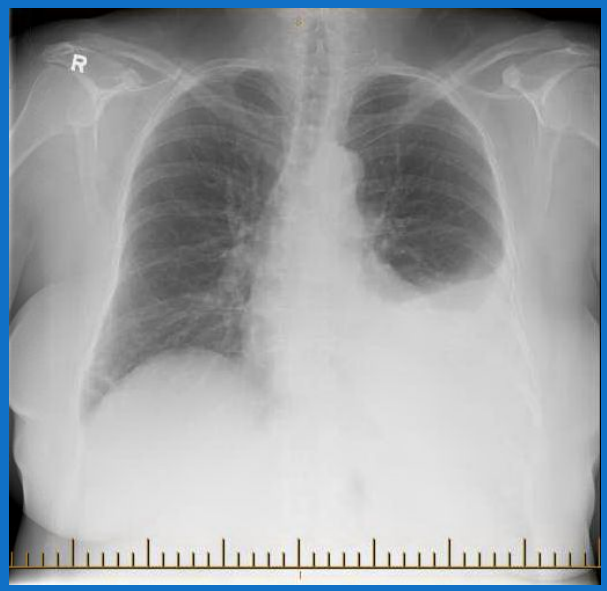
Patient DFCR (CML MBC)

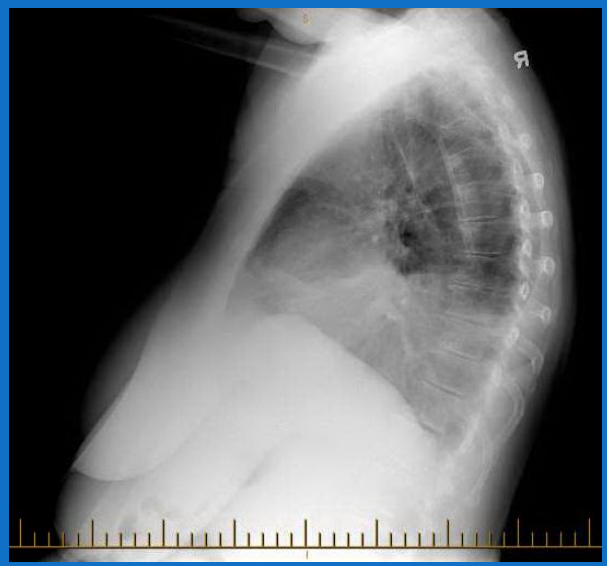


dasatinib 70 mg bid
day+35

-38 y.o. Male
- Resistant IM 800 mg/d
- No TK mutations
- Treated Rt lung aspergillosis
- Rx dasatinib 70 mg/bid
- d+35 grade 4 pleural effusion
- Required chest tube
- Developed GI bleeding
- Died of progressive disease

Patient RT (CML CP)





- 61F, CML CP, recurrent Gr 3 rash on IM
- Long standing eczema
- DA 70 mg bid
- Gr 2 PE d+20, two later recurrences
- Exudates, CD3+ lymphocytes
- On/off DA with eventual dose 20 mg bid
- Adenopathy (6 cm)
    - CD20+ marginal zone hyperplasia
    - No clonal TcR or Ig gene rearrangements
- Adenopathy DA-dose dependent

Immune Dysregulation With Dasatinib

- Pleural effusions – exudates, T-cells[1]
- Lung parenchyma – lymph on BAL[1]
- Rash on IM[2, 10]
- LGL lymphocytosis [3]
- Hyper/hypothyroidism, SLE, SS,AIH[2,8,10]
- Asthma[4]
- Upper respiratory tract infection[4]
- Pre-existing lung pathology[4]
- Polyclonal B-cell hyperplasia[5]
- Panniculitis[6]
- Vasculitis[7]
- Steroid response

- Hypertension[8,10]
- Hypercholesterolemia[10]
- Pulmonary hypertension[8]
- AP/BC > CP[10]

- Inhibition T-reg

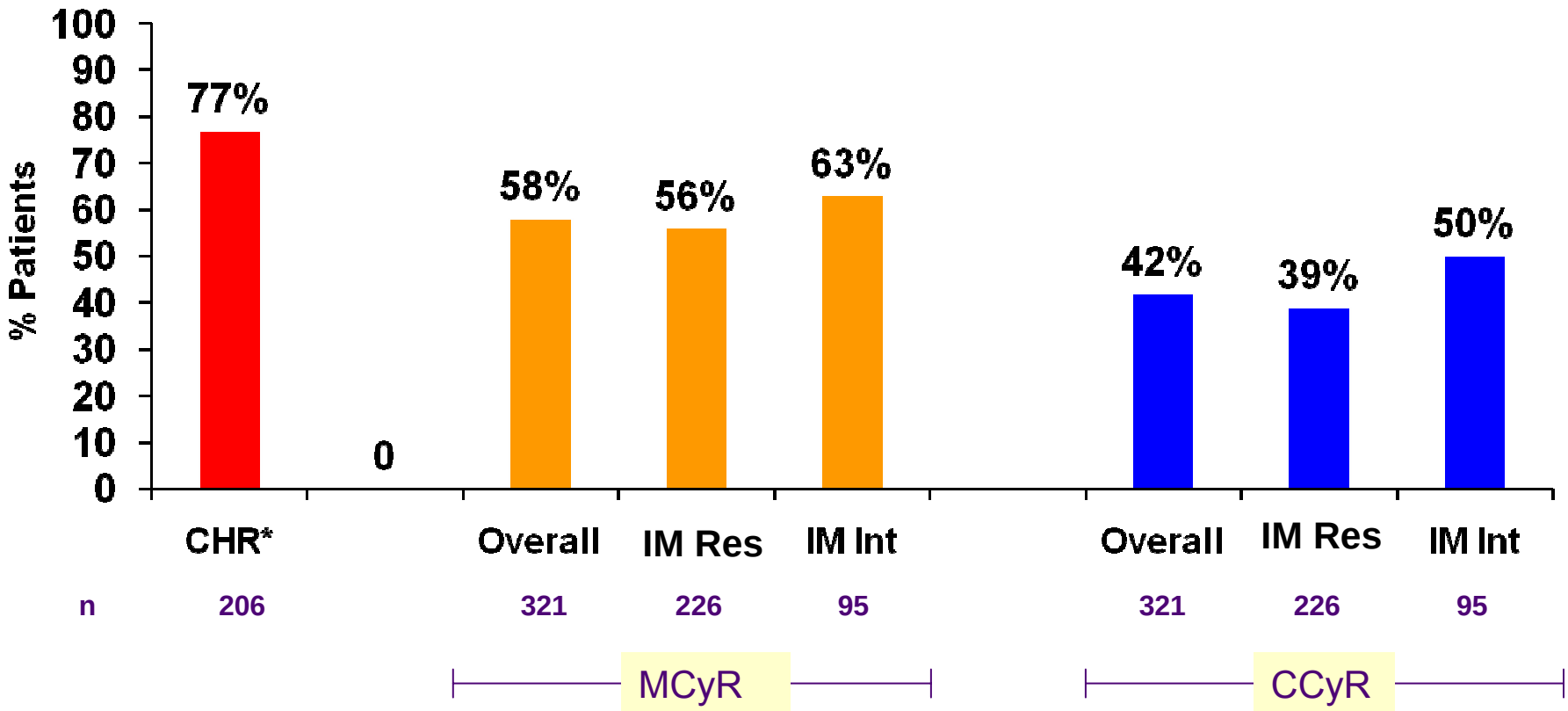
  $CD3^+CD25^+FoxP3^+$
- Vascular factors

References: (1) Bergeron A. *et al* AJRCCM 176:814 (2007), (2) Punnialingam S. *et a*l Abst 2945 ASH 2007, (3) Mustjoki S. *et a*l Abst 2938 ASH 2007, (4) Kim DH. *et al* Clin Leuk 2:55 (2008), (5) Laneuville P. Unpublished, (6) Assouline A. *et a*l NEJM 354:2623 (2006), (7) Laneuville P. *et al* Unpublished, (8) Rea D. *et al* Lancet 372: 713 (2008). (8) Quintas-Cardama A. *et al* JCO 25:308 (2007). (9) Laneuville P. Unpublished. (10) de Lavallade H. *et al* Br. J. Haematol 141:745 (2008),

