When Imatinib Fails, What Else is There?

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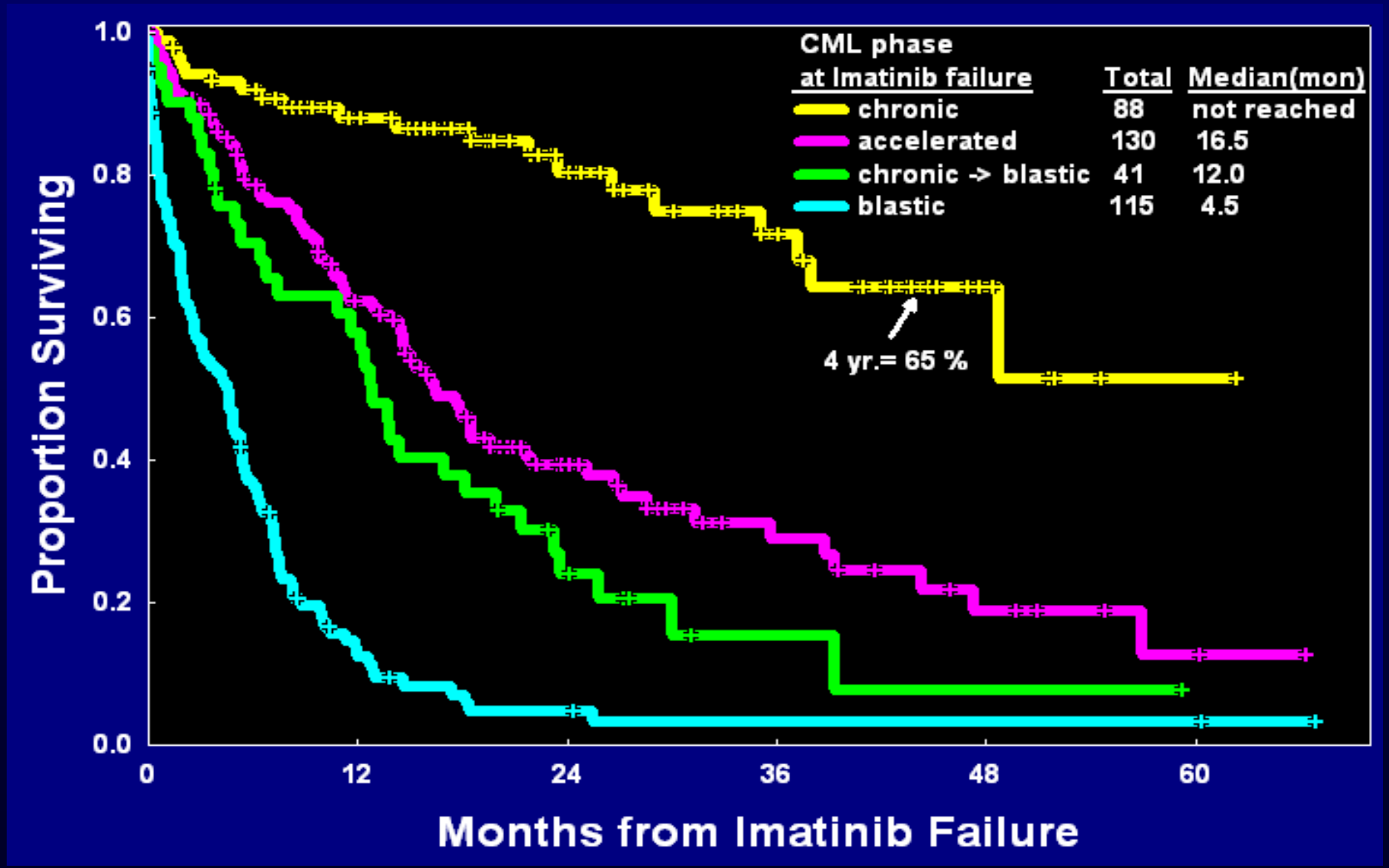
Criteria for Failure and Suboptimal Response to Imatinib

Time (mo)	Response		
	Failure	Suboptimal	Optimal
3	No CHR	No CG Response	<65% Ph+
6	No CHR >95% Ph+	≥35% Ph+	≤35% Ph+
12	≥35% Ph+	1-35% Ph+	0% Ph+
18	≥5% Ph+	No MMR	MMR
Any	Loss of CHR Loss of CCgR Mutation CE	Loss of MMR Mutation	Stable or improving MMR

Baccarani et al. JCO 2009; 27: 6041-51

Survival Post Imatinib Failure by CML Phase



Kantarjian et al. Cancer 2007; 109: 1556-60

Treatment Recommendations for CML CP According to ELN

Status	Recommendation
	First line
All	Imatinib 400mg
	Second line
IM intolerant	Dasatinib or nilotinib
Suboptimal	Imatinib same dose, or ⇑ dose, or dasatinib or niloitnib
Failure	Dasatinib or nilotinib; SCT if AP/BP or T315I
	Third line
2nd TKI suboptimal	Conitnue same; SCT if warnings and EBMT score ≤2
2nd TKI failure	SCT

Baccarani et al. JCO 2009; 27: 6041-51

MDACC – Response to Imatinib Dose Increase After Imatinib Failure

- 84 pts with imatinib dose escalation after imatinib failure
- Dose ⇑: 400 mg⇒800 mg (n=72) or 300 mg⇒600 mg (n=12)

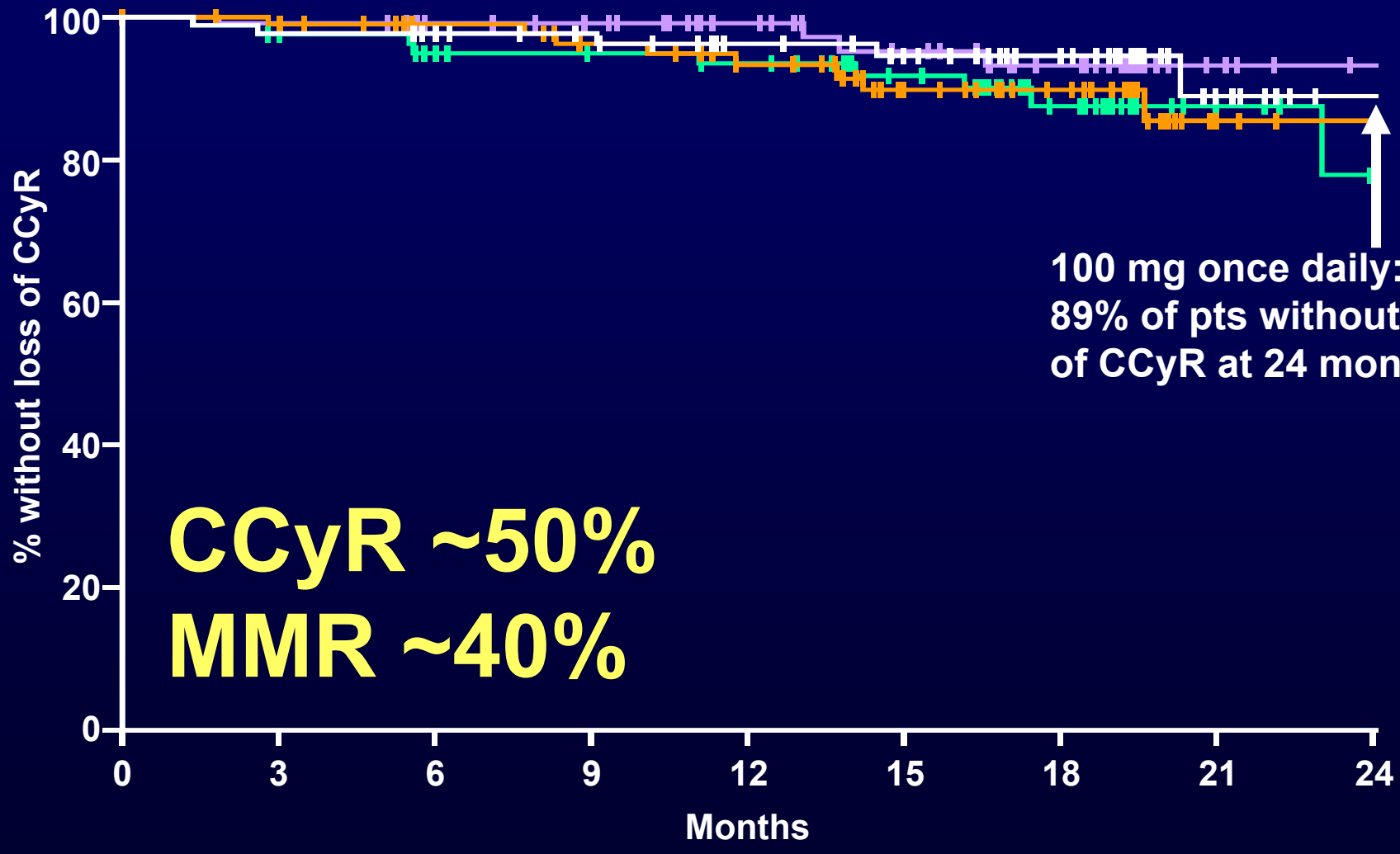
Cytogenetic response	No. (%) Total N = 84	Cy Failure N = 63	Heme Failure N = 21	p-value
Any	50 (60)	47 (75)	3 (14)	<0.001
Partial*	10 (14)	8 (16)	2 (10)	0.77
Complete	34 (40)	33 (52)	1 (5)	<0.001

