Allogeneic Stem Cell Transplant for relapsed CML in chronic phase?

Not now, thank you!

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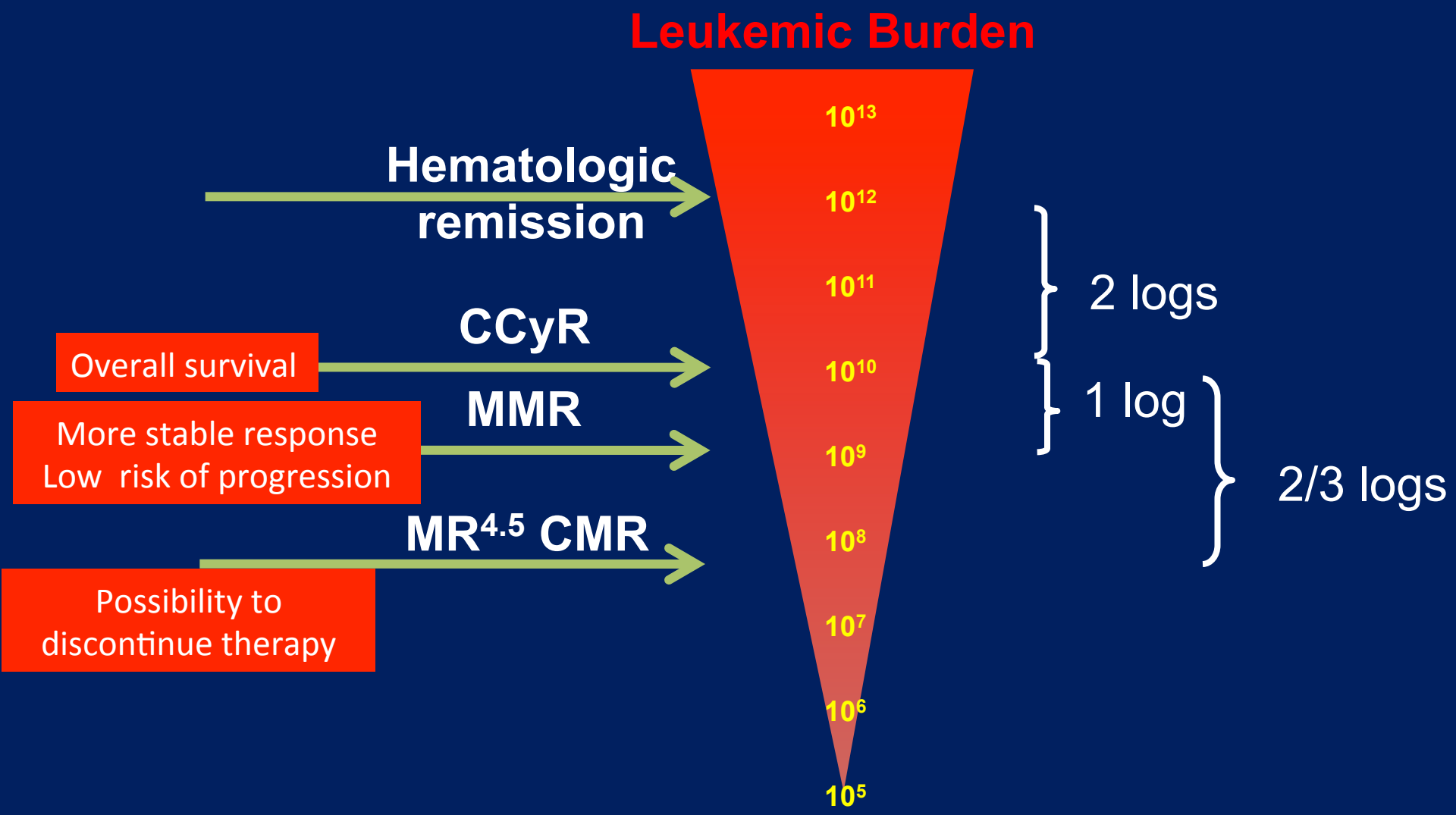
Monitoring Response in CML: Hierarchic Order Of Responses



Optimal Response to imatinib 400 mg per day

CHR within 3 months

With at least minor CyR

PCyR at 6 months

CCyR at 12 months

MMR at 18 months

ELN reccomendations 2009; Baccarani et al. JCO 2009

Definition of Failure and Suboptimal Response (ELN Recommendations, Baccarani et al., JCO 2009)

Time	Failure	Subopt Resp	Warnings
Diagnosis	-	-	High risk ACA in Ph+ cells
3 mos	No CHR	No CyR	
6 mos	No CyR	< PCyR	
12 mos	No PCyR	< CCyR	< MMR
18 mos	< CCyR	< MMR	
Anytime	Loss of CHR Loss of CCyR ACA in Ph+ cells Mutations (IM-insensit.)	Loss of MMR Mutations (IM-sensit.)	Any ↑ BCR-ABL transcript level OCA in Ph- cells

CHRONIC MYELOID LEUKEMIA

1 - FRONTLINE:	IMATINIB 400 mg, INVESTIGATIONAL
2 - IM - INTOLERANT:	DASATINIB, NILOTINIB, INVESTIGATIONAL
3 - IM - SUBOPTIMAL RESPONSE:	SAME IMATINIB DOSE IMATINIB DOSE INCREASE, DASATINIB, NILOTINIB
4 - IM - FAILURE:	DASATINIB, NILOTINIB, INVESTIGATIONAL

ALLOGENEIC STEM CELL TRANSPLANTATION IS AN ESTABLISHED OPTION, PARTICULARLY FOR THE PATIENTS WHO FAIL IM AND 2nd GENERATION TKIs, DEPENDING ON THE EBMT RISK SCORE (Gratwohl et al, Lancet 1998; 352: 1087 - 1092)

Baccarani et al., JCO 2009

First Rule In CML Therapy: Don't Jump Ship Too Early

AlloSCT as immediate response to imatinib failure in CP is to Jump the Ship Too Early!

