

AUBH 2012 Debate:
Optimal therapy for first line treatment of CML
Cure vs. Control ?

In favor of control

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TKI changed the treatment of CML

Cure by Allo-SCT, 1970-2000s



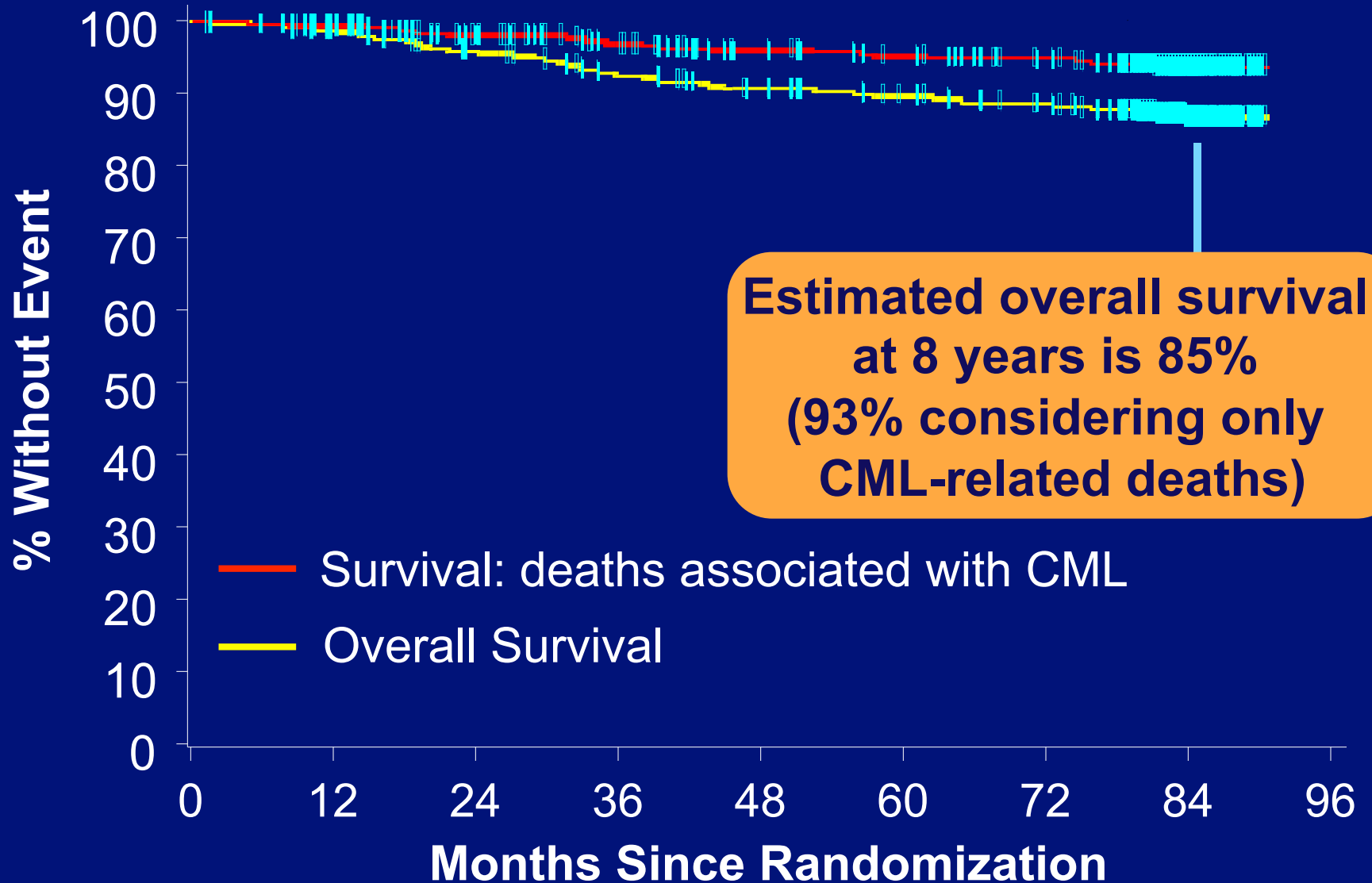
CCyR by Interferon, 1980-2000s

MMR by 1st TKI--Imatinib, 2001-2010