* 71 evaluable patients not in MCyR at time of dose-escalation

- Median time to cytogenetic response 9 months (2-54)
- 80% of MCyR achieved within 12 months

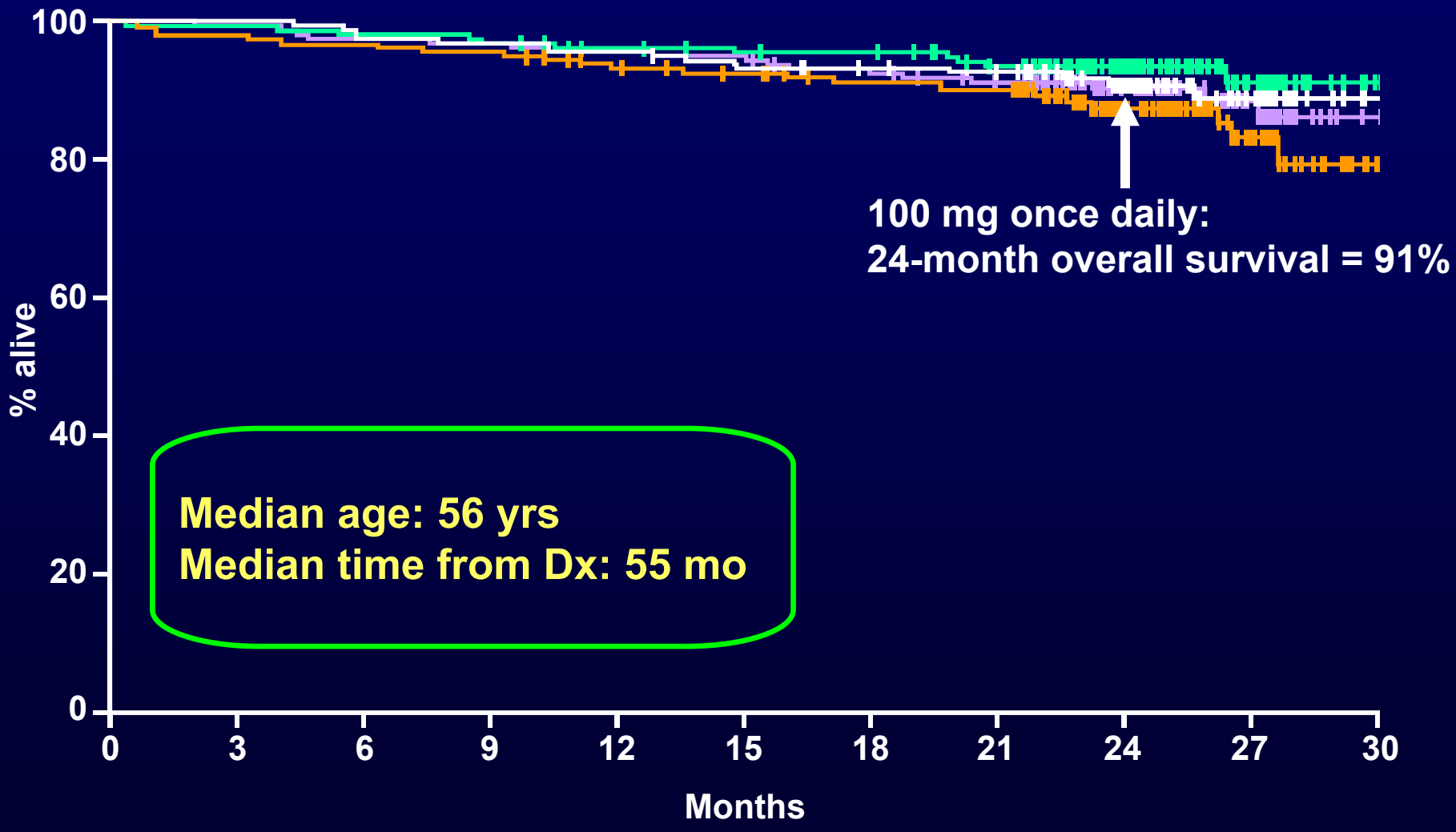
Jabbour et al. Blood 2009; 113: 2154-60

Duration of CCyR Overall Survival With Dasatinib After Imatinib Failure



Shah et al. Hematologica 2010 [E-pub ahead of print]

Overall Survival With Dasatinib After Imatinib Failure



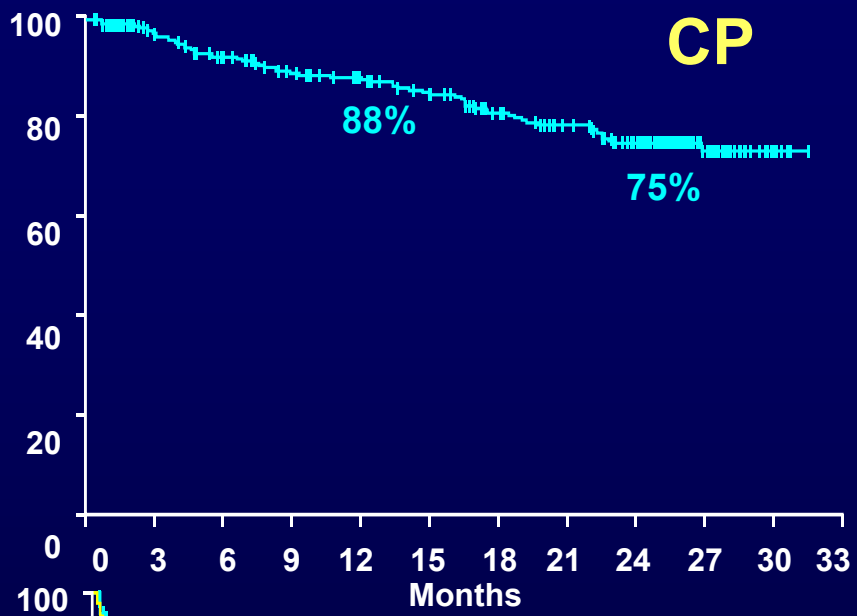
Shah et al. Hematologica 2010 [E-pub ahead of print]