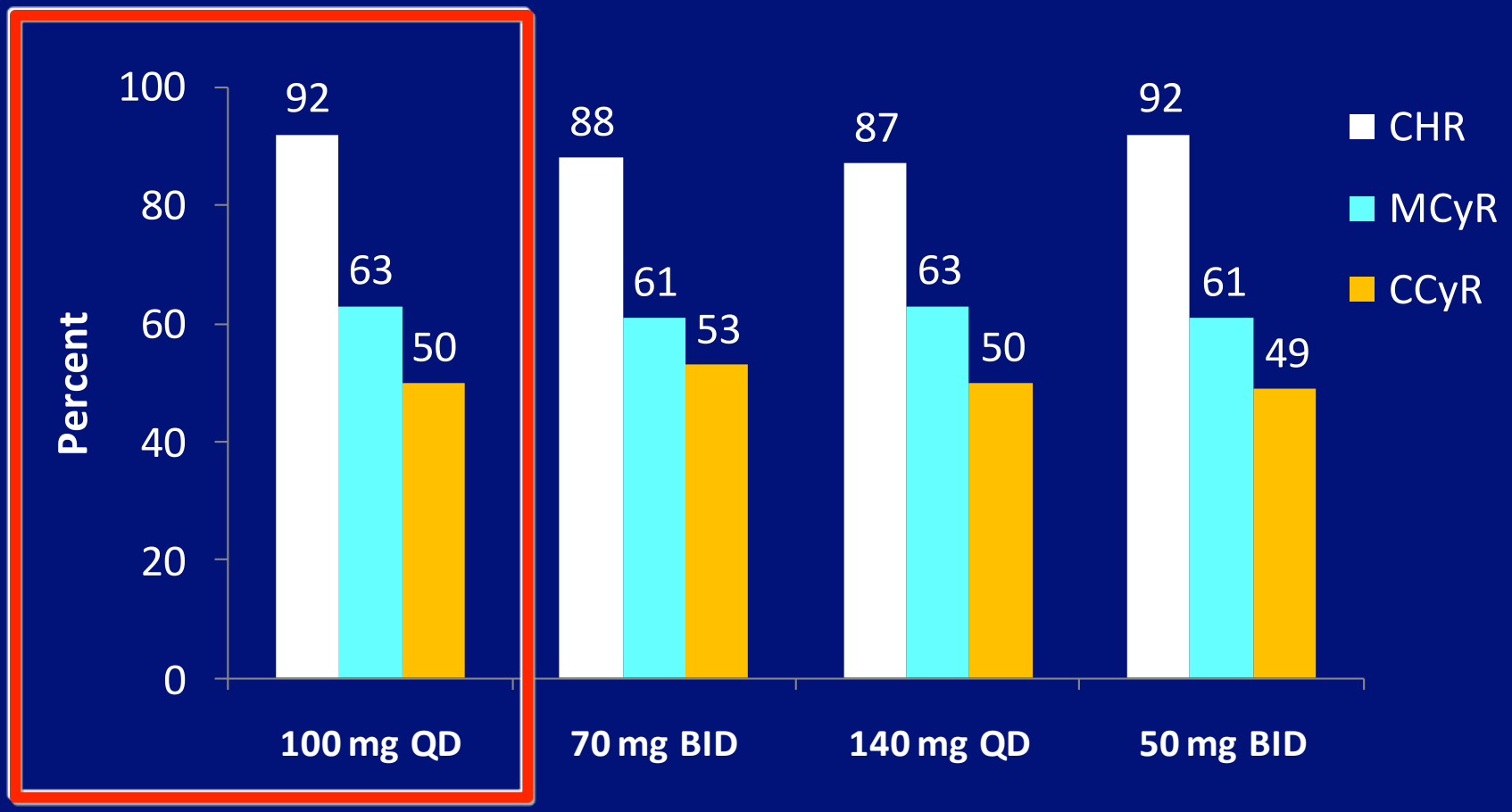
Hagop Kantarijan's cartoon

Second-line TKIs in CP CML

Parameters to consider:

- Efficacy (including efficacy against specific mutations)
- Tolerability
- Safety at short and long-term

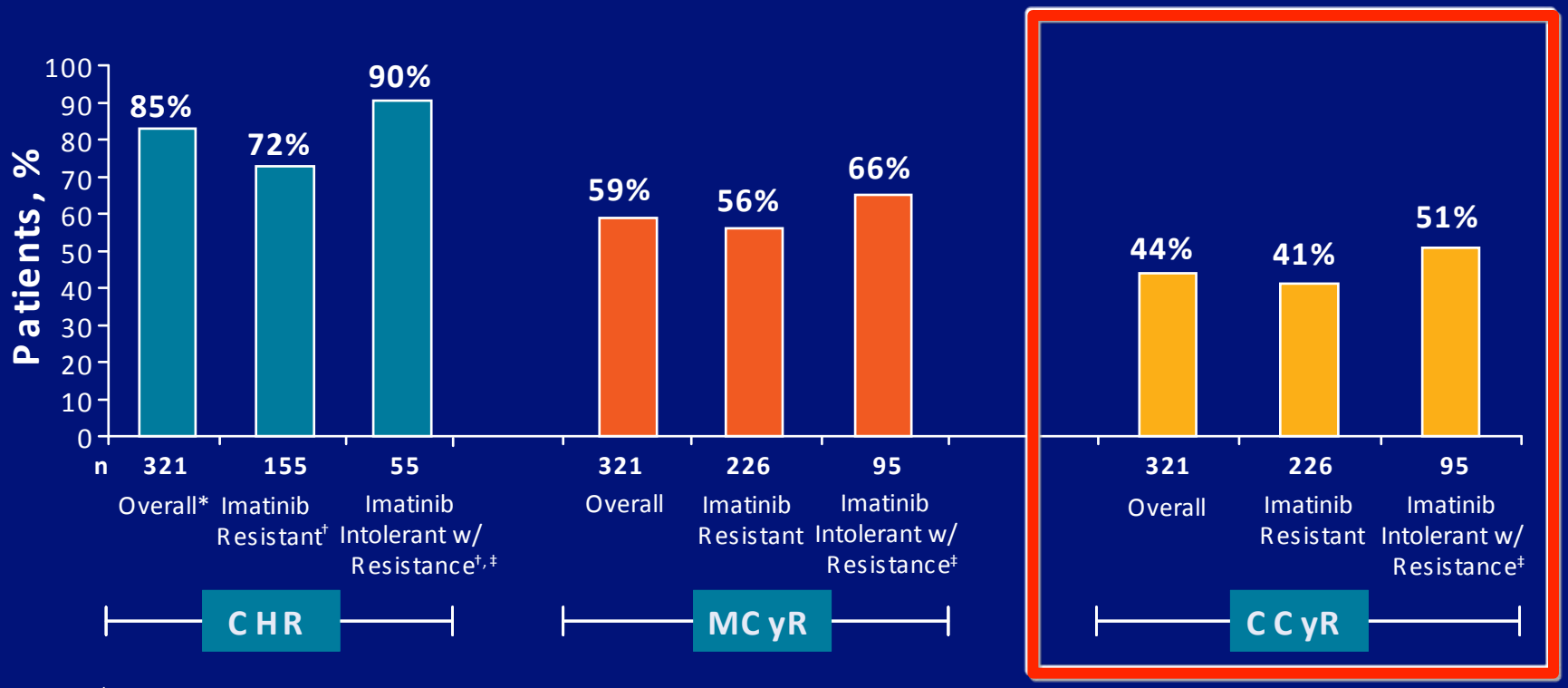
Best overall response[a]



[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

Nilotinib Phase 2 Study: CML-CP

Response in Patients With a Minimum Follow-Up of 24 Months (N = 321)



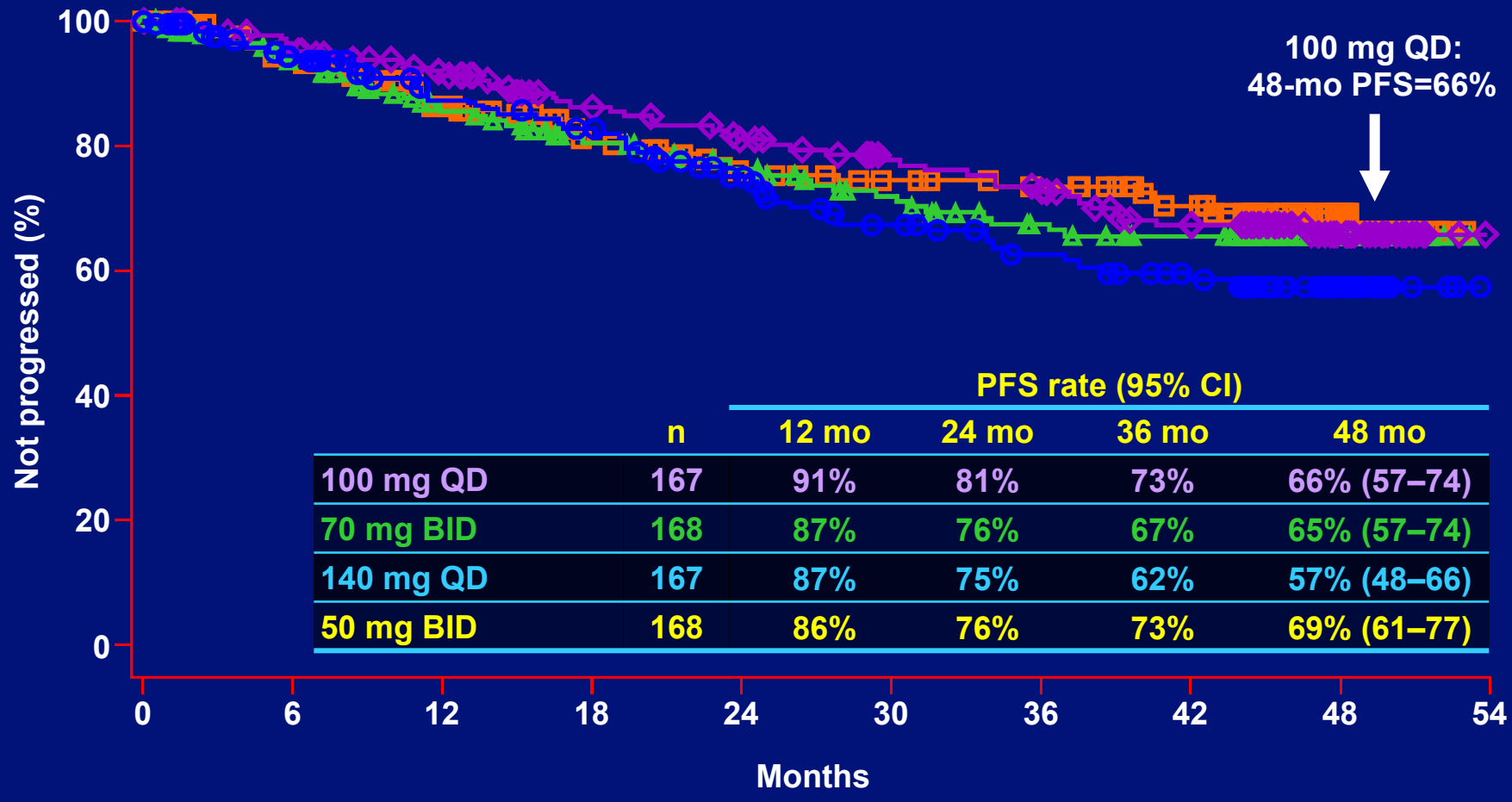
* Patients who achieved (without baseline CHR) or maintained CHR (had CHR at study entry).
† Patients with no CHR at baseline.
‡ See definition of imatinib-intolerant with resistance in the Methods sections.