Nilotinib in CML CP
Phase II Study, ASCO 2008 Update

- Total 321 patients
- Resistant/intolerant to imatinib
- Minimum follow-up 14 months
- Primary endpoint: MCR
- Secondary endpoints: CHR, CCR, TTP, dur MCR, OS

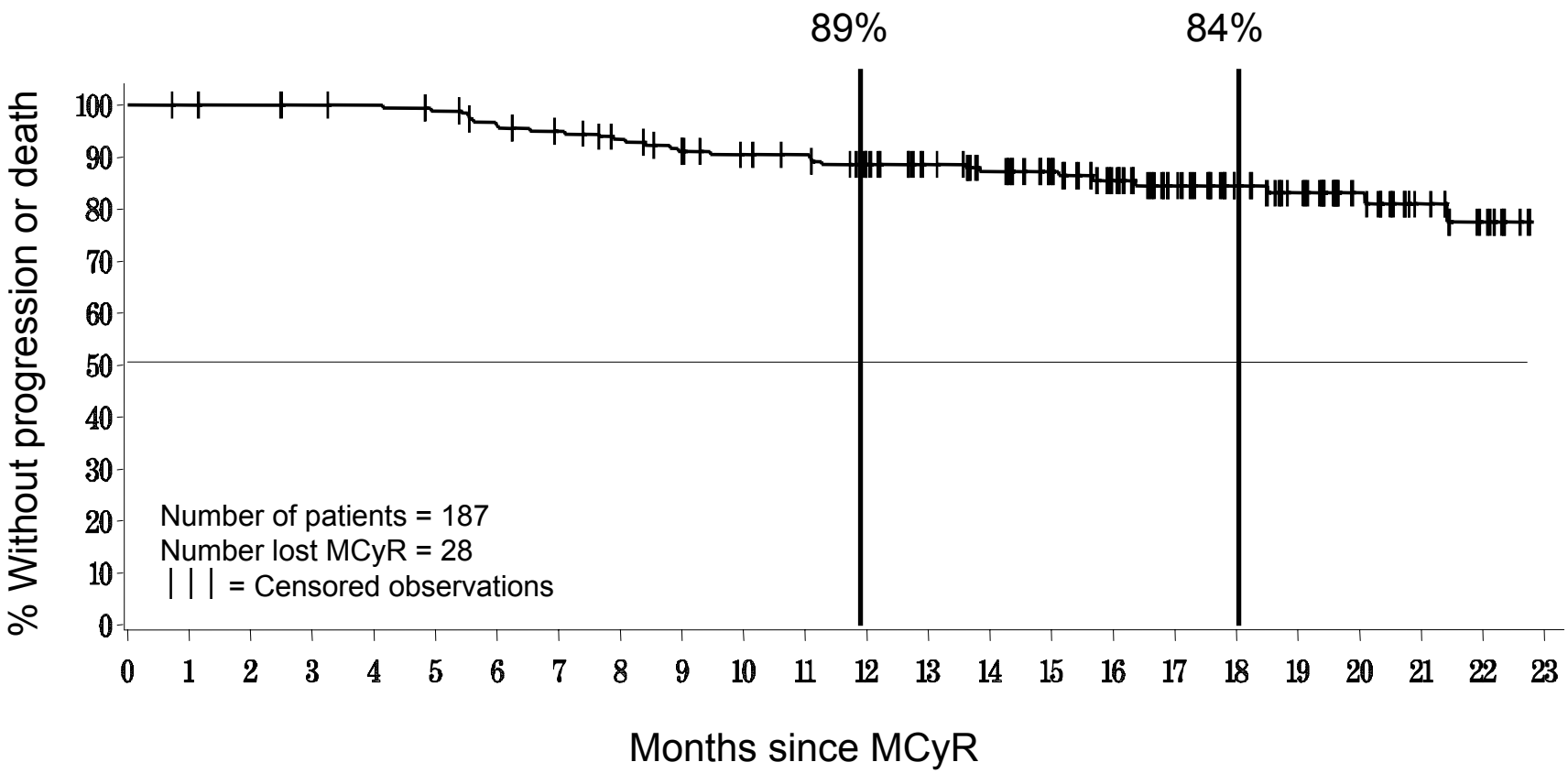
Nilotinib in CML-CP Response (n = 321)



Median time to CHR 1 month; MCyR 2.8 months

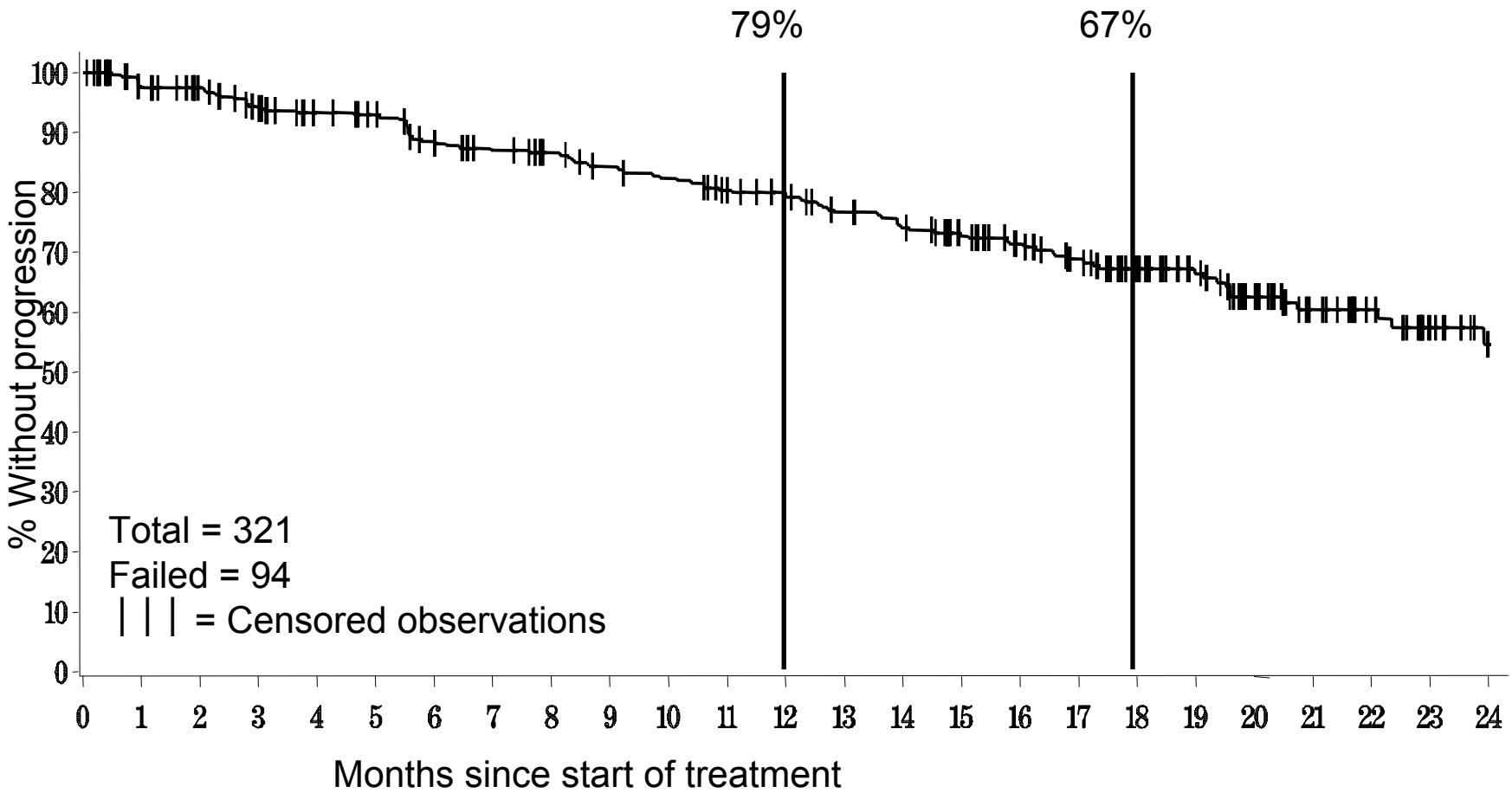
Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP
Duration of MCyR



Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

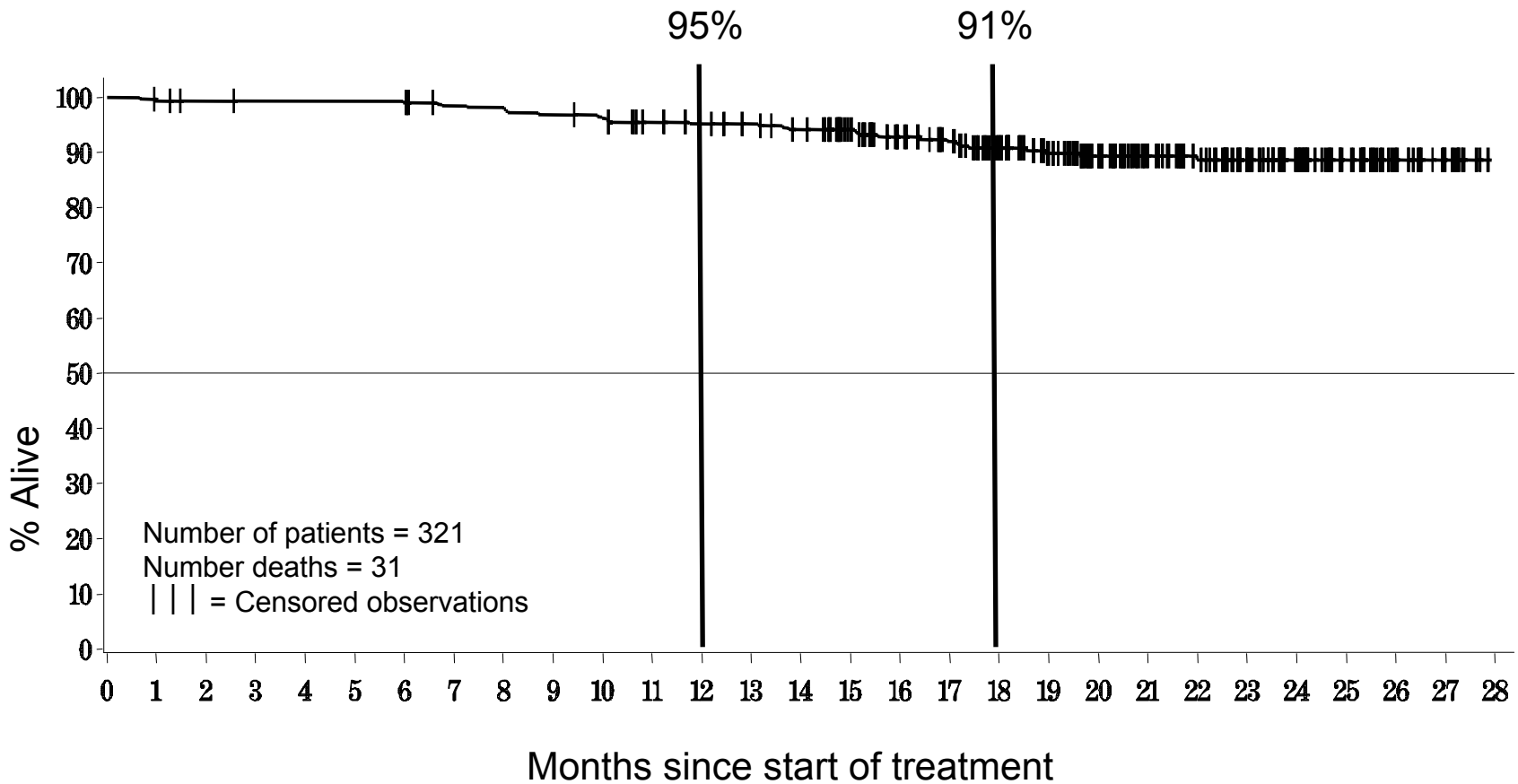
Nilotinib in CML-CP
Progression Free Survival



Event = Progression or death; Progression = AP or BC, loss of CHR, loss of MCyR

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

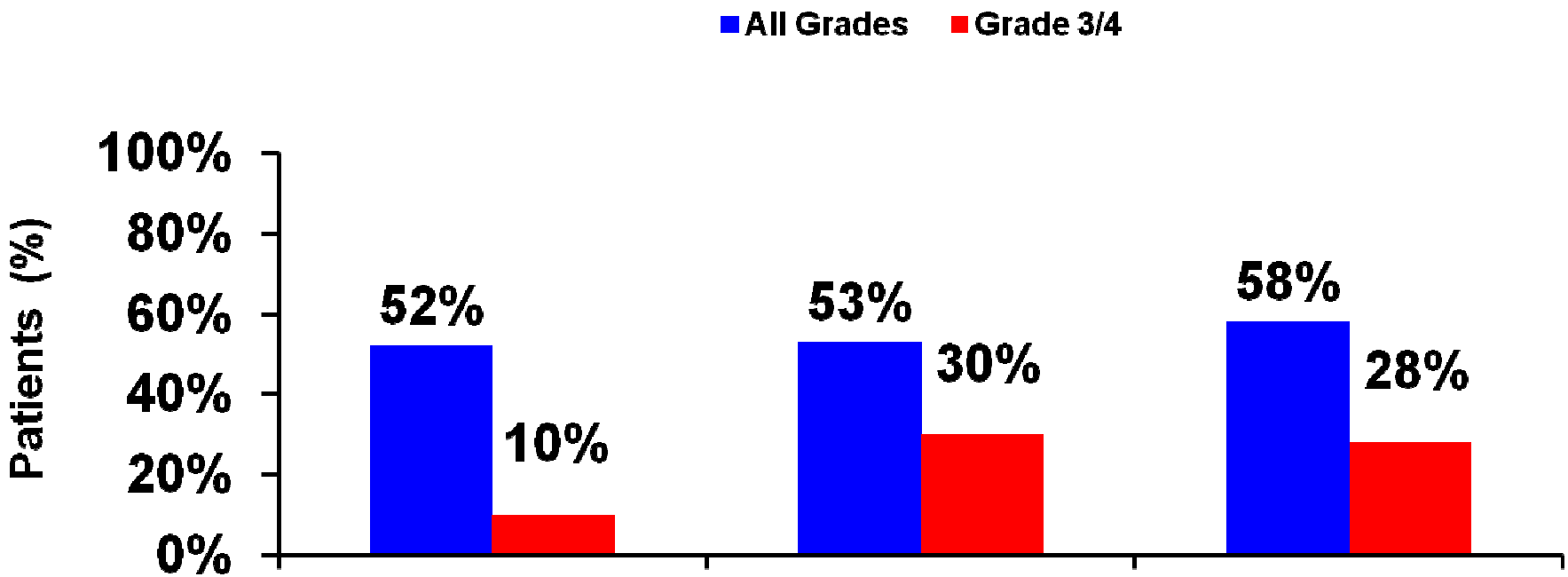
Nilotinib in CML-CP Survival



Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP

Myelosuppression



Grade 3/4	Anemia	Neutropenia	Thrombocytopenia
median duration (days)	9	15	23
Median onset (days)	57	55	42

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP

Most Frequent (>10%) Drug-Related Non-Hematologic AEs

CML-CP	N = 321	
	All Grades (%)	Grades 3/4 (%)
Rash	30	2
Pruritus	25	<1
Nausea	24	<1
Fatigue	20	1
Headache	18	2
Diarrhea	12	2
Vomiting	12	<1
Constipation	12	0

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP
Biochemical Laboratory Abnormalities

CML-CP	N = 321	
	Any (%)	Grades 3/4 (%)
Lipase elevation	45	16
Hypophosphatemia	52	15
Hyperglycemia	70	12
Bilirubin (total)	71	7
ALT	67	4
AST	54	2
Hypocalcemia	49	2
Creatinine	23	< 1
Hypomagnesemia	16	<1

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP
Nilotinib-Associated Fluid Retention & Bleeding

CML-CP	N = 321	
	All Grades n (%)	Grade 3/4 n (%)
Peripheral edema	19 (6)	0
Pericardial effusion	2 (0.6)	1 (0.3)
Pleural effusion	4 (1.2)	2 (0.6)
Pulmonary edema	1 (0.3)	1 (0.3)
CNS bleeding	1 (0.3)	1 (0.3)
GI bleeding	3 (0.9)	1 (0.3)