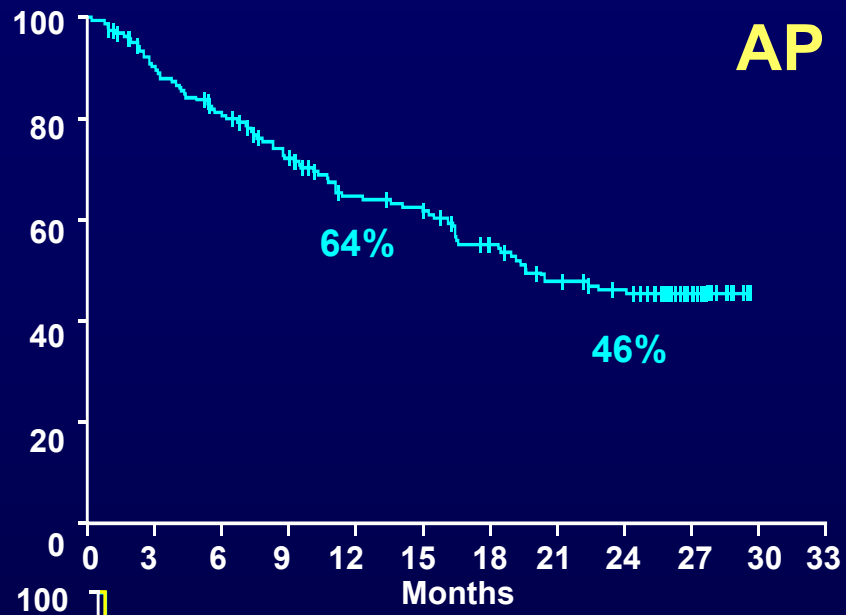
Phase II Studies of Dasatinib After Imatinib Failure

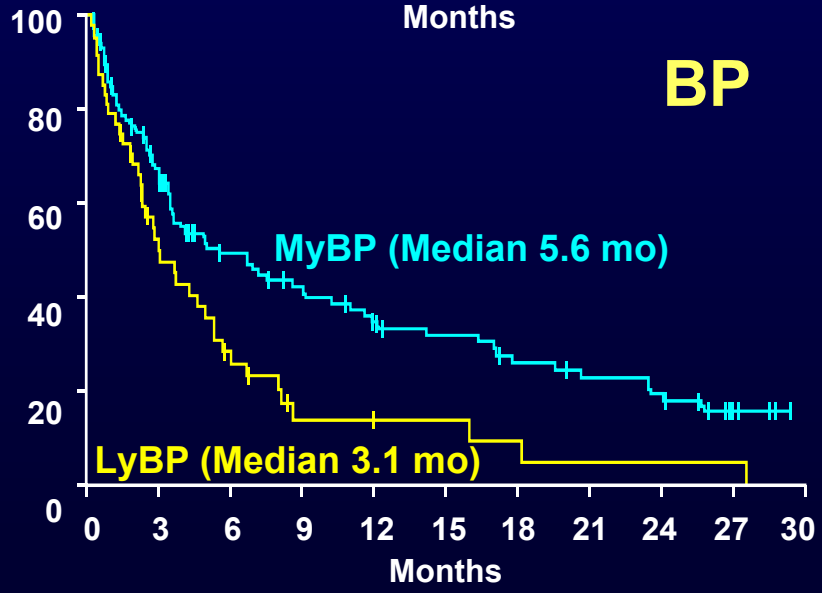
Response	Percent by Disease Stage				
	CP n=387	AP n=174	MyBP n=109	LyBP n=48	ALL n=46
Hematologic	91	64	50	39	49
CHR	91	50	26	29	35
NEL	-	14	7	6	7
Cytogenetic	62	40	47	58	62
Complete	53	33	27	46	54
Partial	9	7	7	6	2

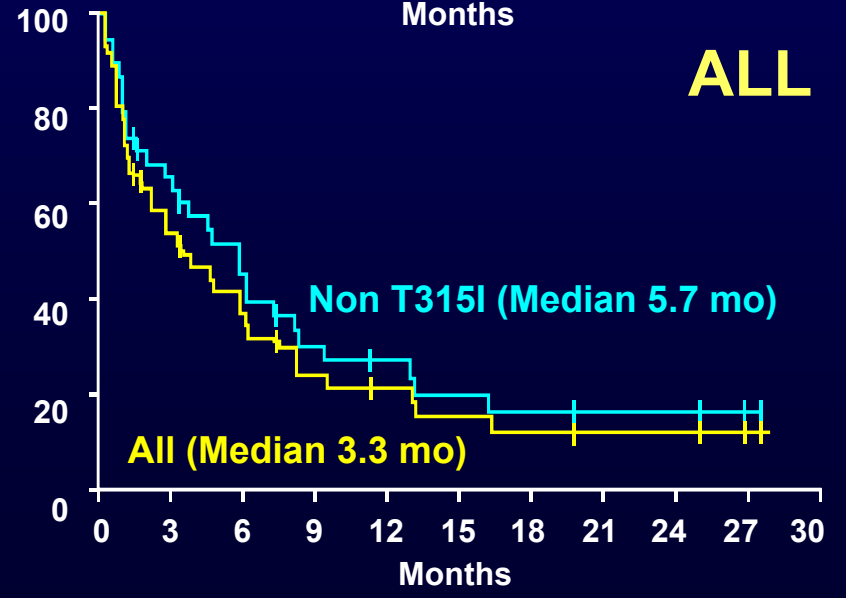
ASCO 2008, abst# 7009 ; Guilhot et al. Blood 2007; 110: abst# 470; Gambacorti et al. Blood 2007; 110: abst# 472; Stone et al. Blood 2007; 110: abst# 734; Porkka et al. Blood 2007; 110: abst# 2810

PFS with Dasatinib in CML After Imatinib Failure









Guilhot et al. Blood 2007; 110: abst# 470; Gambacorti et al. Blood 2007; 110: abst# 472; Stone et al. Blood 2007; 110: abst# 734; Porkka et al. Blood 2007; 110: abst# 2810