CMR by 2nd TKI- Dasatinib, Nilotinib, 2011-

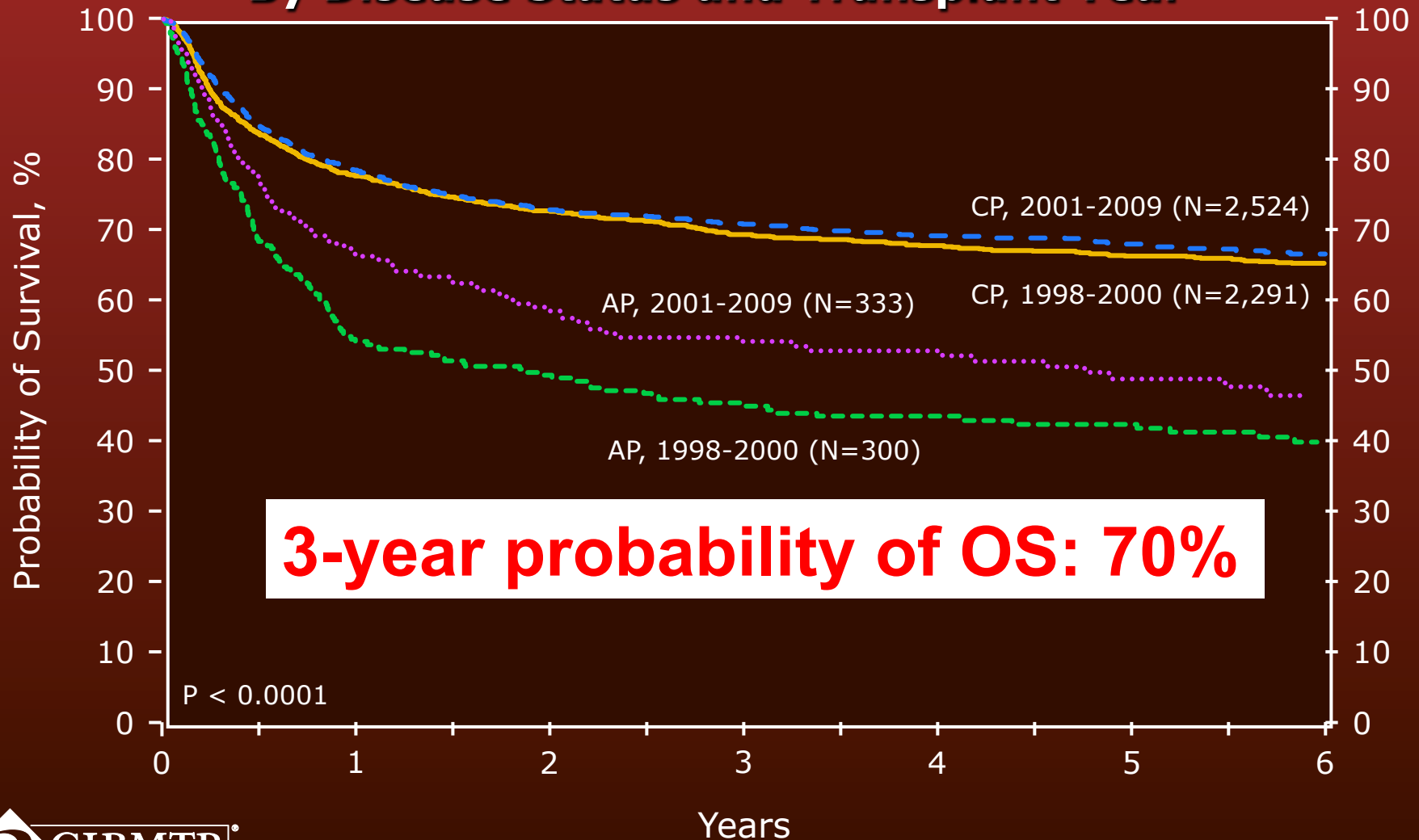
Overall Survival (ITT Principle): Imatinib Arm



Estimated overall survival at 8 years is 85% (93% considering only CML-related deaths)

Probability of Survival after HLA-identical Sibling Donor Transplants for CML, 1998-2009