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML-CP Conclusions

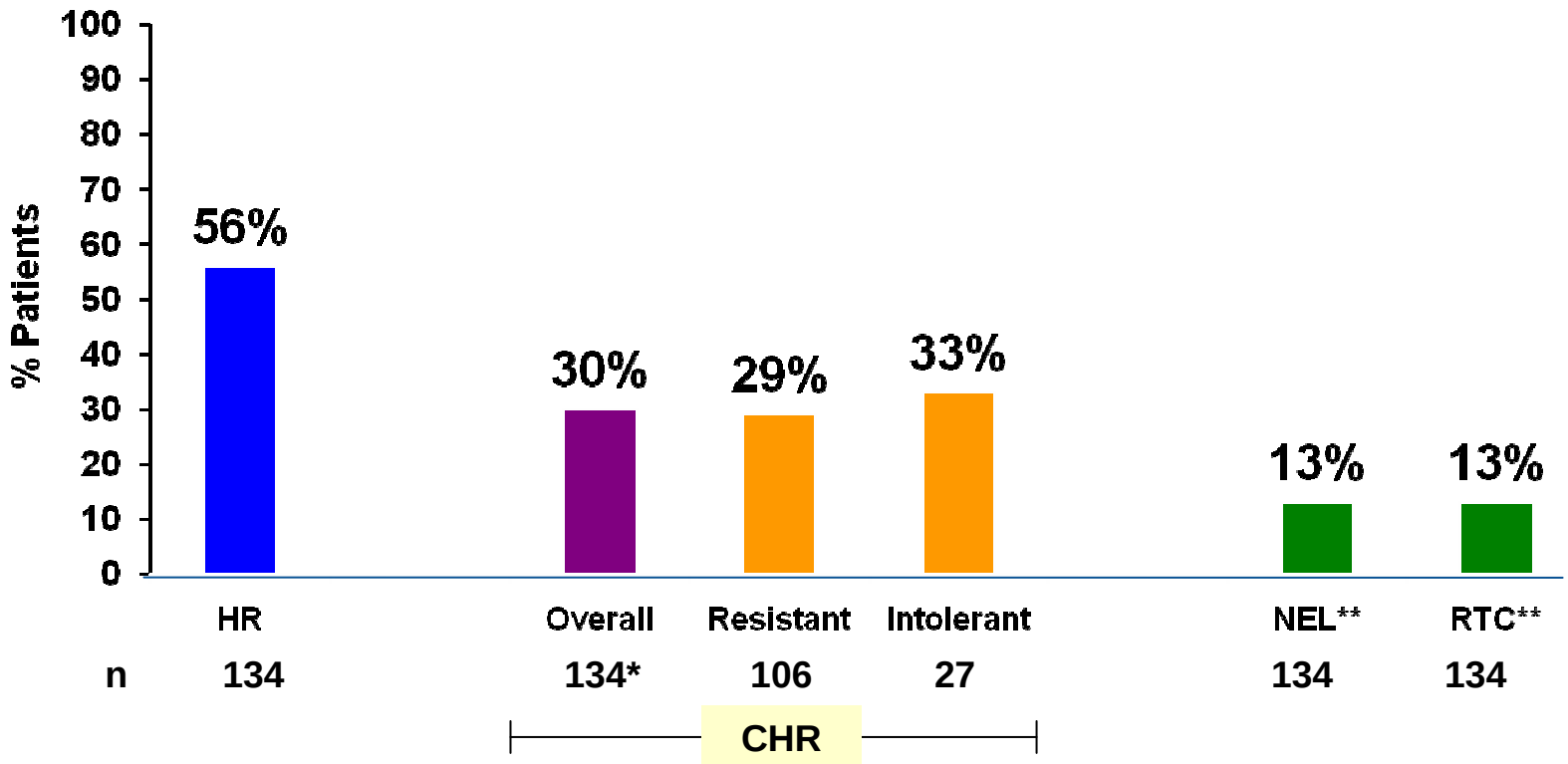
- Significant activity in CML-CP post IM failure: CHR 77%; MCyR 58%; CCyR 42%
- Survival at 18 months 91%
- Excellent tolerability; minimal occurrence of Grade 3/4 AEs

Kantarjian et al. Oral presentation at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7010)

Nilotinib in CML AP
Phase II Study, ASCO 2008 Update

- Total 134 patients (efficacy), 138 (safety)
- Resistant/intolerant to imatinib
- Minimum follow-up 6 months, median 8 months
- Primary endpoint: HR (4 weeks)
- Secondary endpoints: MCR, dur R, MMR, TTF, OS

Nilotinib in CML-AP
Confirmed Hematologic Response



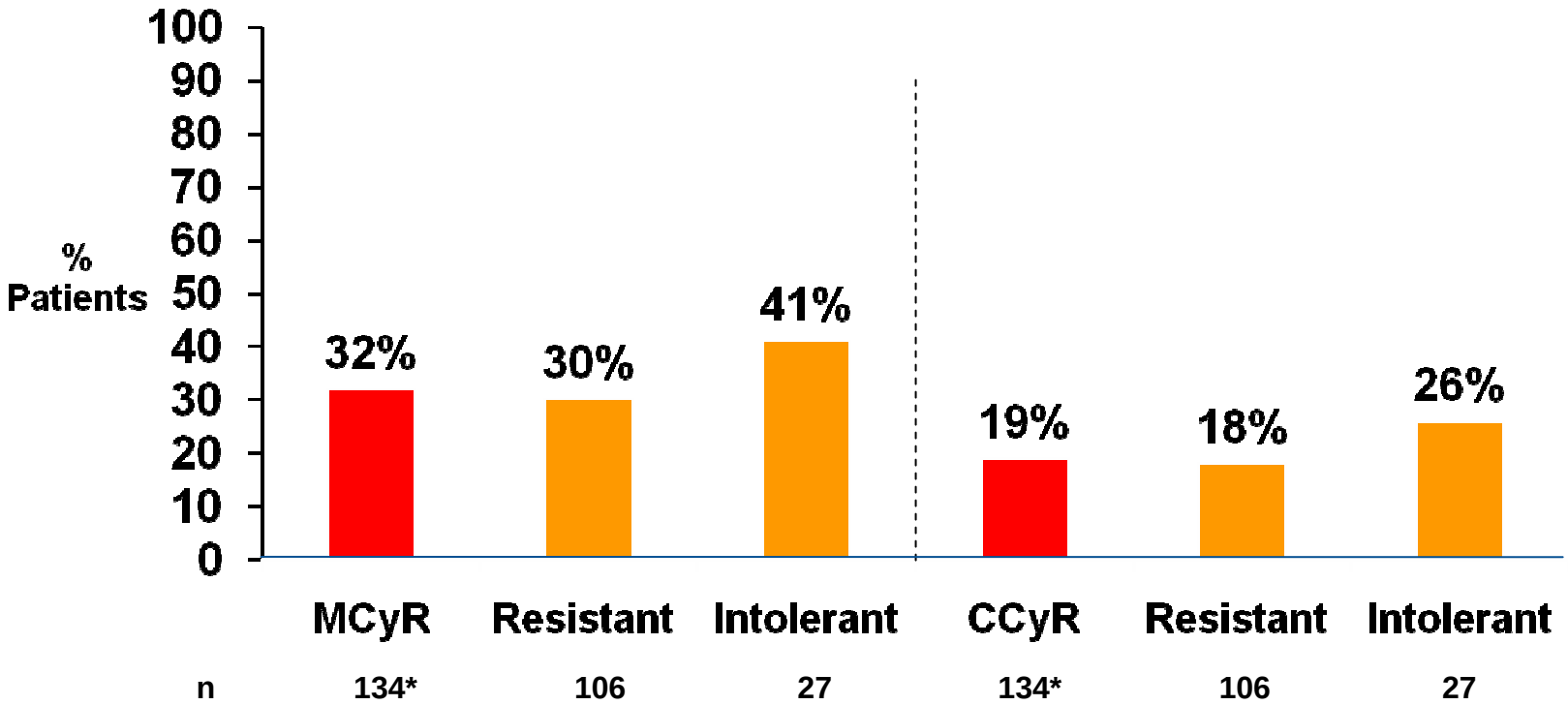
* One patient was not classified with regards to imatinib-resistance vs. -intolerance

** NEL - no evidence of leukemia; RTC - return to chronic phase

- **Median time to first HR is 1 month**
- **Imatinib-resistant and –intolerant patients have similar response rates of CHR**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP
Cytogenetic Response