CCyR, complete cytogenetic response; **CHR**, complete hematologic response; **MCyR**, major cytogenetic response.

Kantarjian H et al., Blood 2011; 217:1141-45

Kantarjian HM, et al. *Blood*. 2009;114(22):464 [abstract 1129] (poster).

PFS[a]

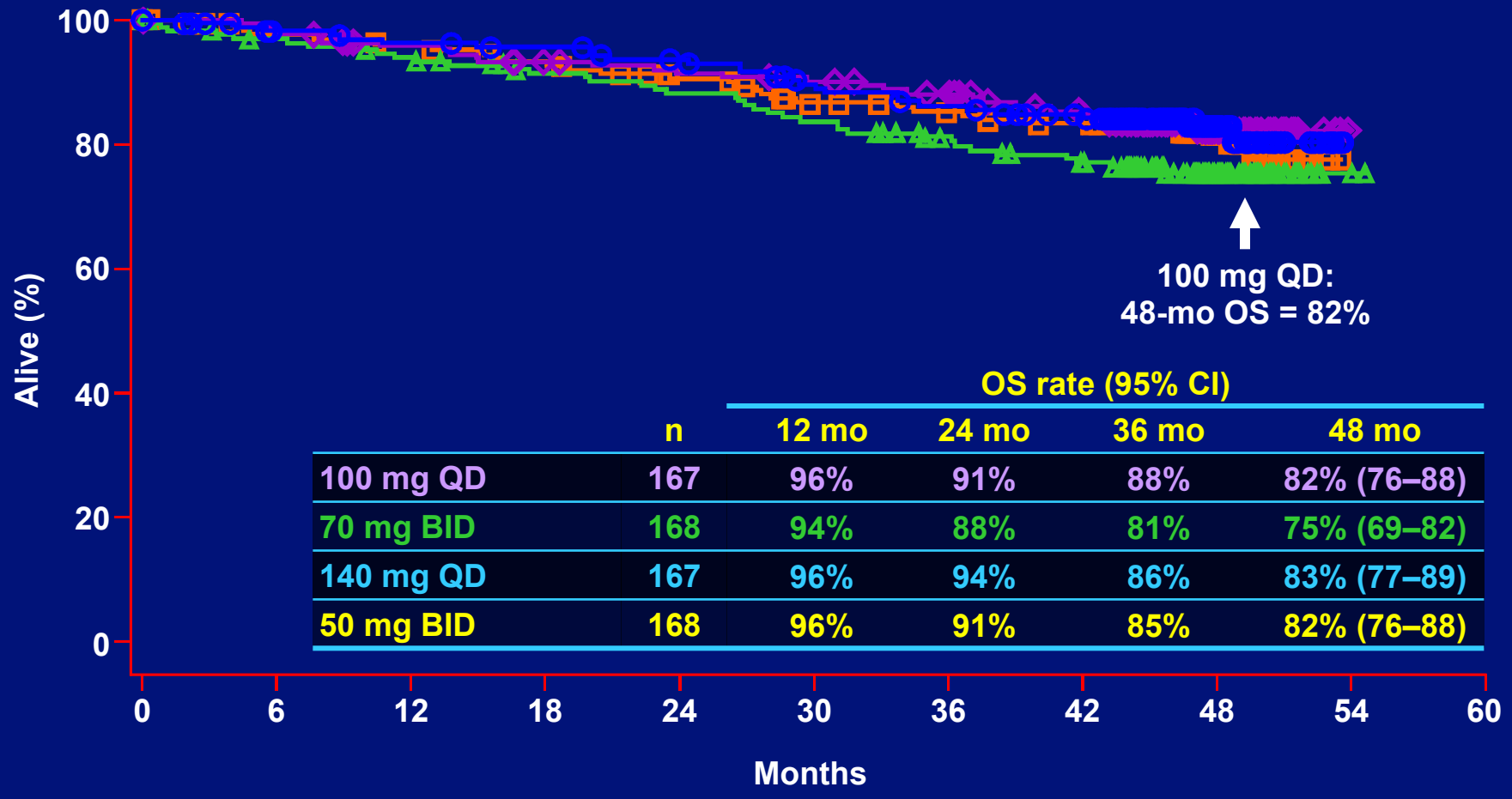


	n	PFS rate (95% CI) 12 mo	24 mo	36 mo	48 mo
100 mg QD	167	91%	81%	73%	66% (57–74)
70 mg BID	168	87%	76%	67%	65% (57–74)
140 mg QD	167	87%	75%	62%	57% (48–66)
50 mg BID	168	86%	76%	73%	69% (61–77)

[a]Progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph(+) metaphases, confirmed AP/BP disease, or death

QD=once daily; BID=twice daily

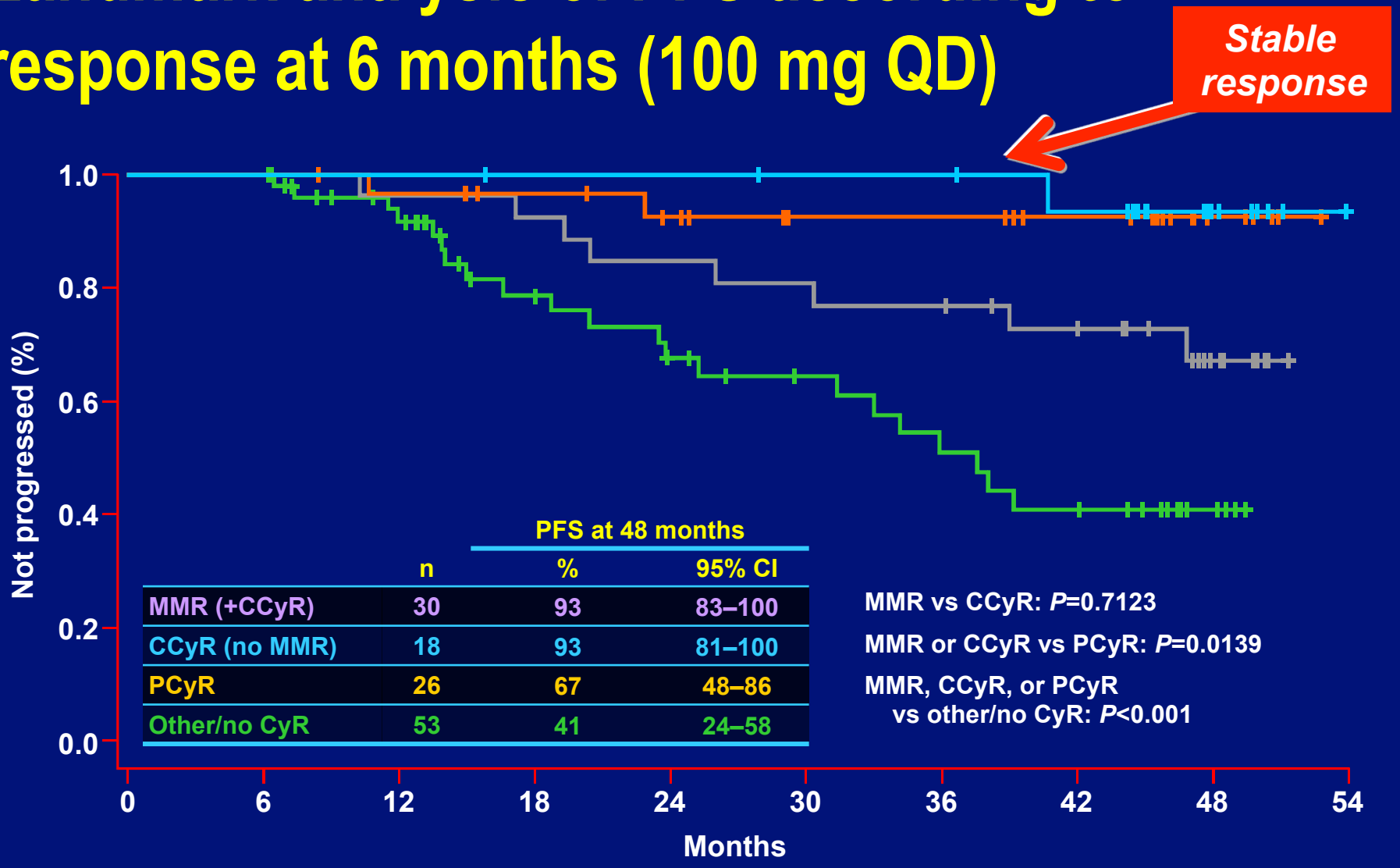
OS



	n	OS rate (95% CI) 12 mo	24 mo	36 mo	48 mo
100 mg QD	167	96%	91%	88%	82% (76–88)
70 mg BID	168	94%	88%	81%	75% (69–82)
140 mg QD	167	96%	94%	86%	83% (77–89)
50 mg BID	168	96%	91%	85%	82% (76–88)