- By Disease Status and Transplant Year -



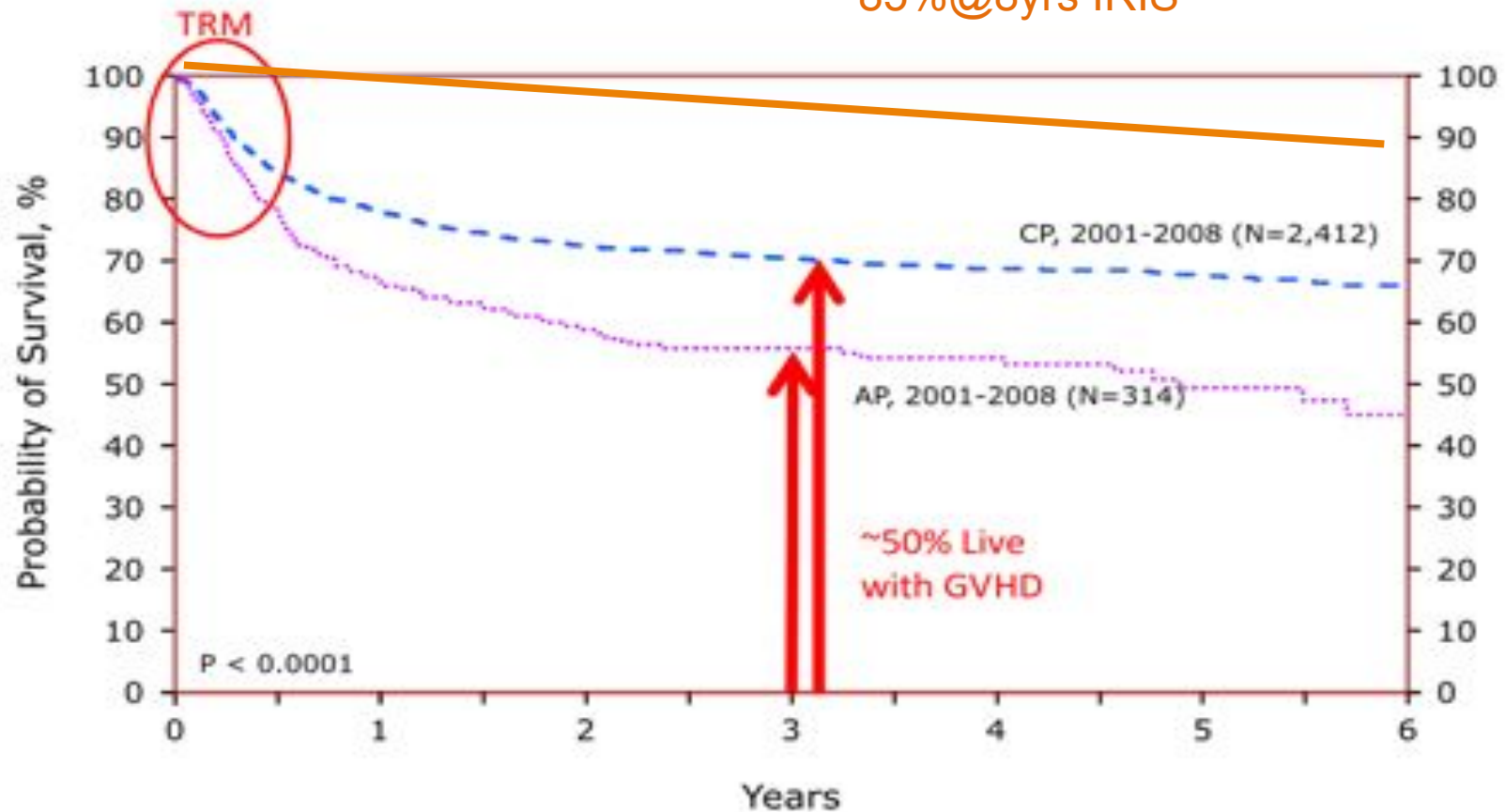
3-year probability of OS: 70%

P < 0.0001