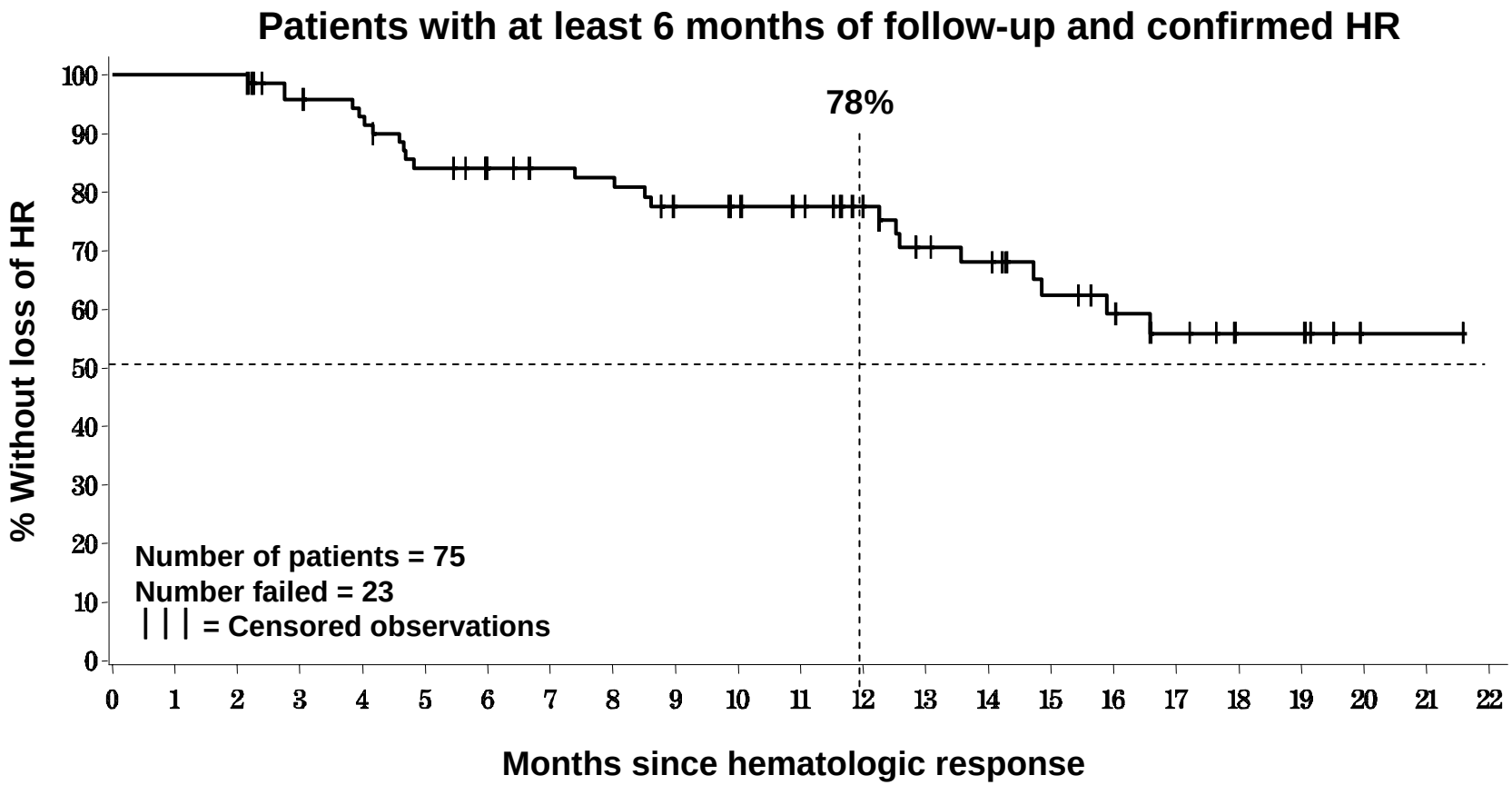


* One patient was not classified with regards to imatinib-resistance vs. -intolerance

- **Median time to first MCyR 2.8 months**
- **Median durations of MCyR and CCyR have not been achieved at the time of data cut-off**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP
Duration of HR

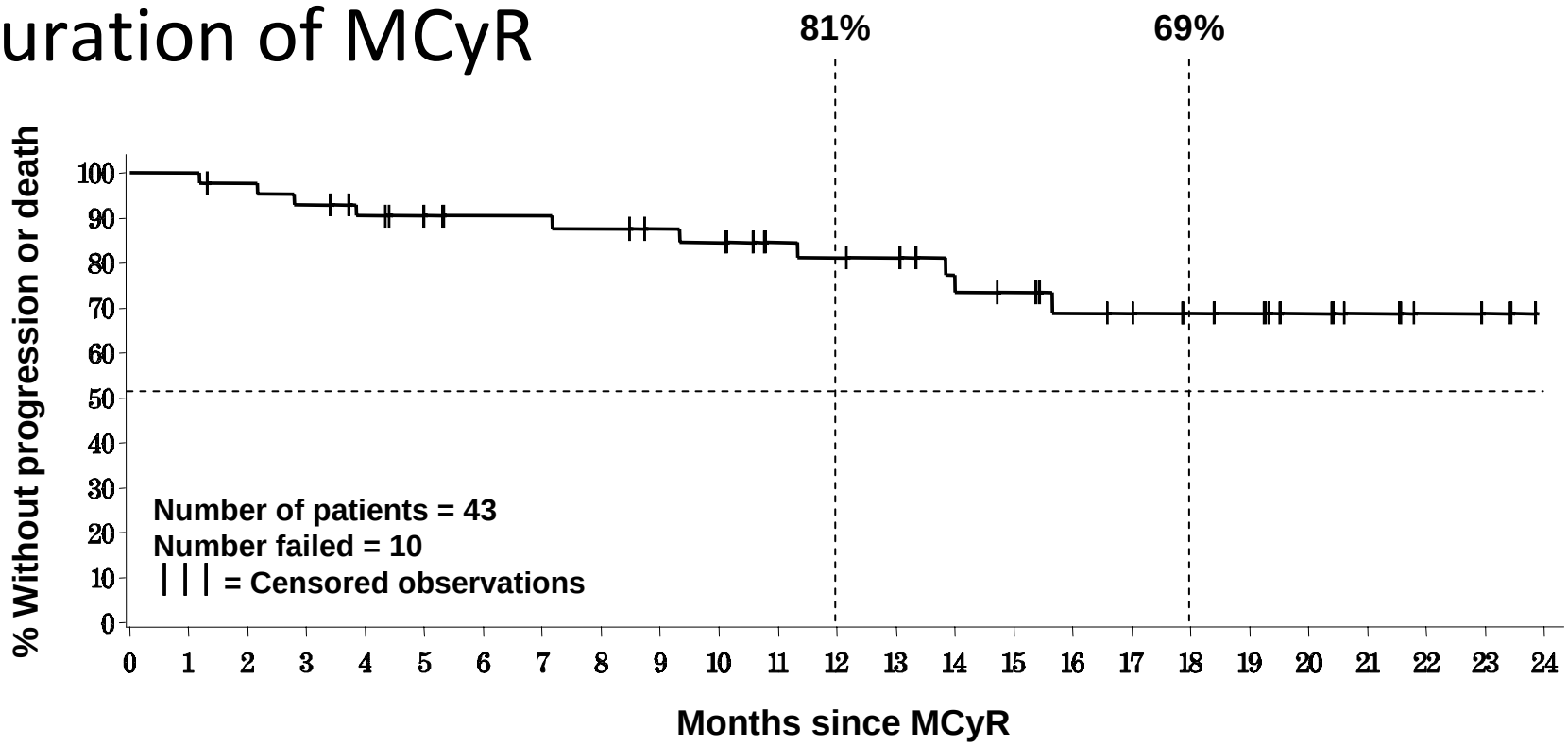


- **Duration of response is defined as the time from the date of first occurrence of the response to the date of discontinuation due to progression or death**
- **Median duration of HR has not been reached at the time of data cut-off**
- **At 12 months, 78% of the patients continue to maintain a hematologic response**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP

Duration of MCyR

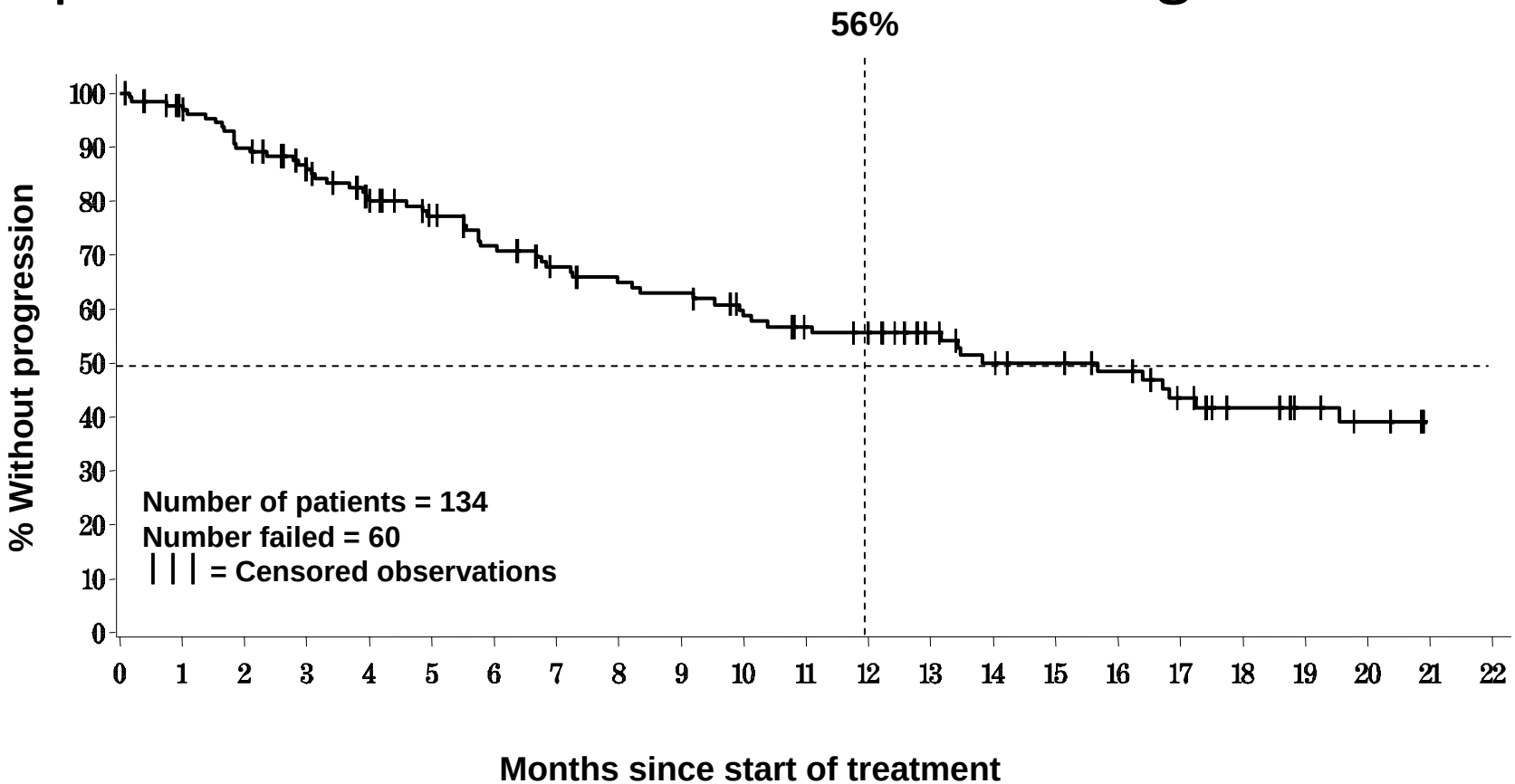


- **Duration of response is defined as the time from the date of first occurrence of the response to the date of discontinuation due to progression or death**
- **Median duration of MCyR has not been reached at the time of data cut-off**
- **At 12 months, 81% of the patients who achieved MCyR continue to maintain a MCyR and at 18 months 69% continue to maintain a MCyR**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP

Kaplan-Meier Estimate of Time to Progression

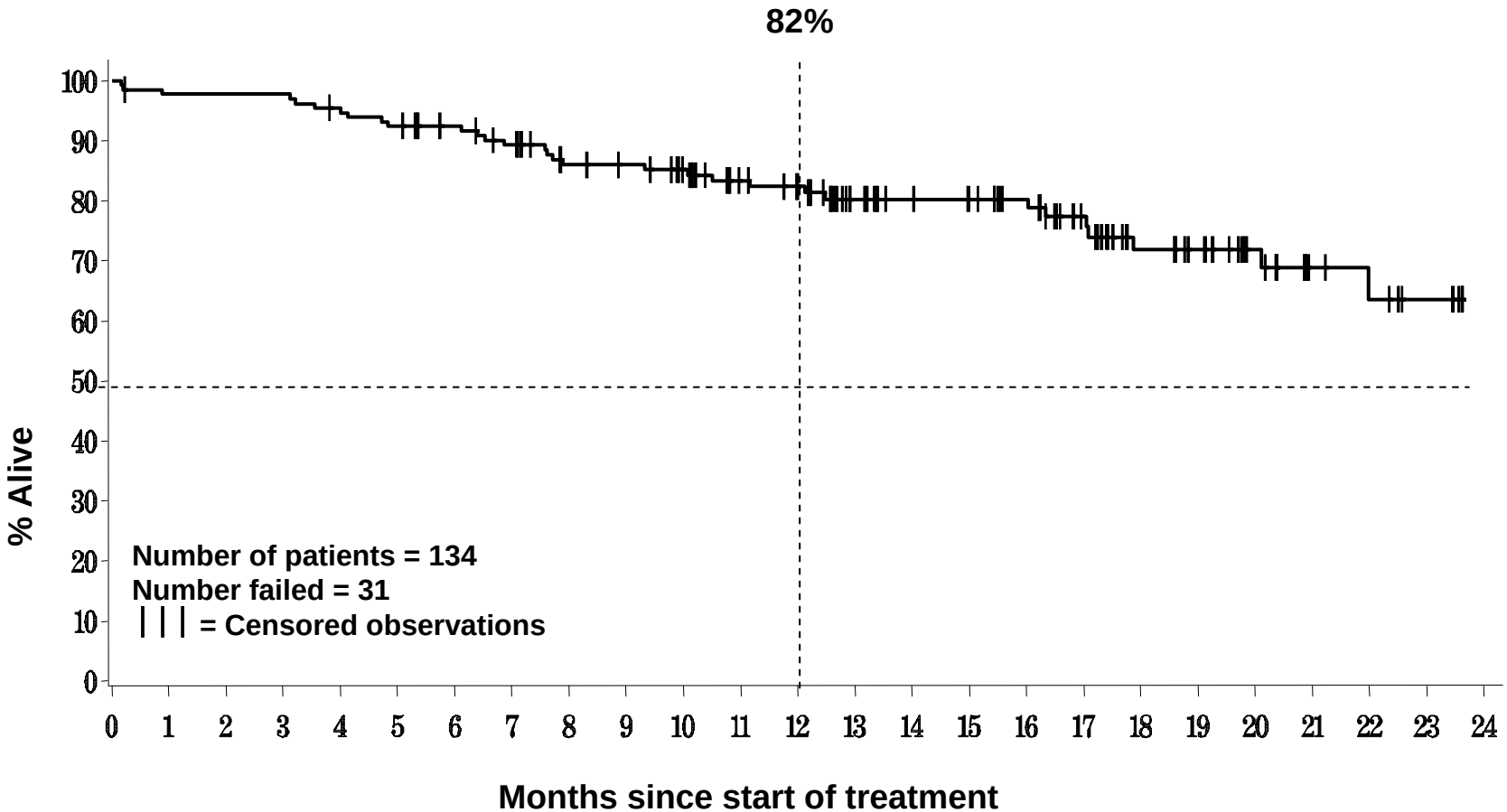


- **Time to progression is defined as the time from the start of study drug to the earliest date of progression or discontinuation due to progression or death**
- **Median time to progression 16 months**
- **At 12 month, 56% of the patients were without progression**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP

Kaplan-Meier Estimate of Overall Survival



- **At the time of data cut-off median duration of overall survival has not been reached**
- **At 12 month, 82% of the patients remain alive**