QD=once daily; BID=twice daily

Landmark analysis of PFS according to response at 6 months (100 mg QD)



	PFS at 48 months		
	n	%	95% CI
MMR (+CCyR)	30	93	83–100
CCyR (no MMR)	18	93	81–100
PCyR	26	67	48–86
Other/no CyR	53	41	24–58

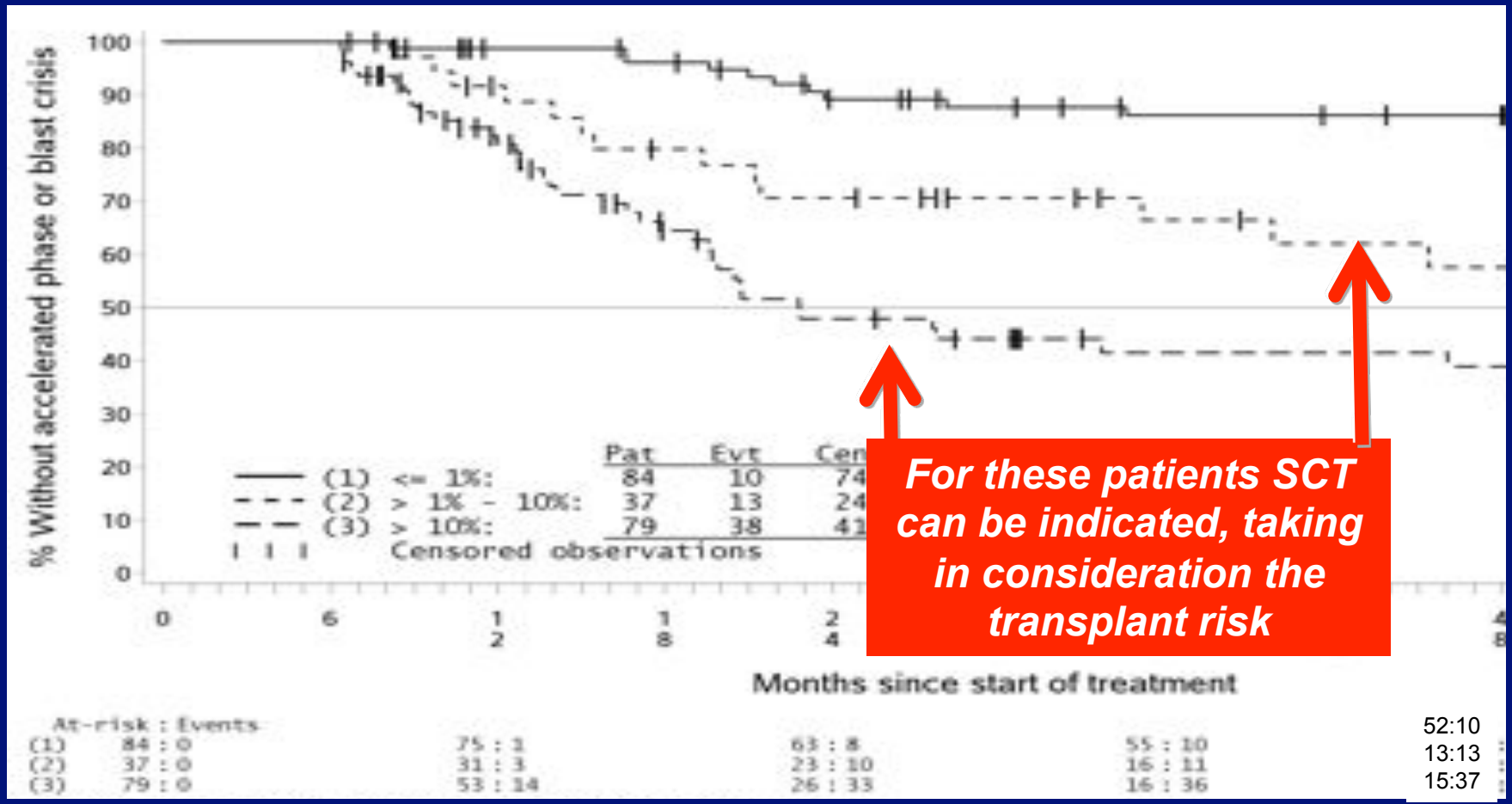
MMR vs CCyR: *P*=0.7123

MMR or CCyR vs PCyR: *P*=0.0139

MMR, CCyR, or PCyR vs other/no CyR: *P*<0.001

Patients not assessed at the landmark (±1.5 months) or with Ph(–) BCR-ABL(+) disease were excluded; progression was defined as increasing WBC count, loss of CHR or MCyR, ≥30% increase in Ph(+) metaphases, confirmed AP/BP disease, or death

Progression to AP/BC by BCR-Abl Ratio at 6 Months



- Freedom from progression to AP/BC at 48 months according to BCR-ABL % (IS) at 6 months: 86%, 58%, 39% for patients with BCR-ABL ≤ 1%, > 1 – 10%, and > 10% , respectively (*P* =.001 for ≤ 1% vs > 1 – 10%, ; *P* = .03 for > 1 – 10% vs >10%)

LeCoutre P. et al. ASH 2011

PACE Initial Results
Response CP-CML Cohorts

Response	n Response / N Evaluable (%)		
	Overall	R/I Cohort	T315I Cohort
CHR	248/271 (92)	193/207 (93)	55/64 (86)
MCyR*	116/248 (47)	79/191 (41)	37/57 (65)
CCyR	96/248 (39)	63/191 (33)	33/57 (58)
MMR	51/265 (19)	31/205 (15)	20/60 (33)

*MCyR is the primary endpoint

Data as of 02 Dec 2011

Last Dasatinib Dose Reported For Patients On Treatment

Number of patients (%)	100 mg QD (n=165)[a]	140 mg QD (n=163)	50 mg BID (n=167)	70 mg BID (n=167)
On treatment	57 (35)	44 (27)	52 (31)	52 (31)
Schedule[b]				
QD	55 (96)	41 (93)	32 (62)	23 (44)
BID	2 (4)	3 (7)	20 (38)	29 (56)
Schedule and total daily dose[b]				
<100 mg QD	20 (35)	15 (34)	18 (35)	13 (25)
100 mg QD	26 (46)	14 (32)	12 (23)	8 (15)
>100 mg QD	9 (16)	12 (27)	2 (4)	2 (4)
<70 mg BID	1 (2)	3 (7)	16 (31)	19 (36)
70 mg BID	1 (2)	0	2 (4)	8 (15)
>70 mg BID	0	0	2 (4)	2 (4)

[a]One patient randomized to the 100-mg QD arm was never treated and another patient was treated with dasatinib 50 mg BID
[b]Percentages are based on patients still on treatment in the corresponding arm

Shah NP, et al. ASCO 2011: Poster 6512.

Patient Disposition (N = 321)

Discontinued study, n (%)	224 (70)
Disease progression	96 (30)
Adverse events	66 (21)
Drug-related	53 (17)
Subject withdrew consent	26 (8)
Abnormal test results	4 (1)
Death	4 (1)
Abnormal laboratory values	3 (0.9)
Lost to follow-up	3 (0.9)
Other*	22 (7)

* Includes administrative issues, protocol violations, and not stated

LeCoutre P. et al. ASH 2011

Shah NP, et al. ASCO 2011: Poster 6512.