TKIs >20% OS advantage than allo-SCT

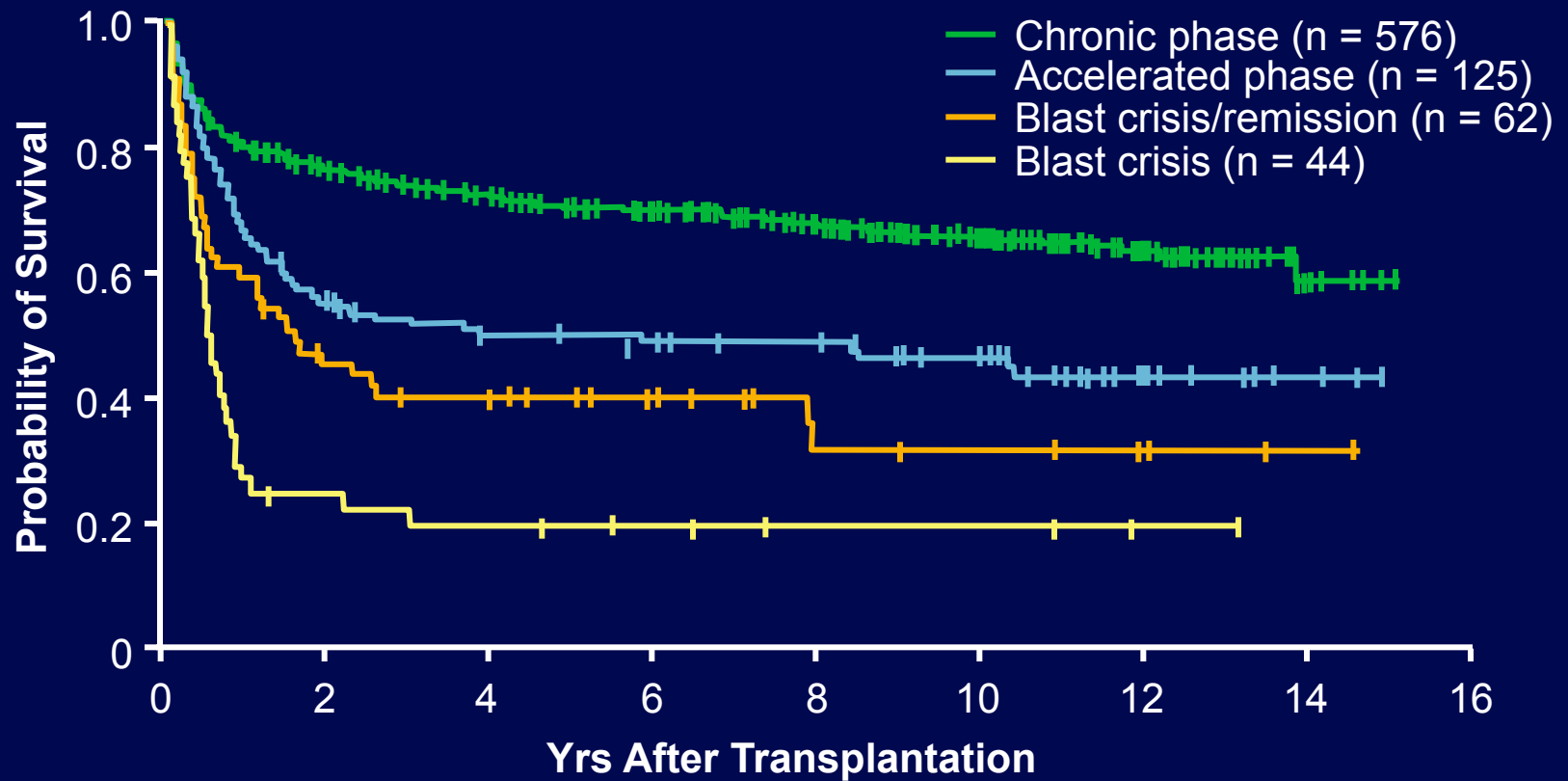
→ Mostly come from the risk of early TRM