Nilotinib in CML Chronic Phase Post Imatinib Failure

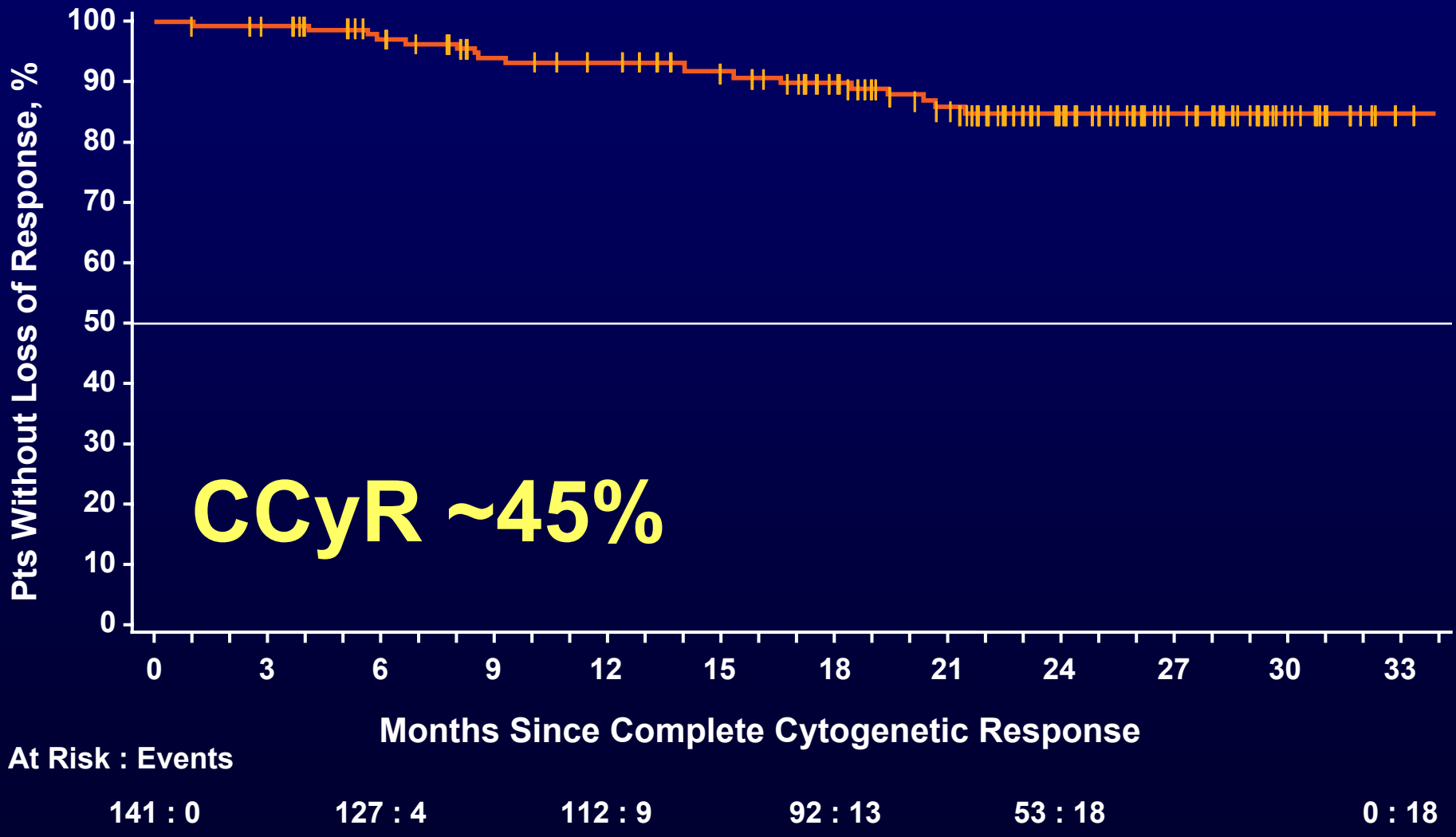
- 321 pts with imatinib resistance (71%) or intolerance (29%)
- Median age 58 yrs; median exposure 19 mo
- Nilotinib 400 mg PO BID ≥ 6 mos

Outcome	Percent
- CHR	85
- MCyR / CCyR	59 / 44
Resistant	56 / 41
Intolerant	66 / 51
- 24-month OS / PFS	87 / 64

- Median dose intensity 789 mg/d
- Grade 3-4 ↓ plts 31%, neut 31%; lipase elevation 17% (pancreatitis <1%), bilirubin 8%

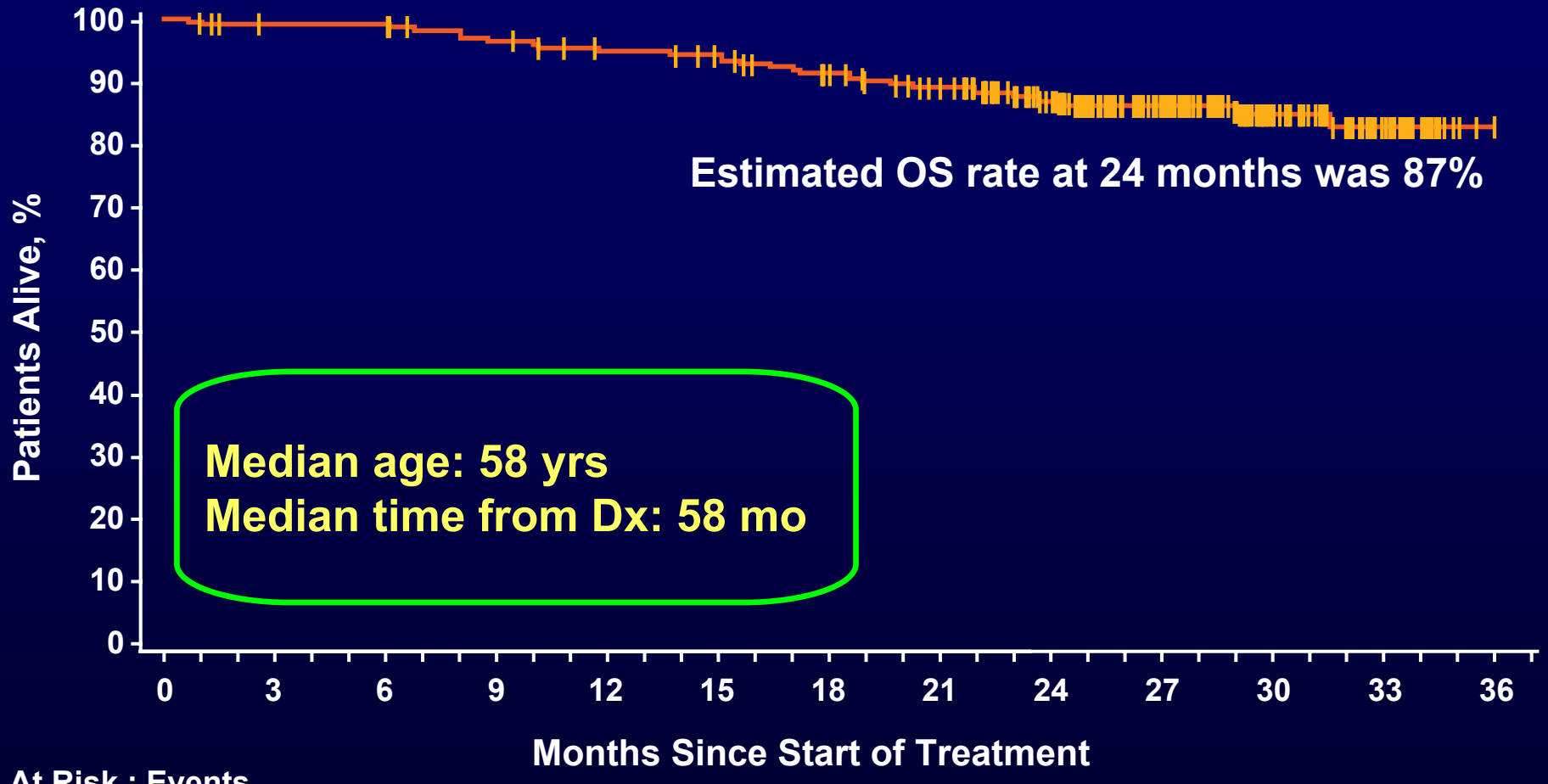
Kantarjian et al. Blood 2009 (Abst# 1129)

Duration of CCyR on Nilotinib after Imatinib Failure



Kantarjian H et al. Blood 2009; 114: Abs # 1129

Overall Survival on Nilotinib after Imatinib Failure



Kantarjian H et al. Blood 2009; 114: Abs # 1129

Bosutinib (SKI–606) in CML and Ph+ ALL

- Src-Abl inhibitor 30x more potent than IM
  - No inhibition of PDGFR, c-kit
- 294 CP pts; median time from Dx 4 yrs
- Bosutinib 400-600 mg/d; Phase II 500 mg/d
- Median follow-up 13 months
- Response (%)