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

Nilotinib in CML-AP Conclusions

- High response rates (HR 55%; MCyR 32%; CCyR 19%) occurred rapidly and were durable with longer follow-up
- 78% maintaining HR and 81% maintaining MCyR at 12 months
- Overall survival after 12 months was 82%
- Low rates of Grades 3/4 myelosuppression
- Nilotinib is an effective therapeutic option in imatinib-resistant and -intolerant CML-AP patients, for whom treatment options are limited

le Coutre et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7050)

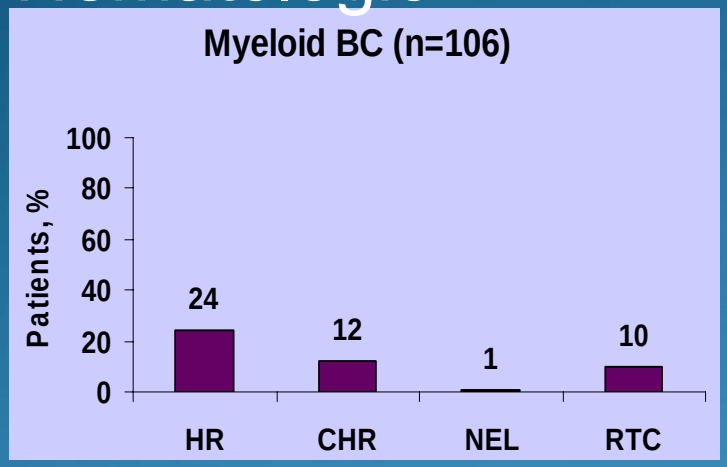
Nilotinib in CML-BC
Demographics and Disease Characteristics

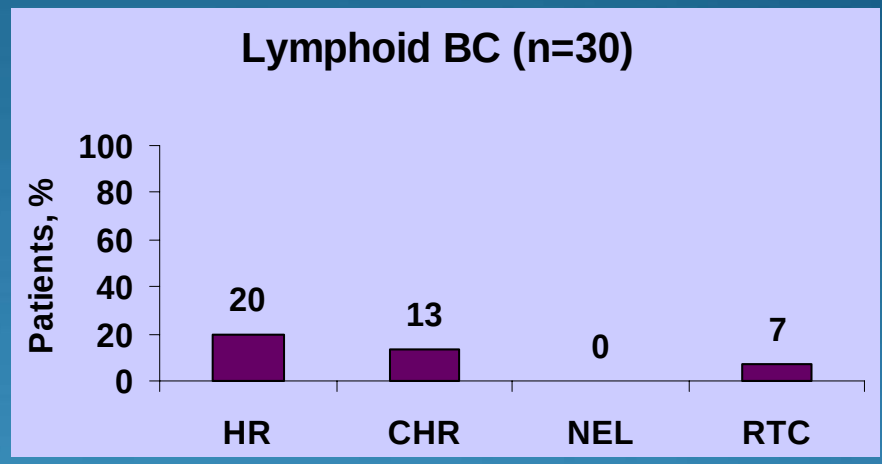
	N=136
Median age, years (range)	54 (18-79)
Male, %	61
Blast crisis, %	
Lymphoid	21
Myeloid	78
Prior history of imatinib, median months (range)	16 (0-107)
Imatinib resistant/intolerant, %	82/18
Prior interferon, %	29
Prior cytarabine, %	37

Giles et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7017)

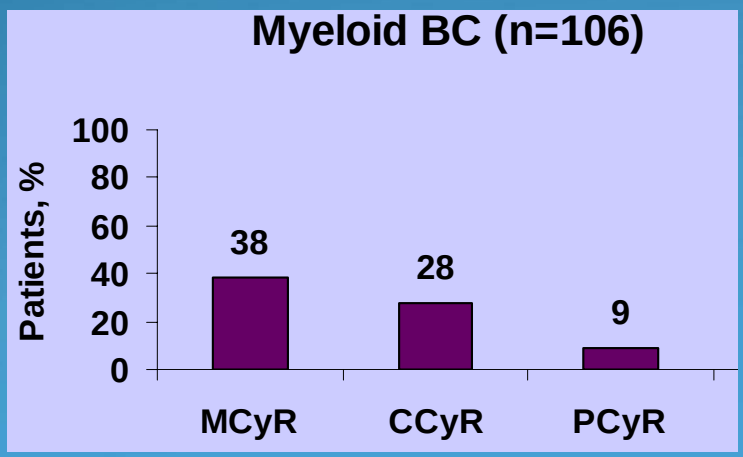
Best Response in CML-BC

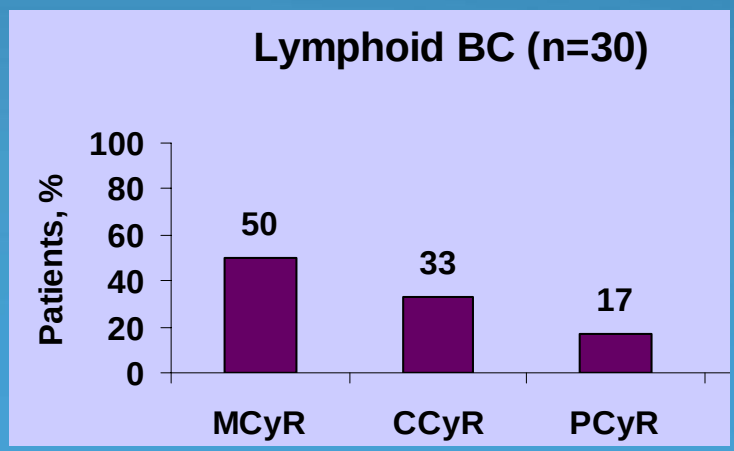
Hematologic





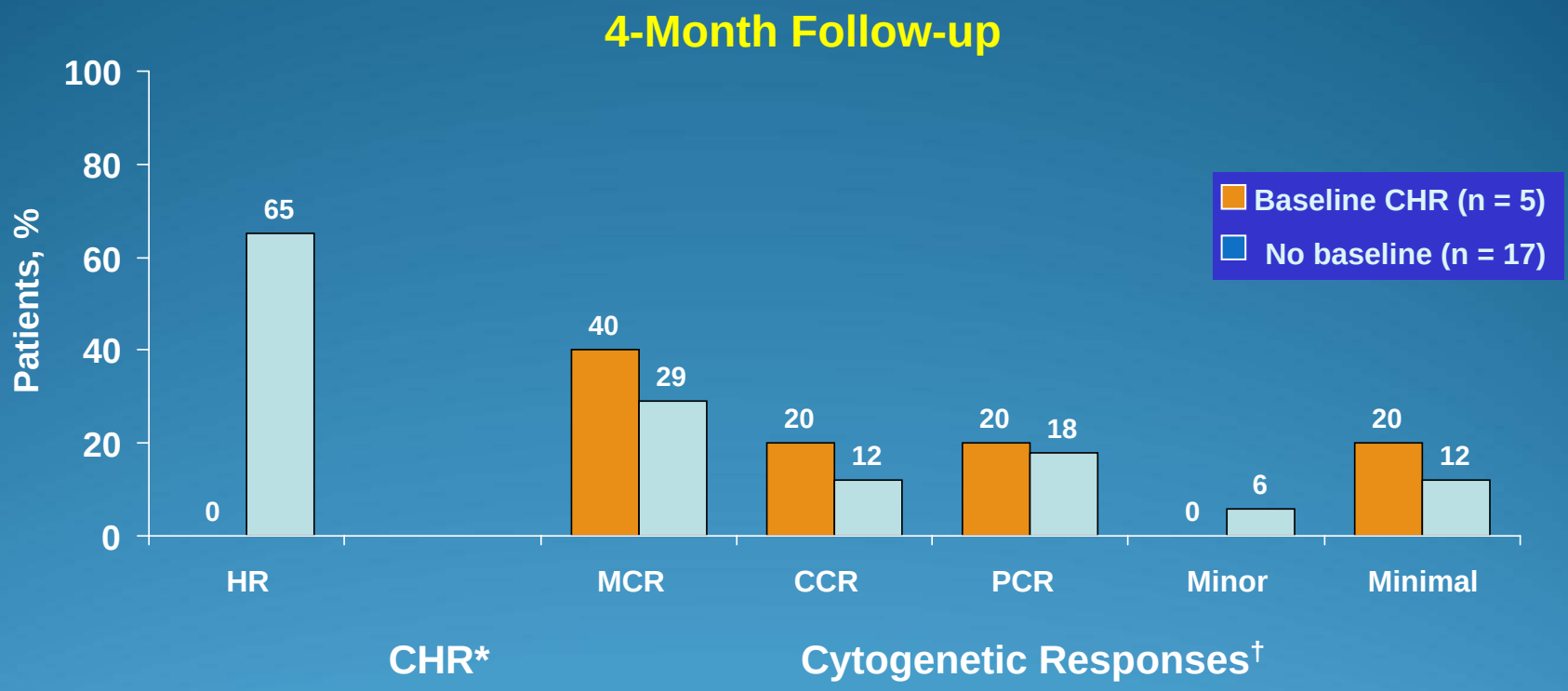
Cytogenetic





Giles et al. Poster presented at ASCO; Journal of Clinical Oncology. 26: 2008 (May 20 suppl; abstract 7017)