85% @ 8yrs IRIS



Late mortality after allo-HSCT for CML

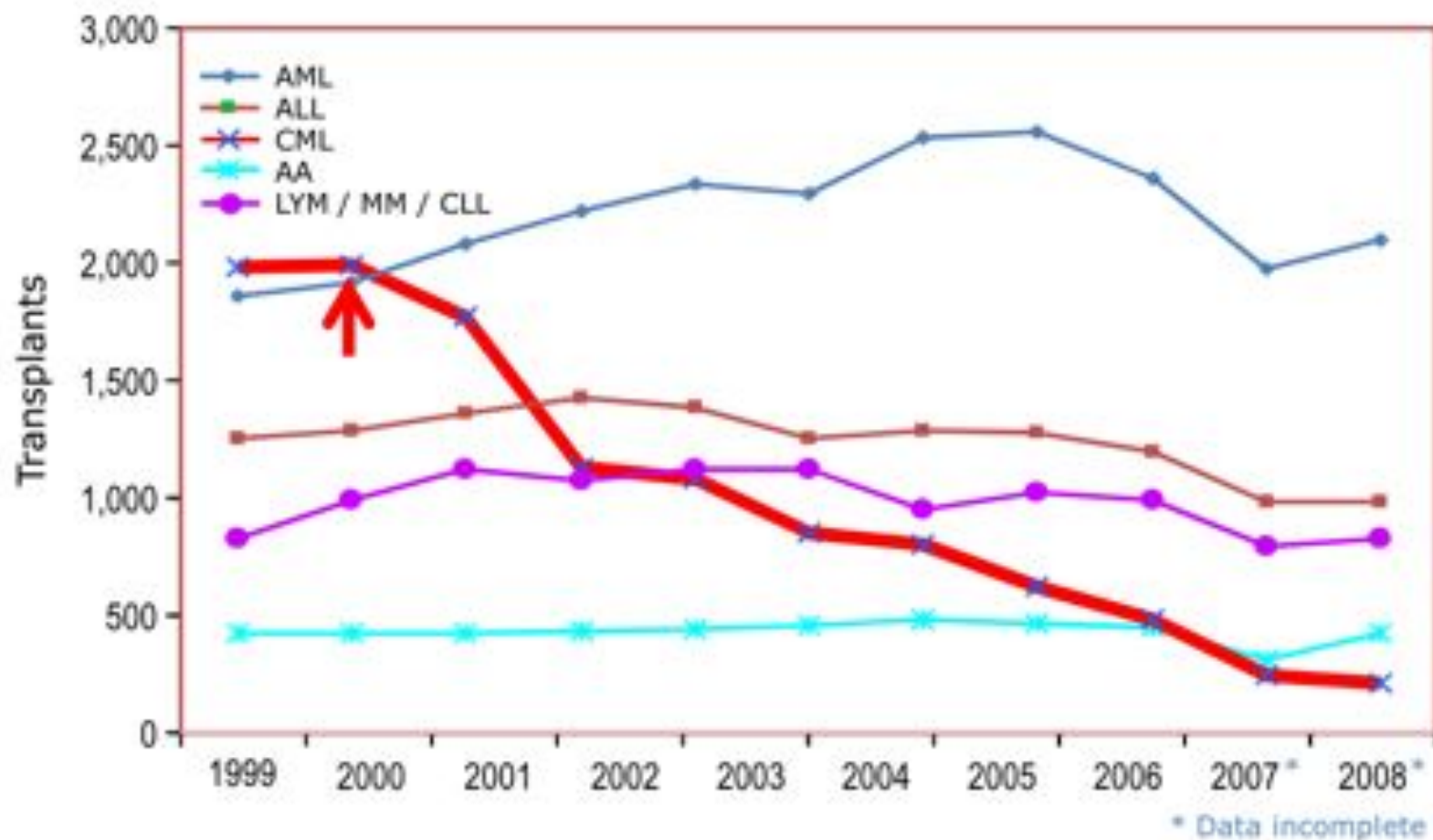
Fred Hutchinson CRC data, 1995-2010



*Includes both matched related and unrelated donors.

Patients receiving allografts at the Fred Hutchinson Cancer Research Center from 1995 to the present. Figure is courtesy of Dr. Ted Gooley. Reprinted with permission.

Allo-SCT for CML Decreased Dramatically



CIBMTR 1998-2008, online data

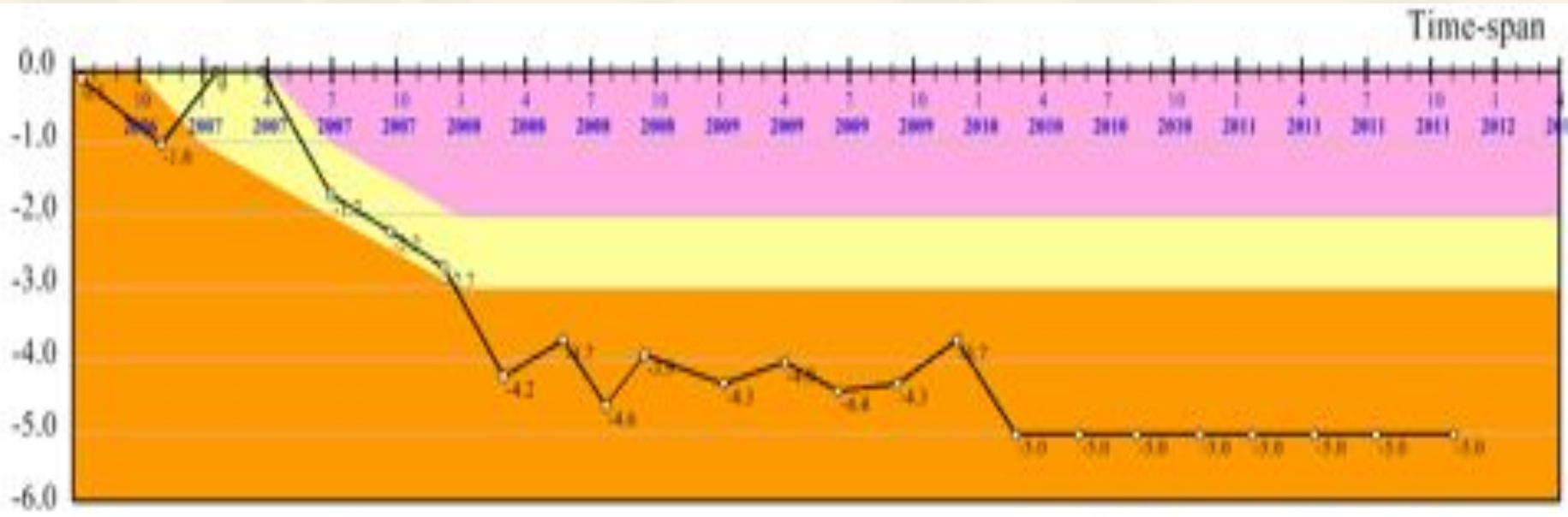
CML: Treatment goal

1. International guidelines (ELN, NCCN, etc)
 - 12M: CCyR
 - 18M: MMR
2. Prevent emergence of resistance
3. Prevent progression to AP/BC
4. Quality life

Case Study 1

Male 54 y/o

2006 CML, CP, t(9;22), started IM 400 mg/day



Interpretation:

CML in durable MMR since IM 18M, in durable CMR since IM 4 yrs

Case Study 2

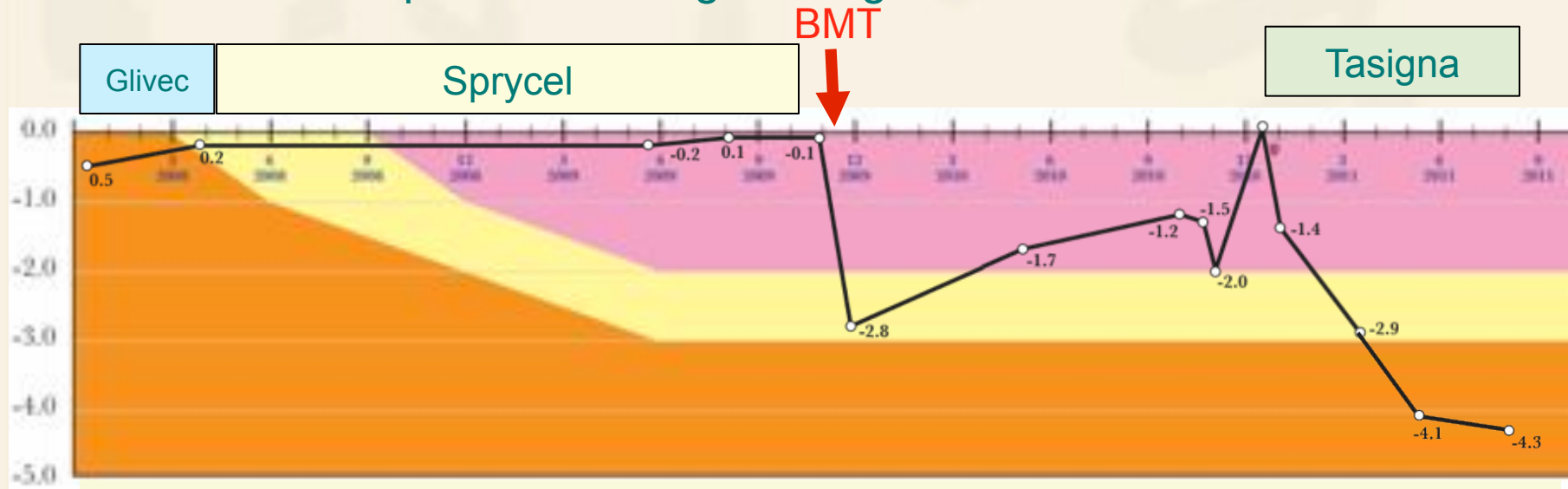
Male 23 y/o

2007-12 CML, CP, t(9;22), started IM 400 mg/d ⇒ intolerance

RQ-PCR no molecular response, switch to Sprycel

2009-08 t(9;22) 100% ⇒ alloH SCT

2011-01 relapsed ⇒ Teasing 800 mg/d



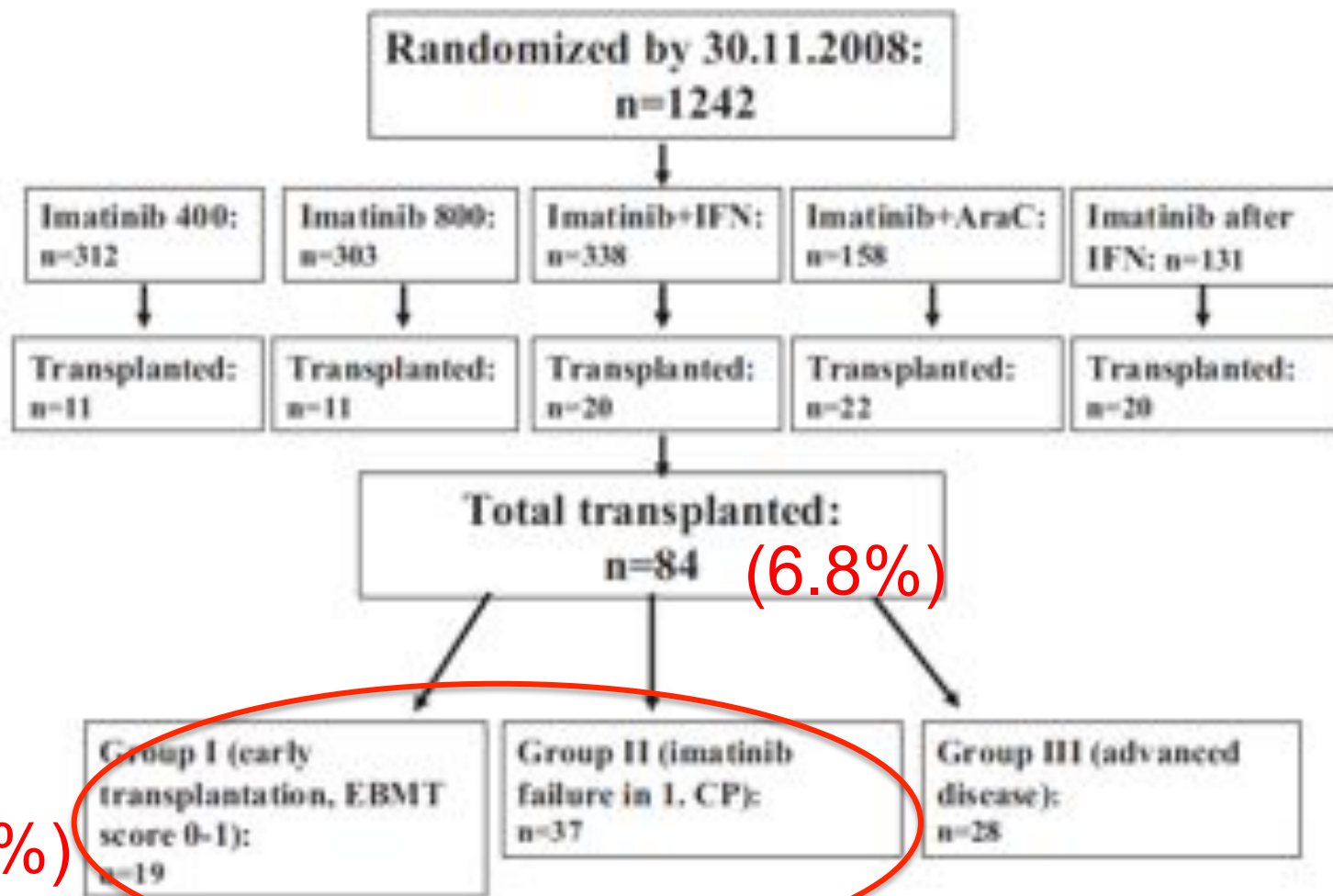
Interpretation:

CML intolerance to IM, resistance to Sprycel and BMT, excellent response to Teasing, in MMR

Upfront HSCT for CML: possible situation

1. CML-CP with poor sokal risk and low HSCT risk score
2. Pediatric CML
3. De novo onset of AP/BC
4. Economic issues

Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV



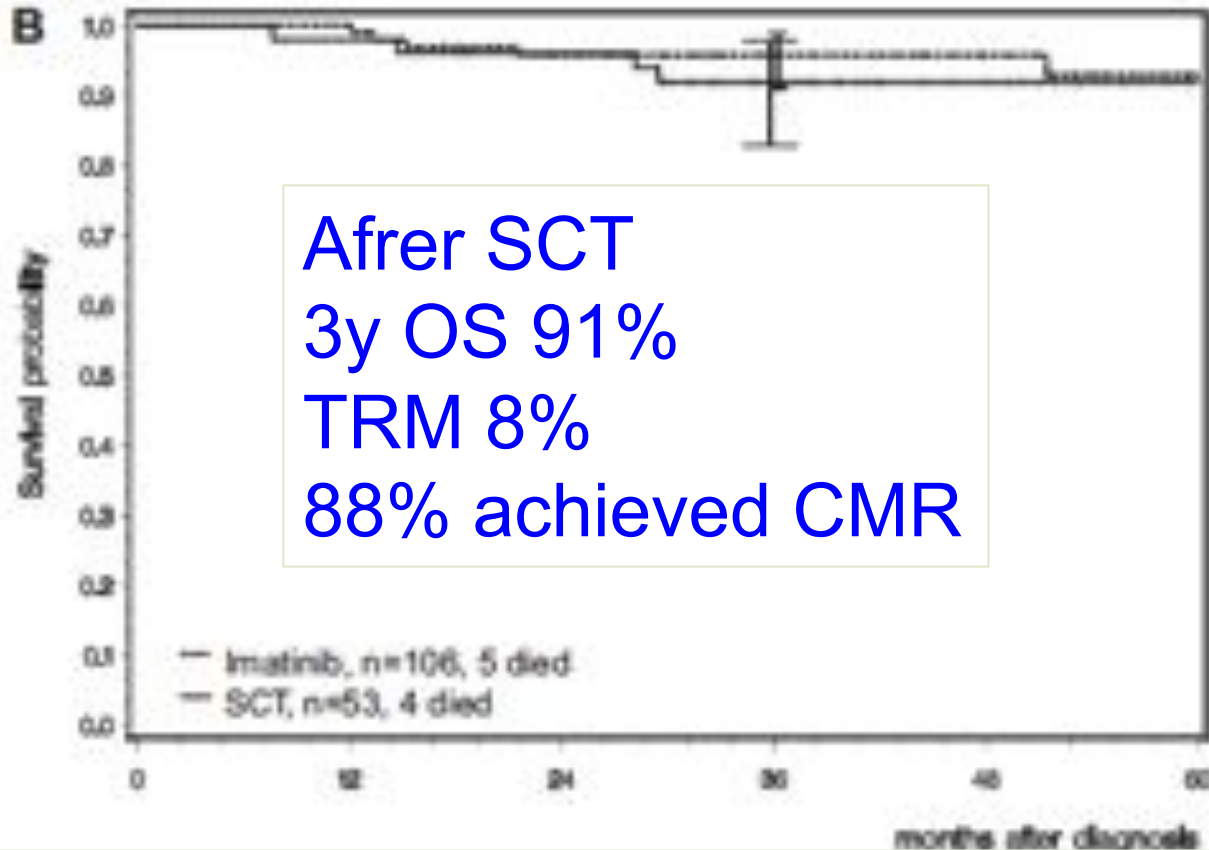
Blood. 2010;115:1880-1885

Allogeneic hematopoietic stem cell transplantation (allo SCT) for chronic myeloid leukemia in the imatinib era: evaluation of its impact within a subgroup of the randomized German CML Study IV