	Resistant N=202	Intolerant N=92
CHR	88	97
MCyR	60	73
CCyR	46	59
MMR	54	49
CMR	30	40

- G 3-4 toxicity: thrombocytopenia 24%, neutropenia 16%, diarrhea 9%, rash 9%,

Cortes et al. ASCO 2010

2nd-Generation TKI in CML CP Post- Imatinib Failure

Toxicity	Dasatinib	Nilotinib
Myelosuppression	++	++
Pleural effusion	++	-
Liver	+	+
Transaminases	+	+
Bilirubin	+	+(+)
Rash	+	+
Lipase	- (+)	+
Glucose	-	+
Hypophosphatemia	++	++
Bleeding	++	-
Cardiac	+	+

Minimal cross intolerance between dasatinib / nilotinib and imatinib

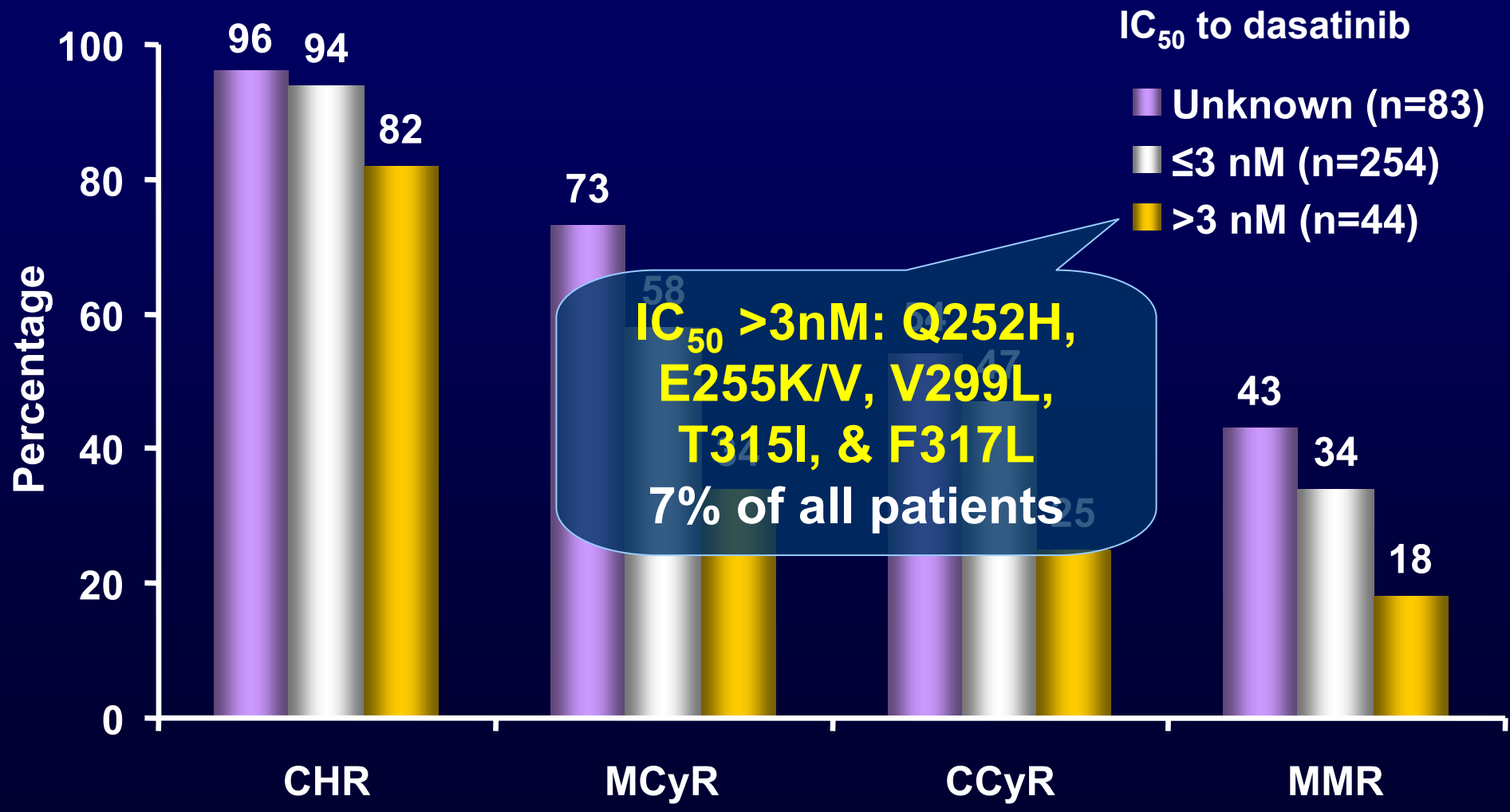
Sensitivity of ABL KD Mutations to TKI

	Ba/F3 cell proliferation IC_{50} (nM)		
	Imatinib	Nilotinib	Dasatinib
WT	260	13	0.8
M244V	2000	38	1.3
G250E	1350	48	1.8
Q252H	1325	70	3.4
Y253F	3475	125	1.4
Y253H	>6400	450	1.3
E255K	5200	200	5.6
E255V	>6400	430	11
V299L	540	ND	18
T315A	971	61	125
T315I	>6400	>2000	>200
F317L	1050	50	7.4
F31TV	350	ND	53
E355G	2300	ND	1.8
F359V	1825	175	2.2
V379I	1630	51	0.8
H396P	850	41	0.6
H396R	1750	41	1.3

Highly Resistant / Resistant / Sensitive

O'Hare et al. Blood 2007; 110: 2242-9

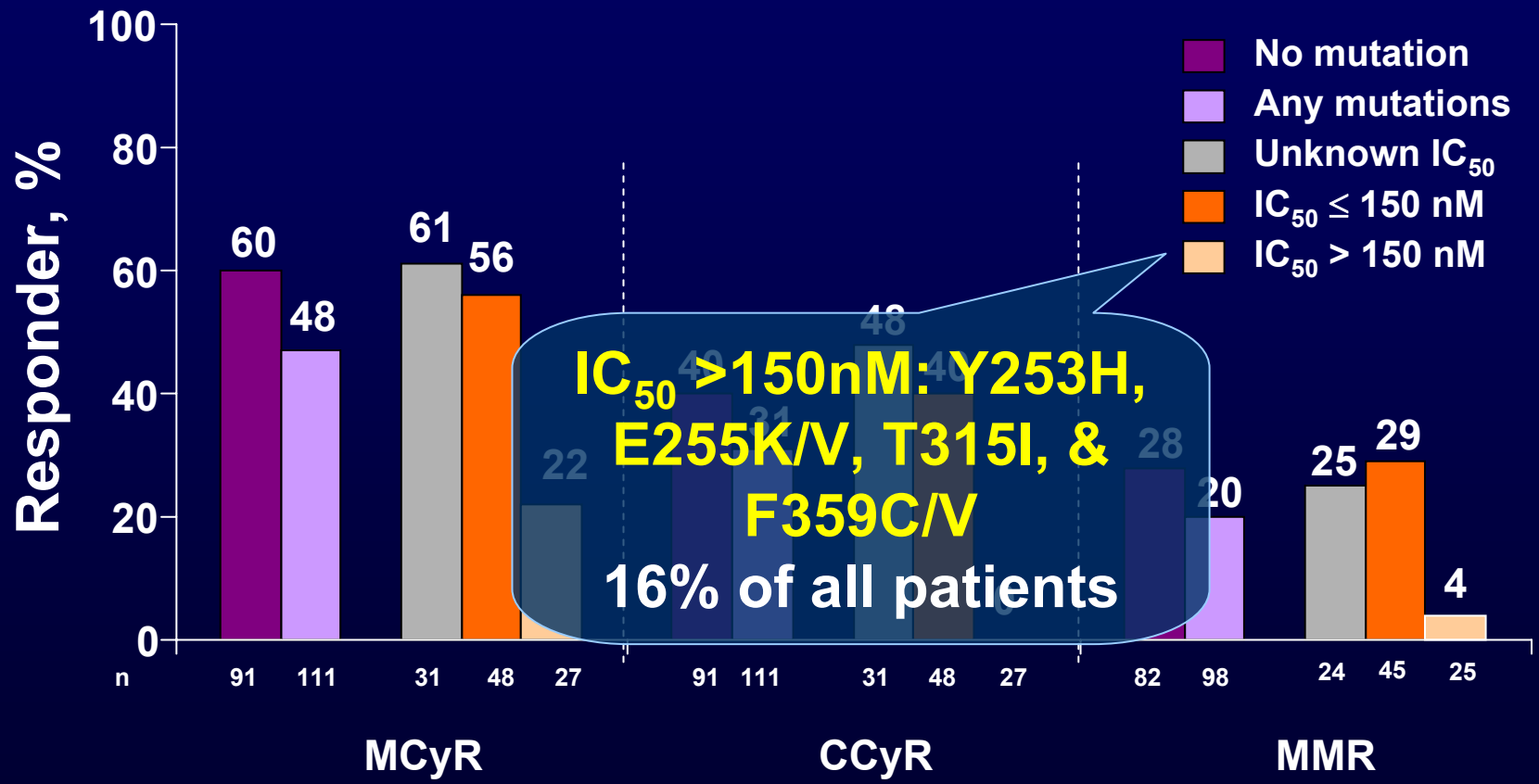
Response Rates by Individual Mutation
In vitro IC_{50} to Dasatinib (Excluding T315I)