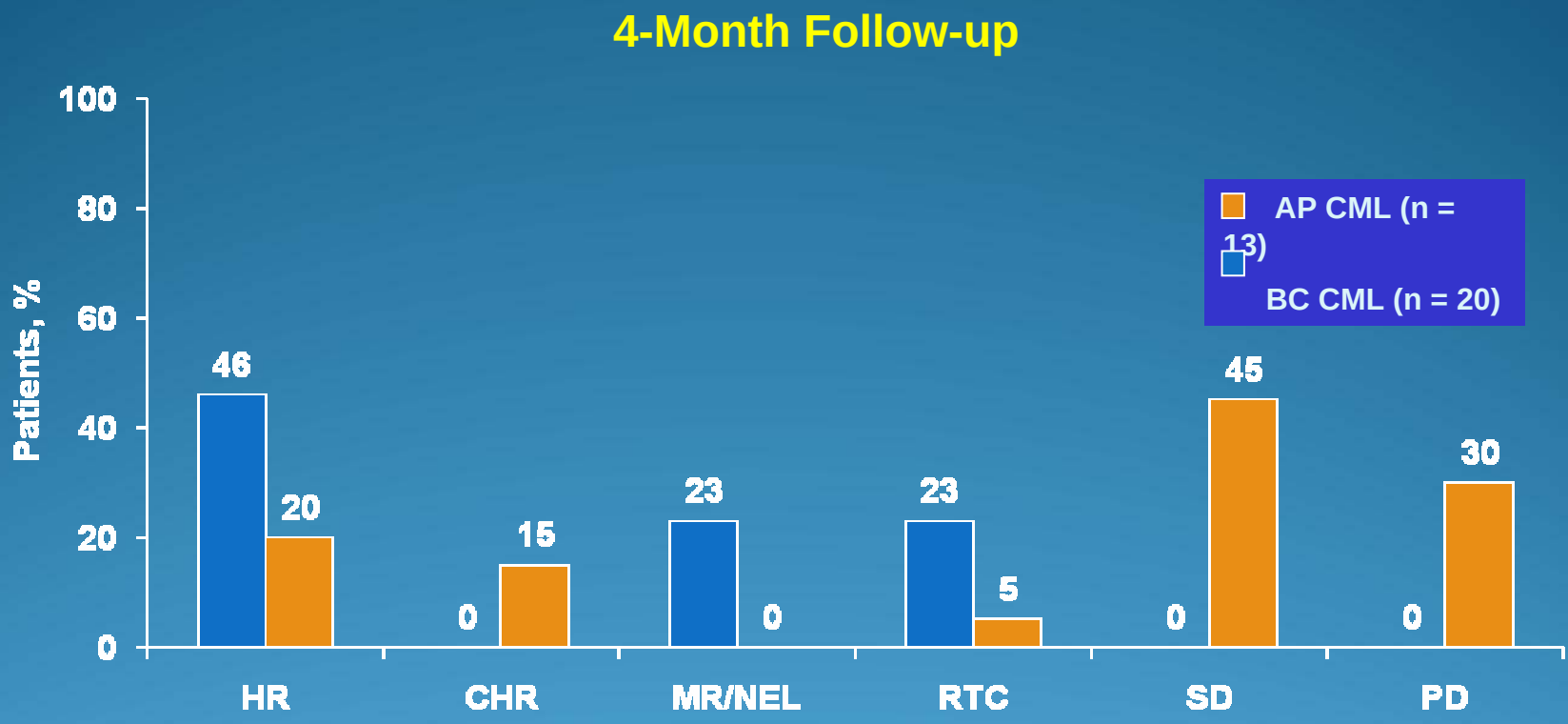
Nilotinib After Dasatinib Failure: Best Response in CP CML



*** Evaluable only in patients without CHR at baseline.**
† MCR = CCR + PCR; CCR = 0% Ph+ cells; PCR = 1%-35% Ph+ cells.

Giles FJ et al. Poster presented at the 49th ASH Annual meeting. *Blood*. 2007;110(11):Abstract 1029.

Nilotinib After Dasatinib Failure: Best Response in AP*/BC† CML



* Response confirmed after 4 weeks.
† Best, unconfirmed, investigator response.
‡ One patient (5%) not adequate for response.
§ Includes stable disease for AP CML.

Giles FJ et al. Poster presented at the 49th ASH Annual meeting. *Blood*. 2007;110(11):Abstract 1029.

2nd Generation TKIs in Allogeneic SCT

- Imatinib prior to SCT safe
- Imatinib after SCT safe, alternative to DLI

- Patients going to SCT are now imatinib resistant
- 2nd generation TKIs used as bridge to SCT
- 2nd generation TKIs necessary in relapsed patients post SCT
- Limited experience (under study by the EBMTG)
- Dasatinib – immunosuppressive agent, immune dysregulation
- Bosutinib – not generally available, diarrhea
- Nilotinib – no effect on immune system, LFTs

Incidence of Cardiac AEs observed with nilotinib and dasatinib

	Nilotinib		Dasatinib
	NDS[1] (n=371) %	+120 day[2] (n=438) %	FDA Medical Review[3] (n=489) %
QTc > 500 msec	0.5	0.7	0.7
QTcF increase >60 ms	1.3	2.1	2.9
Myocardial Ischemia	3.0	3.7	1 - < 10% (USPI)
Atrial Arrhythmia	2.2	2.3	2.5
Myocardial Infarction	1.6	1.6	1.2[4]
Cardiac Failure	0.8	0.9	4.1
Ventricular Arrhythmias	0.8	0.5	0.4
Syncope	1.3	2.1	1.6

1) Nilotinib NDS: median duration of follow up are 5.2 months for CML-CP and 3.9 months for CML-AP
2) Nilotinib 120 day update: median duration of follow up are 8.1 months for CML-CP and 4.5 months for CML-AP
3) Dasatinib FDA medical review: median duration of follow up are 5.6 months for CML-CP and 5.5 months for CML-AP
4) FDA ODAC Briefing Document

Sudden Deaths with Nilotinib is similar to that reported with other CML studies .....

TKI	Study	CML Patients	n (%)
Imatinib	0110	Late CP	3/532 (0.6%)
	0109	AP	2/235 (0.9%)
Dasatinib	ODAC	CP, AP, BC	3/511 (0.4%)
Nilotinib	2101	All arms	5/940 (0.5%)
	2101	CP & AP	2/447 (0.4%)
	2109	CP, AP, BC	4/1100 (0.4%)

Which TKI for Second Line Rx ?

#1

Consideration of Mutations, if present

#2

Selection 2nd Generation TKIs Based on Co-Morbidities

	Dasatinib	Nilotinib
Liver Disease	√	X
Pancreatitis	√	X
Chest/lung pathology	X	√
Auto-immune disease	X	√
Heart disease	?	?

Conclusions

- Dose 400 mg BID is safe and effective
- Response Rate (CP): CHR 77%, MCR 58%, CCR 42%
- Response Rate (AP): HR 55%, MCR 32%, CCR 19%
- OS 91% @ 18 months (CP), 82% @ 12 months (AP)
- Responses observed in patients failing dasatinib
- Useful as bridge to SCT in imatinib resistant patients
- Should be considered in IM-resistant relapse post SCT
- Progression BL mutations >> no BL mutations
- Co-morbidities less of a problem


Thank you for your attention !