Nilotinib Phase 2 Study: CML-CP

Baseline Demographics

	CML-CP (N = 321)
Median age, years (range)	58 (21-85)
Median duration of CML, months (range)	58 (5-275)
Median duration of prior imatinib therapy, months (range)	32 (< 1-94)
Active disease prior to therapy, n (%)	206 (64)
Imatinib resistant/intolerant, (%)*	70/30
Prior highest imatinib dose ≥ 600 mg/day, n (%)	232 (72)
Patients ≥ 65 years, n (%)	114 (36)
Other prior therapy, n(%)	
Hydroxyurea	266 (83)
Interferon	134 (42)
Cytarabine	78 (24)

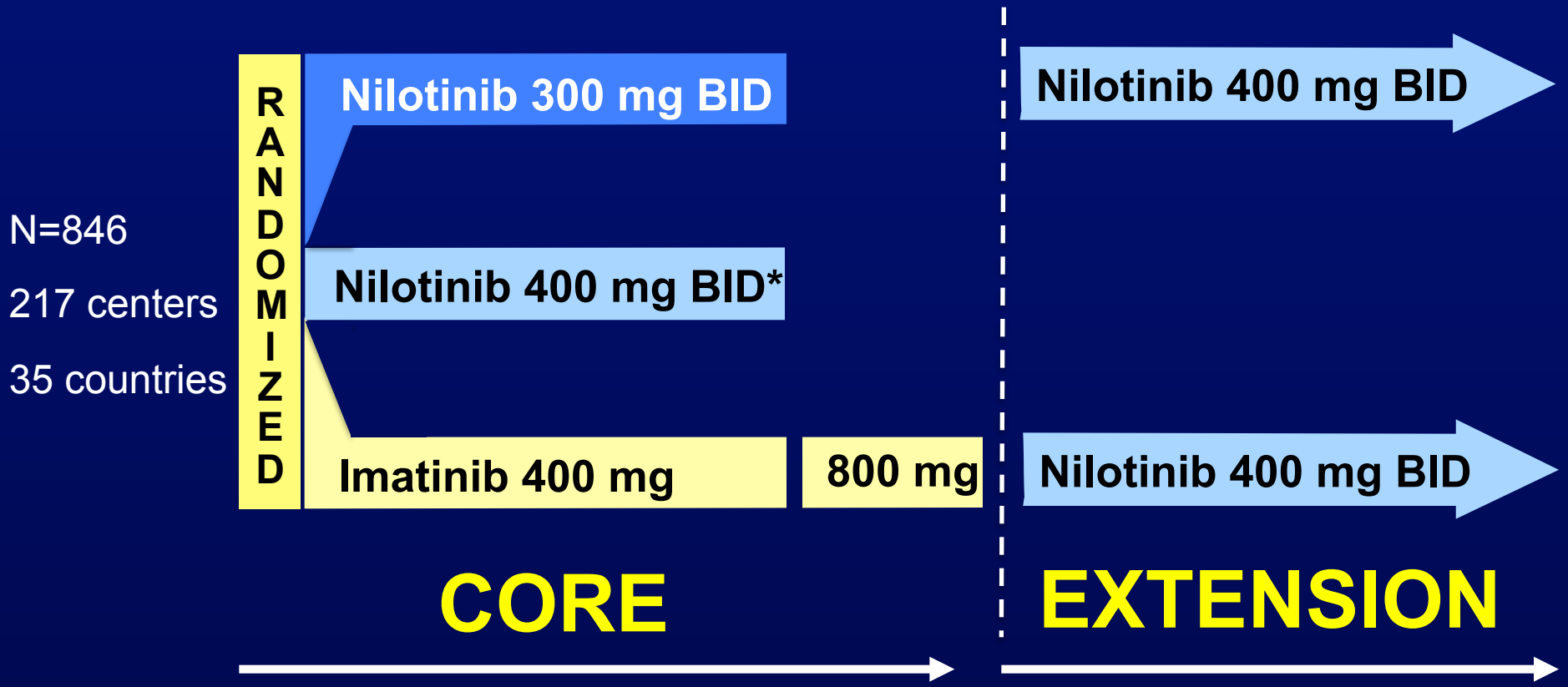
CHR, complete hematologic response; **CML**, chronic myeloid leukemia; **MCyR**, major cytogenetic response.

*Intolerant patients were also resistant and were not allowed to have prior MCyR at study entry.

Kantarjian H et al., Blood 2011; 217:1141-45

Kantarjian HM, et al. *Blood*. 2009;114(22):464 [abstract 1129] (poster).

Design of the ENESTnd Studies

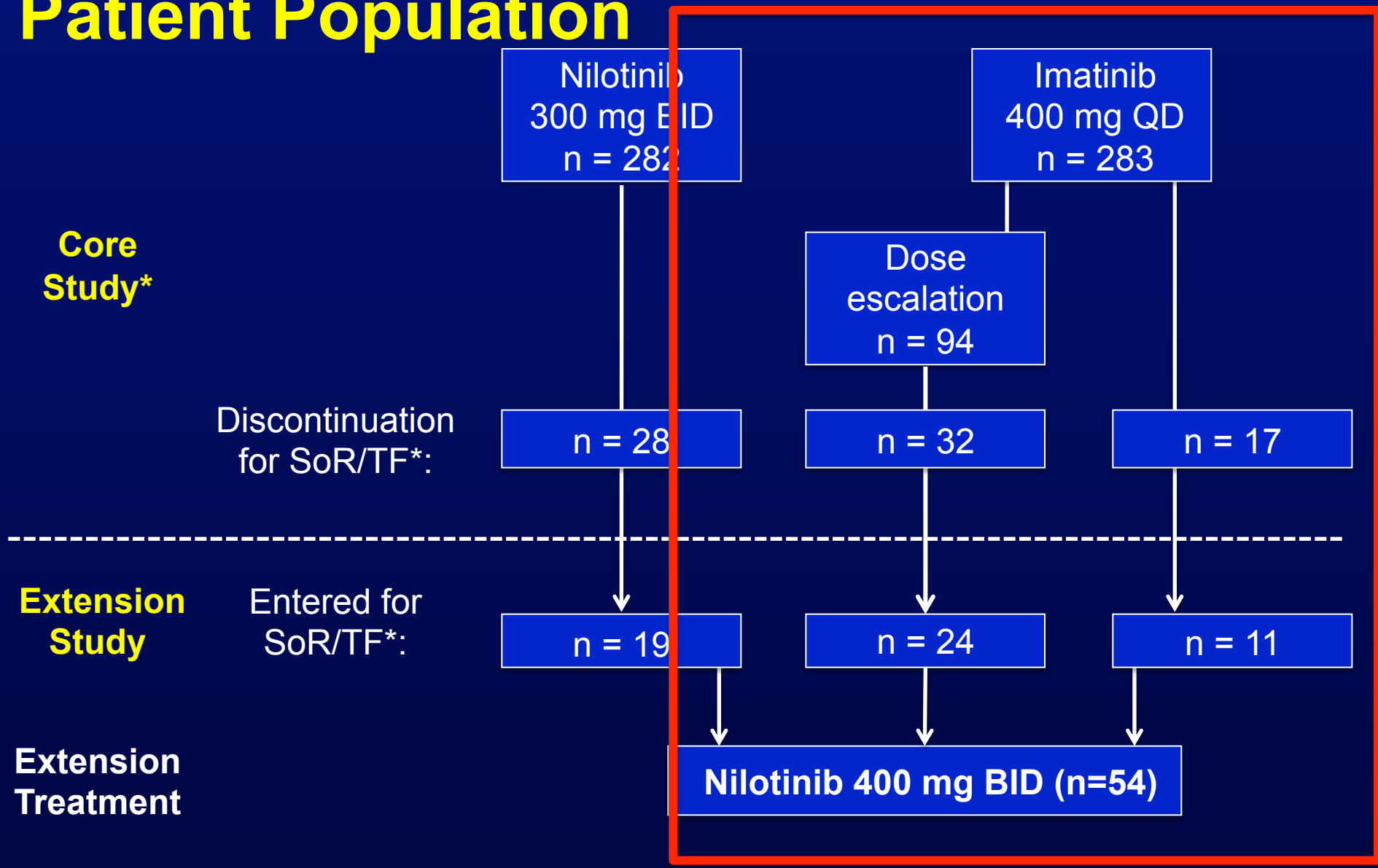


- Patients with SoR/TF on imatinib 400 mg QD (including patients receiving dose escalation to imatinib 400 mg BID) on core study were allowed to enter the extension study receiving nilotinib 400 mg BID
- Patients with SoR/TF on nilotinib 300 mg BID on core study were allowed to enter the extension study receiving nilotinib 400 mg BID

*Of 11 patients who discontinued nilotinib 400 mg BID due to TF in the core study, only 3 entered the extension study and received imatinib 400 mg BID. These patients are not summarized here.