Muller et al. Blood 2009; 114: 4944-53

Nilotinib Efficacy According to Baseline BCR-ABL Mutations in CML-CP

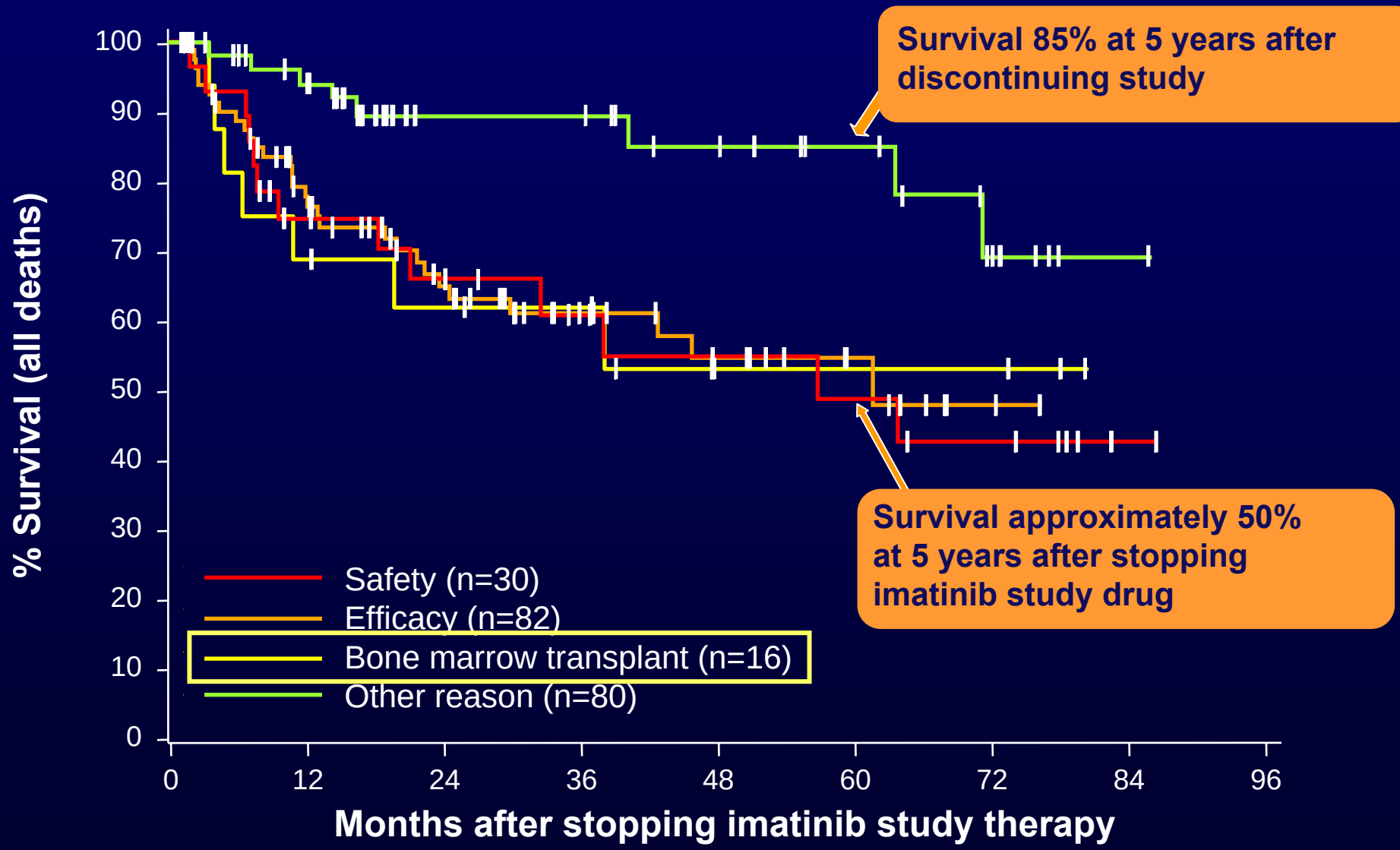
Best Responses Within 12 Months of Therapy by Baseline BCR-ABL Mutation Status*