Hochhaus A. et al. ASH 2011

ENESTnd Core and Extension Studies: Patient Population

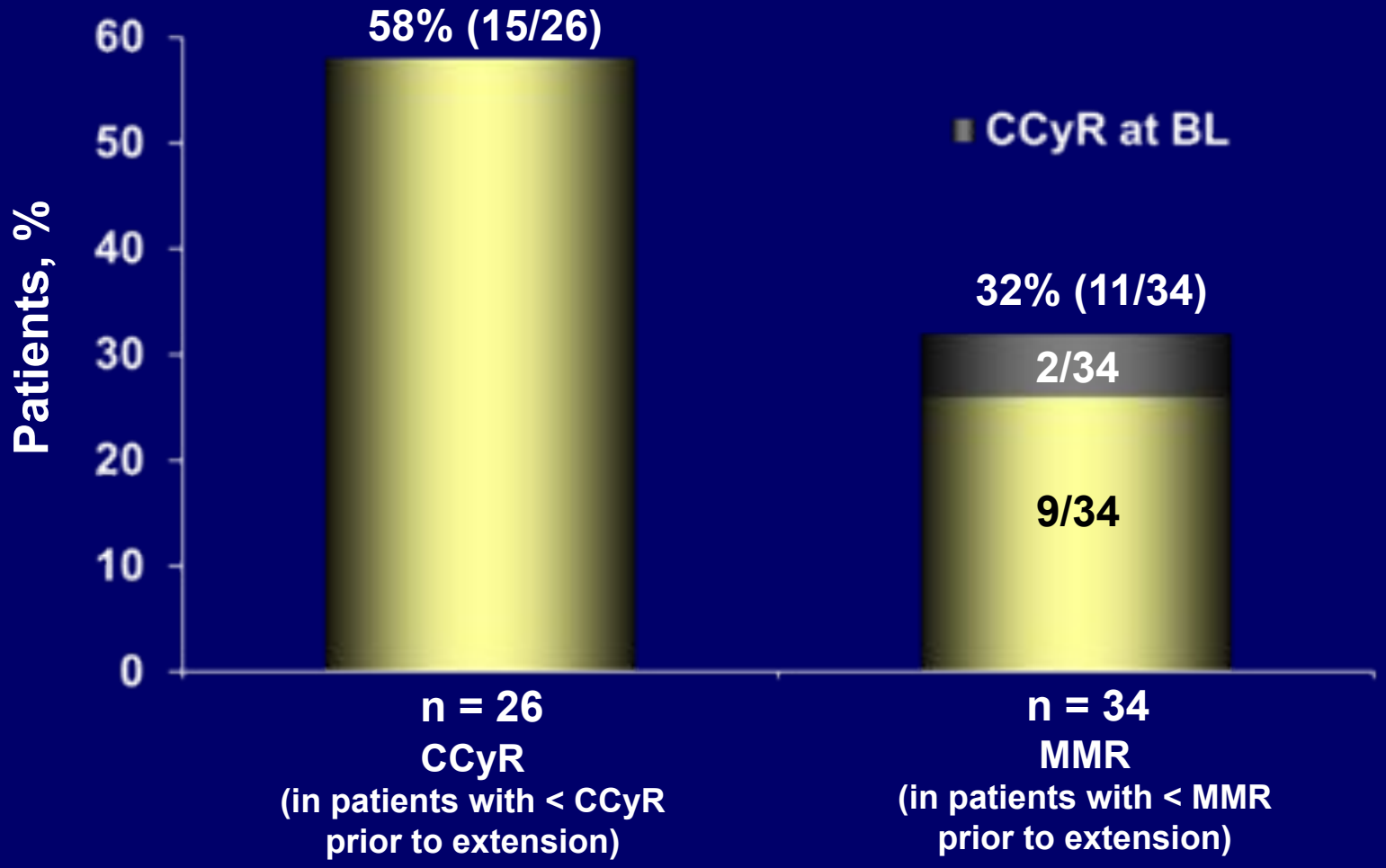


*Progression to AP/BC included as TF.

Hochhaus A. et al. ASH 2011

Data cut-off: 27Jul2011.

Response Achieved On Extension Treatment With Second-line Nilotinib 400 mg BID (n=34)



- 9/15 (60%) patients who had prior imatinib dose escalation achieved CCyR on nilotinib 400 mg BID
- 7/23 (30%) patients who had prior imatinib dose escalation achieved MMR on nilotinib 400 mg BID

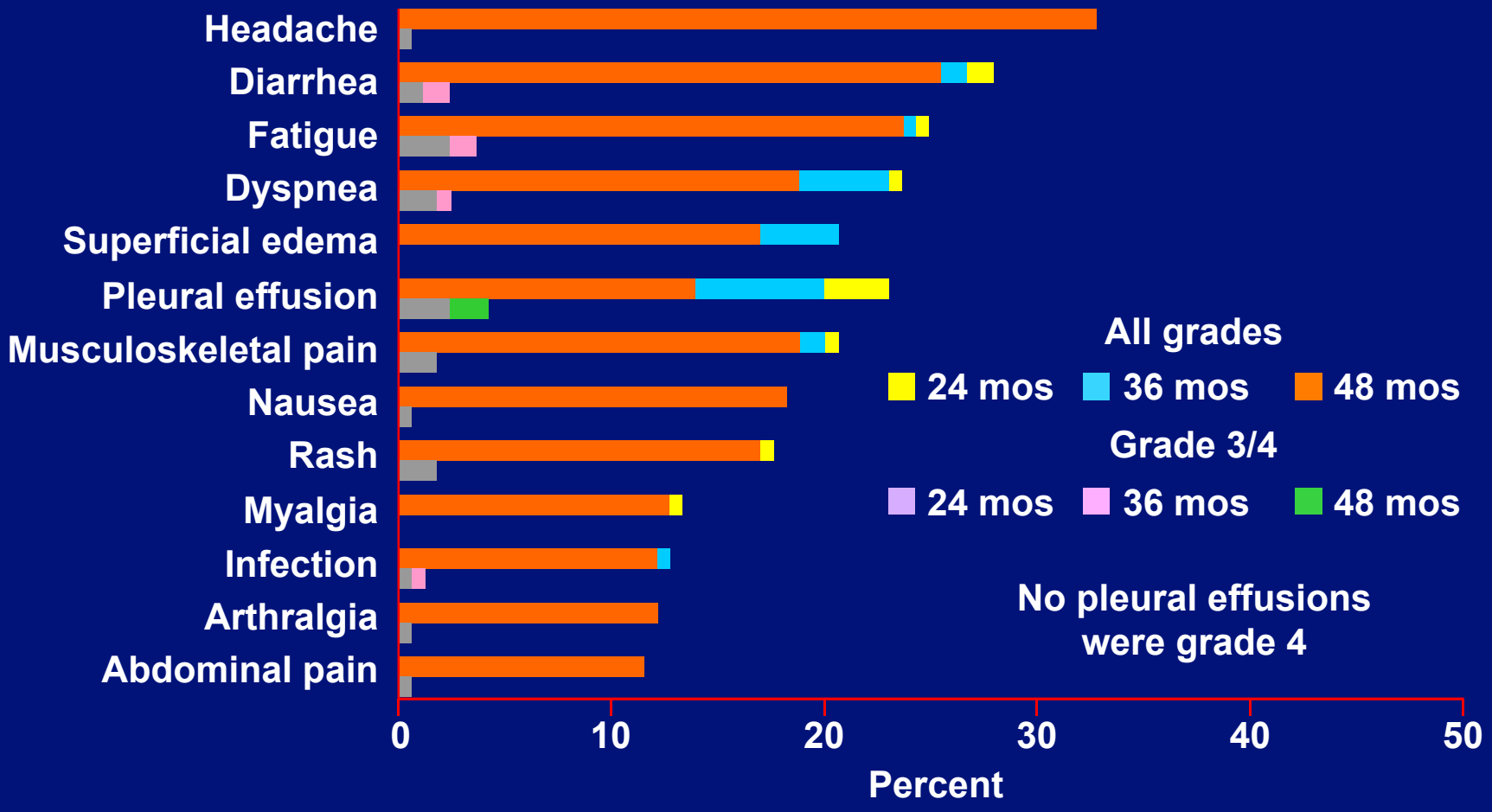
Hochhaus A. et al. ASH 2011

Data cut-off: 27Jul2011.