* Patients with T315I were excluded

Hughes et al. JCO 2009; 27: 4204-10

IRIS - Survival of Patients Who Discontinued Imatinib Study Therapy



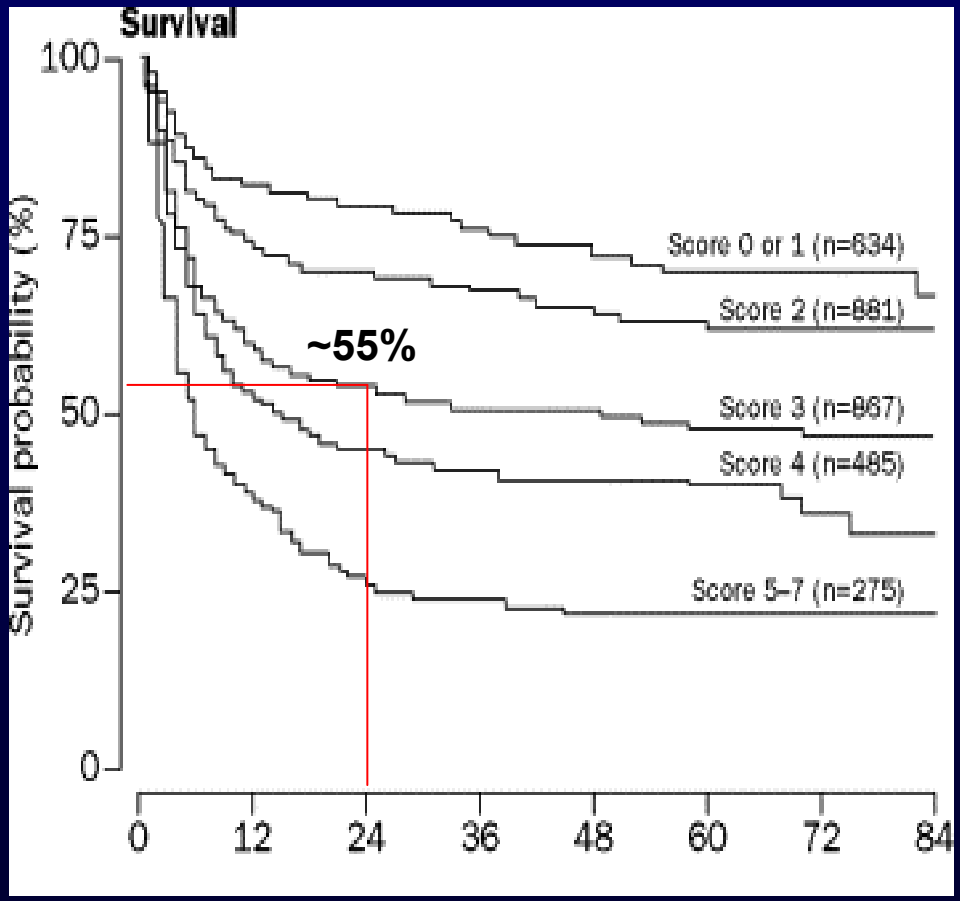
O'Brien et al. Blood 2008; 112: abst# 186

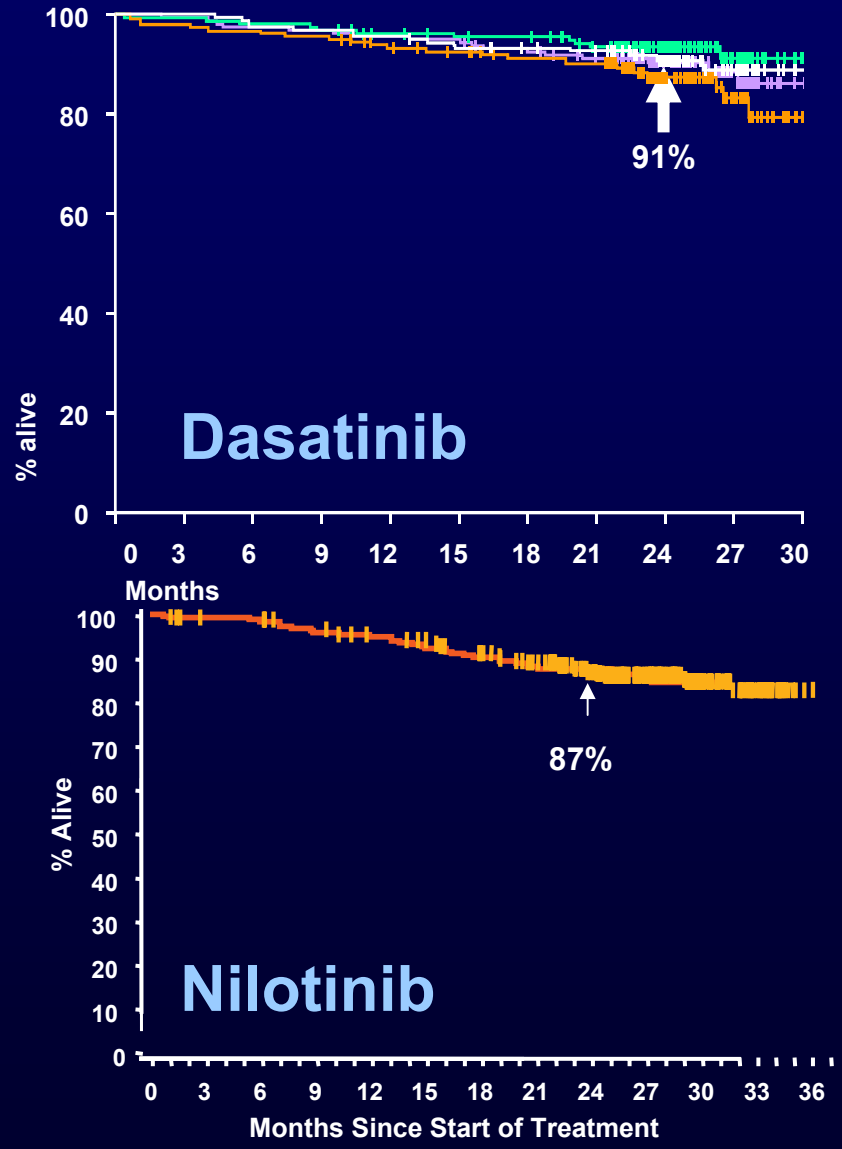
Risk Assessment for SCT in CML

Risk factor	Group	Score
Donor type	HLA-identical sibling	0
	MUD	1
Stage	CP	0
	AP	1
	BP, ≥2nd CP	2
Age	<20	0
	20-40	1
	>40	2
Sex match	All other	0
	M-rec/F-don	1
Time from Dx	<12 mo	0
	>12 mo	1

Gratwohl et al. Lancet 1998; 352: 1087-92

Overall Survival With TKI After Imatinib Failure or With SCT





Shah et al. Hematologica 2010 [E-pub ahead of print]
Kantarjian H et al. Blood 2009; 114: Abs # 1129;
Gratwohl et al. Lancet 1998; 352: 1087-92

Criteria for Failure to 2nd Generation TKI (ELN)

Time (mo)	Suboptimal	Failure	Warning
Baseline	NA	NA	Imatinib heme resistance CE Mutations
3 mo	Ph+ 36-65%	Ph+ >95% New mutation	Ph+ 66-95%
6 mo	Ph+ 1-35%	Ph+ 66-95% New mutation	Ph+ 36-65%
12 mo	No MMR	Ph+ > 35% New mutation	

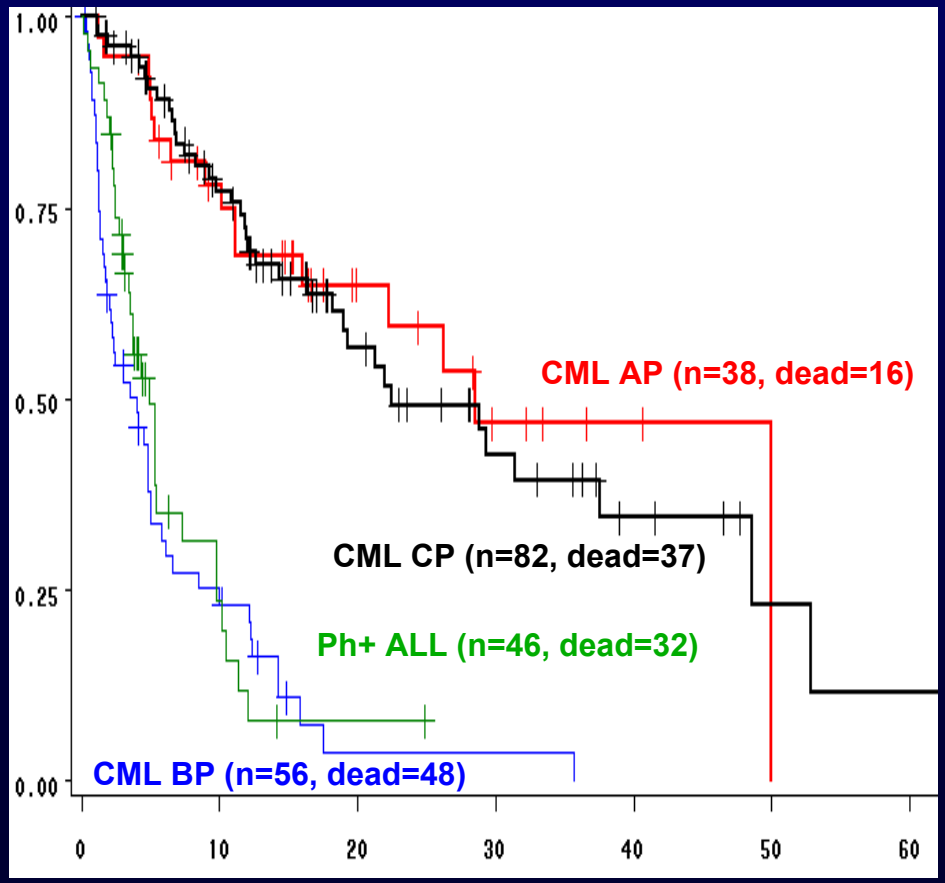
Baccarani et al. JCO 2009; 27: 6041-51

Response (and Failure) to 2nd Generation TKI: What Does this Mean?

- Most patients do well
- Low probability of response: monitor closely
- Failure if: No CHR by 3 months; no cytogenetic response by 6 months; no MCyR by 12 months
- MMR at 12 months desirable but should not define failure
- Approach depending of clinical setting:
  - Young, matched sibling ⇒ SCT
  - T315I ⇒ SCT, HHT, 3rd generation TKI
  - Other ⇒ Monitor closely (alternative TKI if sensitive mutation)

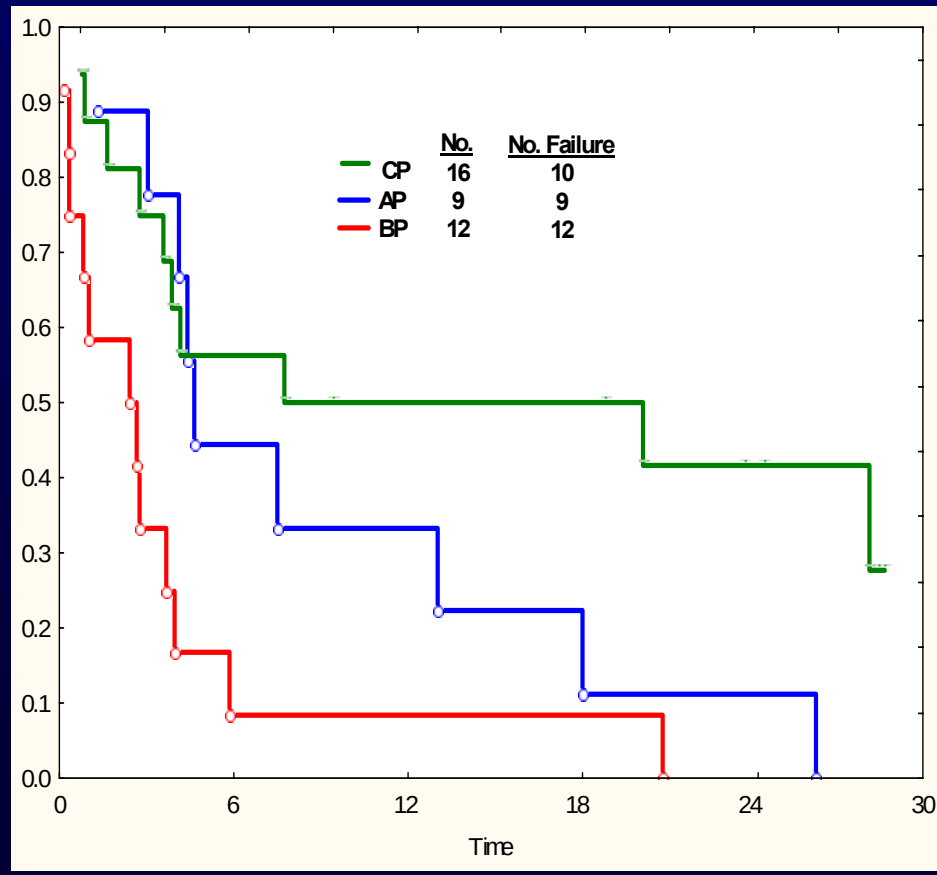
Outcome of Patients who Fail ≥2 TKI or with T315I

T315I
Overall Survival



Nicolini et al. Blood 2009; 114: 5271-8

≥2 TKI Failure (CP)
Failure-Free Survival



Garg et al. Blood 2009; 114; 4361-8

Treatment Options for CML with T315I or After ≥2 TKI

- Multi-kinase inhibitors
  - MK-0457
  - AP24534
  - XL228
  - PHA-739358
  - DCC-2036
  - KW-2449
- Omacetaxine (Homoharringtonine)
- Histone deacetylase inhibitors
- Stem cell transplant

Phase I Study of AP24534 Best Response to Therapy (Ph+)

- 44 pts with Ph+ leukemia; 81% 3 prior TKI
- AP24534 2-60mg/d
- DLT: Pancreatitis / ↑ lipase-amylase

Best Response	No. (%)		
	CP	AP, BP, ALL	Overall
Hematologic	N=12*	N=11	
CHR	10 (83)	--	10 (83)
MHR	--	4 (36)	4 (36)
Cytogenetic	N=20	N=11	N=31
MCyR	9 (45)	1 (9)	10 (32)
CCyR	5 (25)	1 (9)	6 (19)
Minor	3 (15)	1 (9)	4 (12)

Phase II study to open soon in Europe, US, Asia, Australia

* 10 additional pts entered in CHR and maintained CHR

Cortes et al. Blood 2009; 114: Abst# 643

Omacetaxine for CML with T315I Response to Therapy

- 81 pts with T315I CML
- Omacetaxine 1.25 mg/m^2 BID x14d, then x7d
- Prior TKI: 1 in 21%, 2 in 53%, and 3 in 26%

Response	No. (%)		
	CP N=49	AP N=17	BP N=15
Hematologic	42 (86)	6 (35)	7 (47)
CHR	42 (86)	5 (29)	3 (20)
HI	NA	3 (18)	1 (7)
RCP	NA	1 (6)	4 (27)
Cytogenetic	20 (41)	1 (6)	-
MCyR	13 (27)	1 (6)	-
CCyR	9 (18)	1 (6)	-
PCyR	4 (8)	-	-
Minimal	7 (14)	-	-

Data independently adjudicated by Data Monitoring Committee

Cortes et al. Blood 2009; 114: Abst# 644

SCT for Patients with T315I CML

- Survey of pts with T315I+ CML and Ph+ ALL from 9 countries
- 33 (15%) of 222 pts referred to SCT
  - Median age 42 (22-68) yrs
  - 63% conventional SCT, 30% RIC, 7% unk
  - 85% MUD, 15% related

	1 year OS*	3 year OS*
CP (n=8)	69%	69%
AP (n=7)	71%	71%
BP (n=14)	16%	0%
Ph+ ALL (n=4)	33%	NA

Nicolini et al. Blood 2009; 114 (abst# 645)

Managing Refractory CML

- Best way to manage resistance is to prevent it
- Proper identification of treatment failure
- Early intervention in case of *TRUE* treatment failure
  - Management of suboptimal response?
- In case of failure, mutation studies may help:
  - T315I: no role for 2nd genaration TKIs; allo SCT; new agents (HHT, "T315I inhibitors")
  - Nilotinib IC_{50}>150nM (e.g. Y253H, E255V, F359V) ⇒ Dasatinib
  - Dasatinib IC_{50}>3nM (e.g. F317L, V299L) ⇒ Nilotinib

Questions?

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