Recommendation for Dasatinib- or Nilotinib-Resistant Mutants

- Y253H, E255 K/V, F359 C/V
  ⇨ switch to dasatinib
- V299L, F317L
  ⇨ switch to nilotinib
- T315I Resistance against both drugs
  ⇨ ponatinib or transplantation if available option

Drug-related nonhematologic side effects[a] with dasatinib 100 mg QD (n=165)



[a]Reported worst-grade AE with a minimum follow-up of 24, 36 and 48 months

Nilotinib Phase 2 Study: CML-CP

Most Frequent (> 10%) Drug-Related Nonhematologic Adverse Events (N = 321)

Adverse Event	All Grades (%)	Grades 3/4 (%)
Rash	31	2
Pruritus	26	< 1
Nausea	25	< 1
Fatigue	20	1
Headache	18	2
Diarrhea	12	2
Vomiting	13	< 1
Constipation	13	< 1

- Severe nonhematologic adverse events were infrequent on nilotinib therapy

Kantarjian H et al., Blood 2011; 217:1141-45

Kantarjian HM, et al. *Blood*. 2009;114(22):464 [abstract 1129] (poster).

Nilotinib Phase 2 Study: CML-CP

Biochemical Laboratory Abnormalities* (N = 321)

Laboratory Abnormality	Any Grade (%)	Grades 3/4 (%)
Lipase elevation	47	18

What about long-term toxicity?

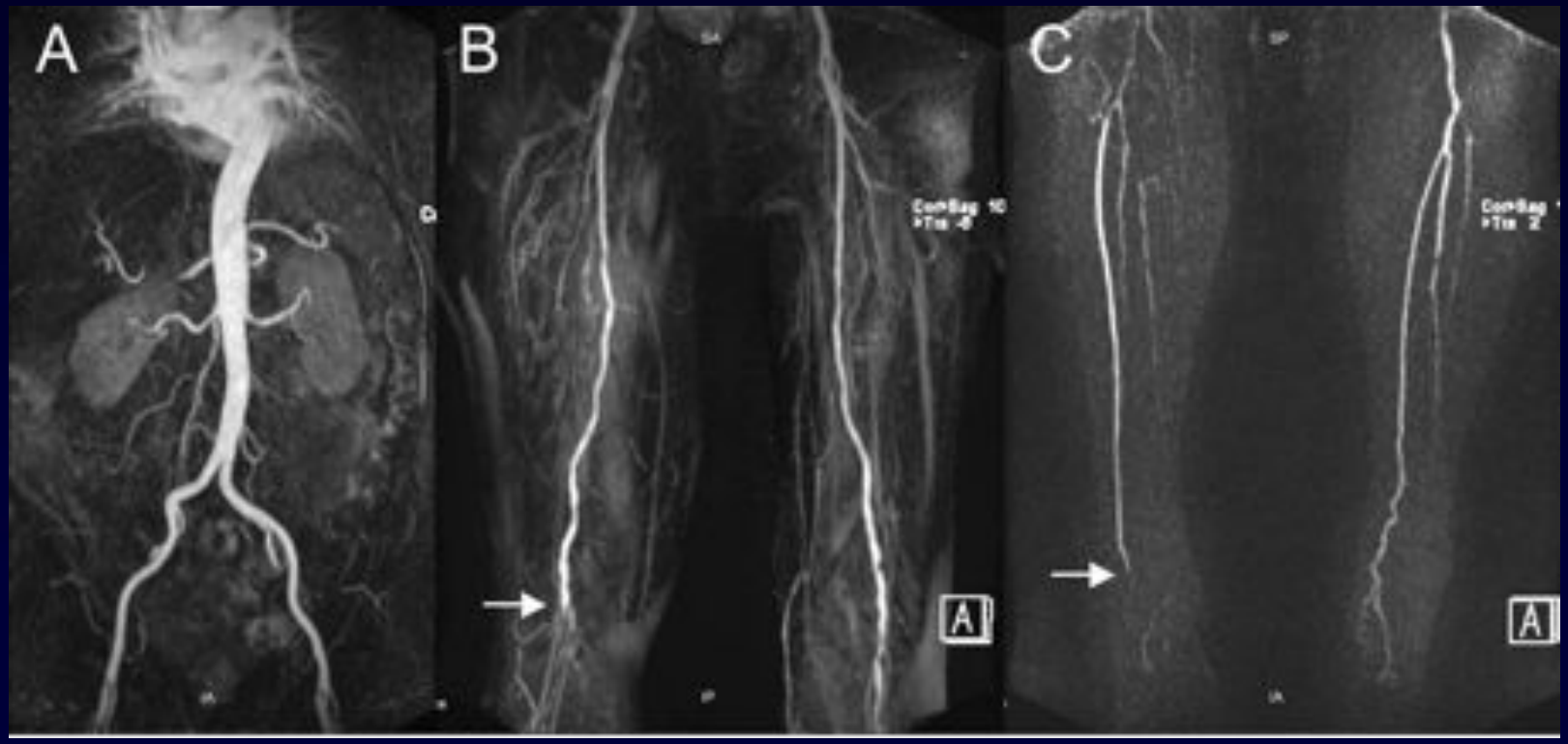
SCT is considered a definitive and curative treatment, whereas TKIs can have long-term toxicity

Kantarjian H et al., Blood 2011; 217:1141-45

Kantarjian HM, et al. *Blood*. 2009;114(22):464 [abstract 1129] (poster).

Progressive peripheral arterial occlusive disease (PAOD) and vascular events during Nilotinib therapy

- 3 out of 24 patients with nilotinib treatment developed PAOD in University of Vienna (AJH 2011;86:533-539) – no previous Hx. – repeated angioplasty and/or multiple surgeries – change to imatinib



Aichberger KJ et al., AJH 2011;86:533-539

PAOD Events At Any Time

Patients, n	Nilotinib 300 mg BID n = 279		Nilotinib 400 mg BID n = 277		Imatinib 400 mg QD n = 280	
	All Grades	Grade 3/4	All Grades	Grade 3/4	All Grades	Grade 3/4
PAOD	4	3	3	0	0	0
With risk factors at BL*	3	3	3	-	-	-
No risk factors	1	0	0	-	-	-
Study drug-related	2	2	0	-	-	-

* Hypertension, hyperlipidemia, diabetes, smoking, preexisting CV disease.
BL, baseline.

- Prevalence of PAOD is over 10% in people > 60 years of age[1]
- 2 new cases of PAOD occurred in the nilotinib 400 mg BID arm since the 2-year analysis
  - No PAOD event led to treatment discontinuation during the study
  - Most patients with PAOD had pre-existing risk factors
  - No patient discontinued due to PAOD

1. Criqui M, et al. *Vasc Med.* 2001;6:3-7.

Data cut-off: 27Jul2011.

Pulmonary Arterial Hypertension in Patients Treated by Dasatinib

- From the approval of dasatinib in France 9 cases treated by dasatinib at the time of PH diagnosis were identified.
- At diagnosis, patients had moderate to severe pre-capillary PH with functional and hemodynamic impairment.
- Clinical and/or haemodynamic improvements were observed within 4 months of dasatinib discontinuation in all but one patient.
- Three patients required PH treatment with endothelin receptor antagonist (n=2) or calcium channel blocker (n=1).
- After a median follow-up of 9 months, the majority of patients failed to demonstrate complete clinical and hemodynamic recovery and no patients reached a normal value of mean pulmonary artery pressure (≤20 mmHg)

Montani et al, Circulation 2012

Considerations

- Most of these complications have been described in patients not even suitable for SCT (age, performance status etc…)

- Longer the treatment and the exposition to TKIs and greater the risk of long-term toxicity even for jounger patients?
- Probably yes, but no data at the moment

- Possibility of discontinuation even with second generation TKIs if a good molecular response is achieved

STABLE MMR BY 6 MONTHS

- Following 2G-TKI cessation, 8 pts lost MMR after a median time off-therapy of 2 months (2-5)

However I should admit that the SCT can probably become again an actractive therapeutic option for specific groups of CML patients?

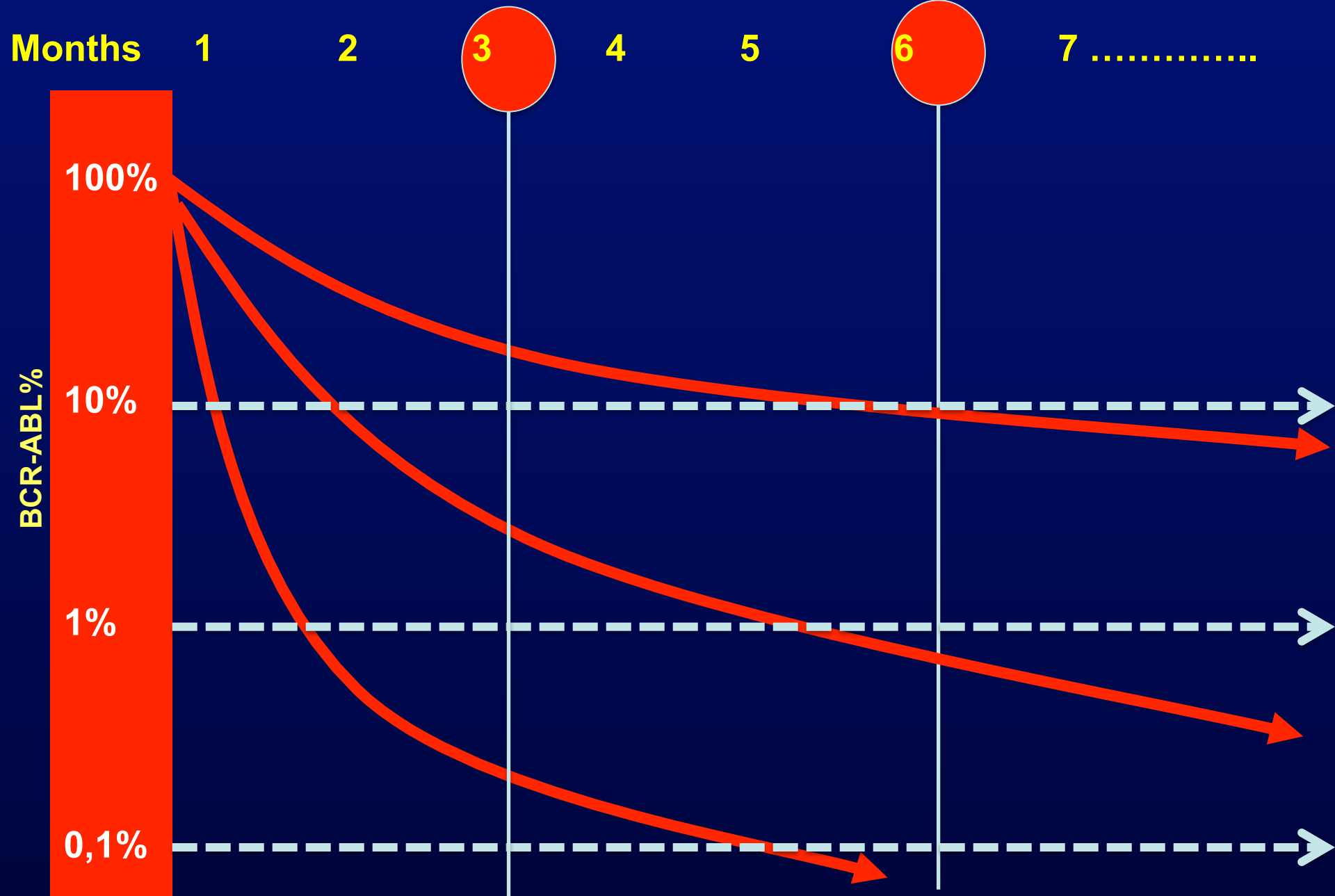
Rea D. ASH 2011

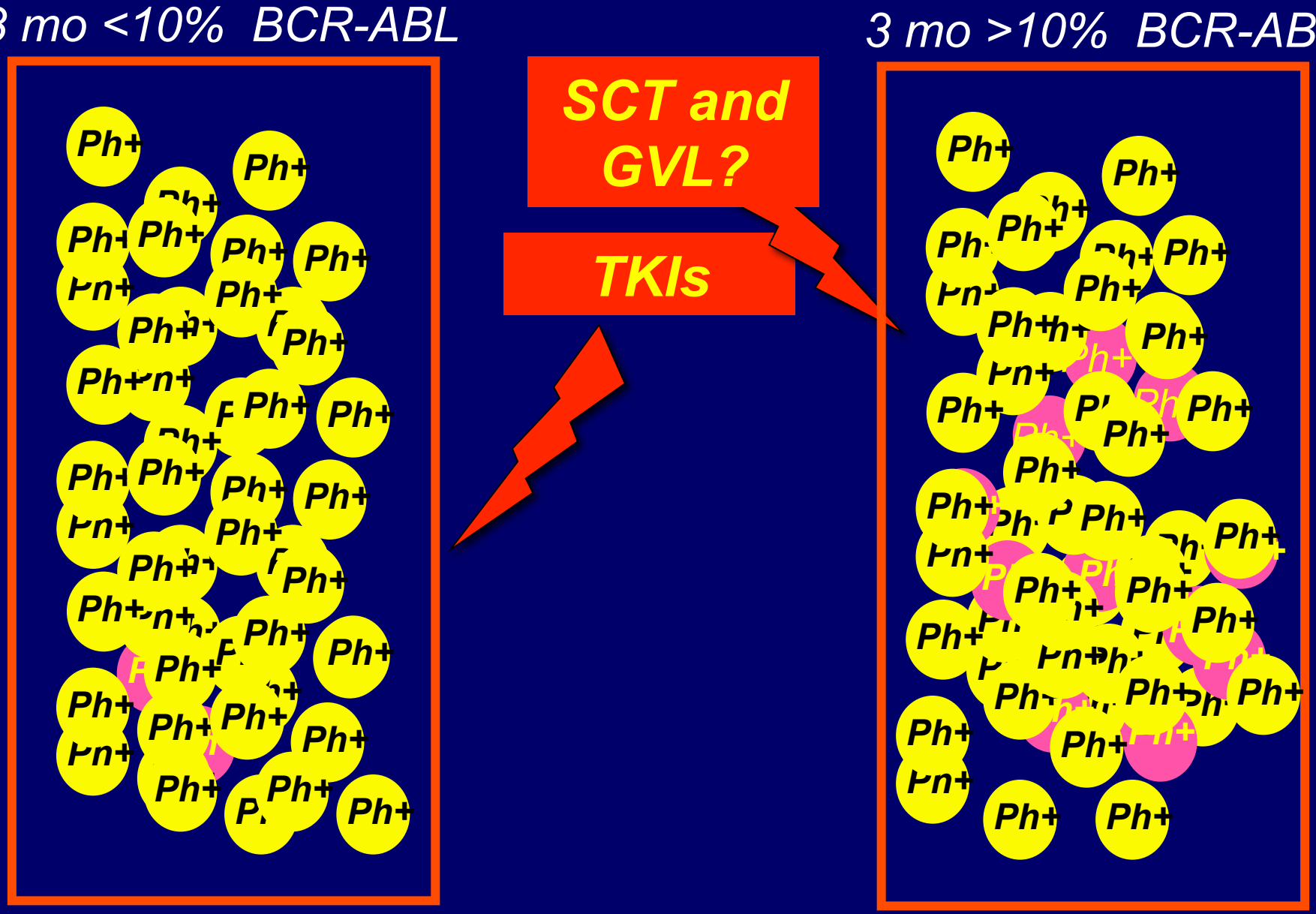
“BCR-ABL1 Transcript Levels at 3 Months Is the Only Requirement for Predicting Outcome for CML Patients Treated With TKIs”

Outcome	RR for Transcript Level (Log) RR	*P*	Cutoff (%)	No. of Patients at Risk	8-Year Probability of the Outcome %	*P*
BCR-ABL1 transcript level at 3 months						
OS	0.161	< .001				< .001
Low risk			≤ 9.84	211	93.3	
High risk			> 9.84	68	56.9	
PFS	0.162	< .001				< .001
Low risk			≤ 9.54	208	92.8	
High risk			> 9.54	71	57.0	
EFS	0.102	< .001				< .001
Low risk			≤ 9.84	211	65.1	
High risk			> 9.84	66	6.9	
CCyR	5.17	< .001				< .001
Low risk			≤ 8.58	169	99.4	
High risk			> 8.58	79	21.7	
MMR	12.98	< .001				< .001
Low risk			≤ 2.81	141	82.5	
High risk			> 2.81	137	21.1	
CMR	10.95	< .001				< .001
Low risk			≤ 0.61	57	84.7	
High risk			> 0.61	222	1.5	

Marin D., JCO 2012

Differences in early kinetics of response
WHY?




3 mo <10% BCR-ABL
3 mo >10% BCR-ABL
SCT and GVL?
TKIs
Ph+

Thank you!