Table 1. Patient characteristics of 106 matched imatinib-treated patients and 53 patients who underwent transplantation in first CP (matched pair analysis)

	Transplantation	Imatinib
No.	53	106
Sex, % male	56.6	56.6
Median age, y	37	36.5
EURO risk score, %		
Low	41.5	41.5
Intermediate	35.8	35.8
High	22.6	22.6

No survival difference between SCT and IM for CML-CP

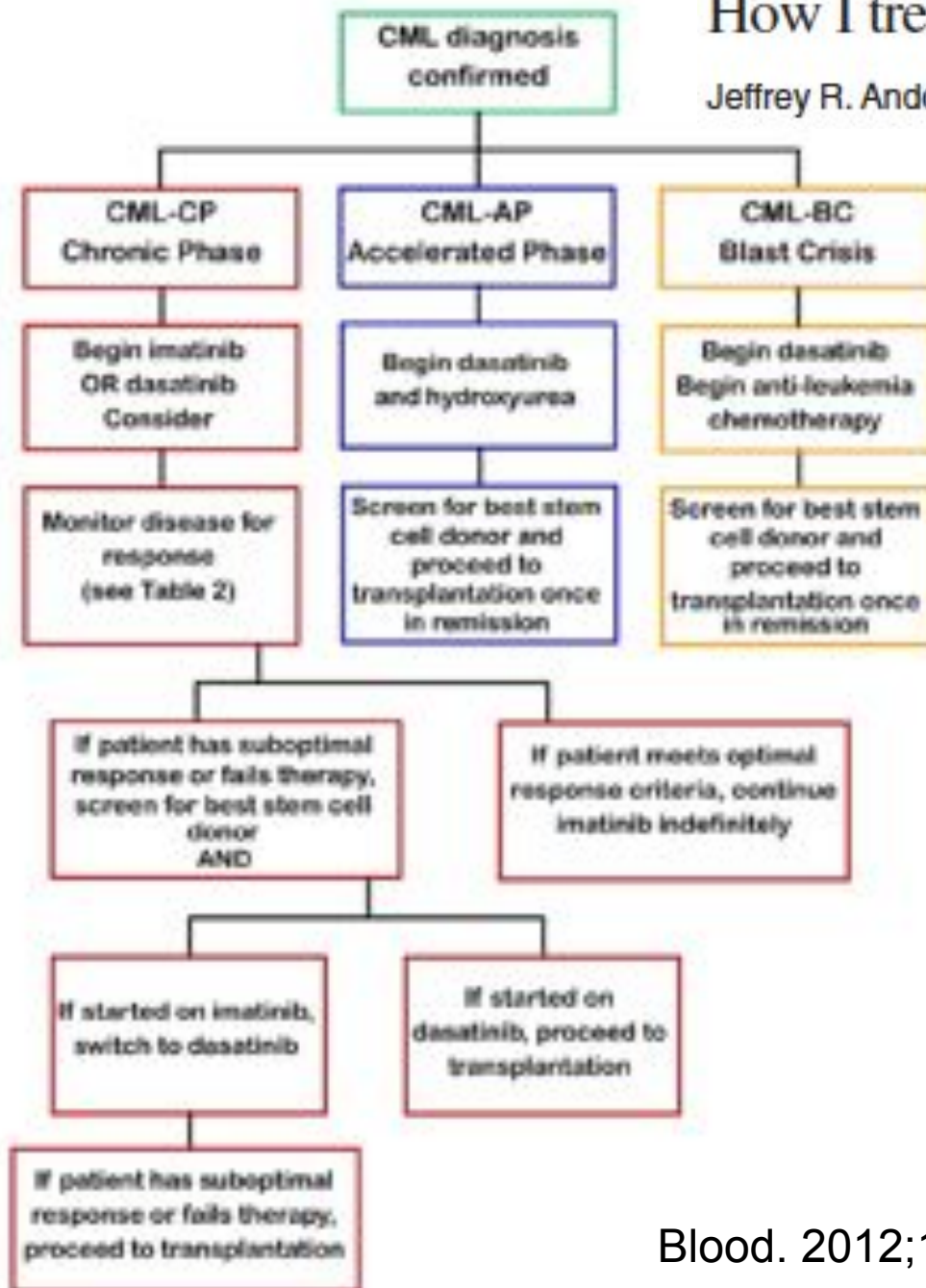


Author conclusion:

Allo SCT could become the preferred second-line option after imatinib failure for suitable patients with a donor.

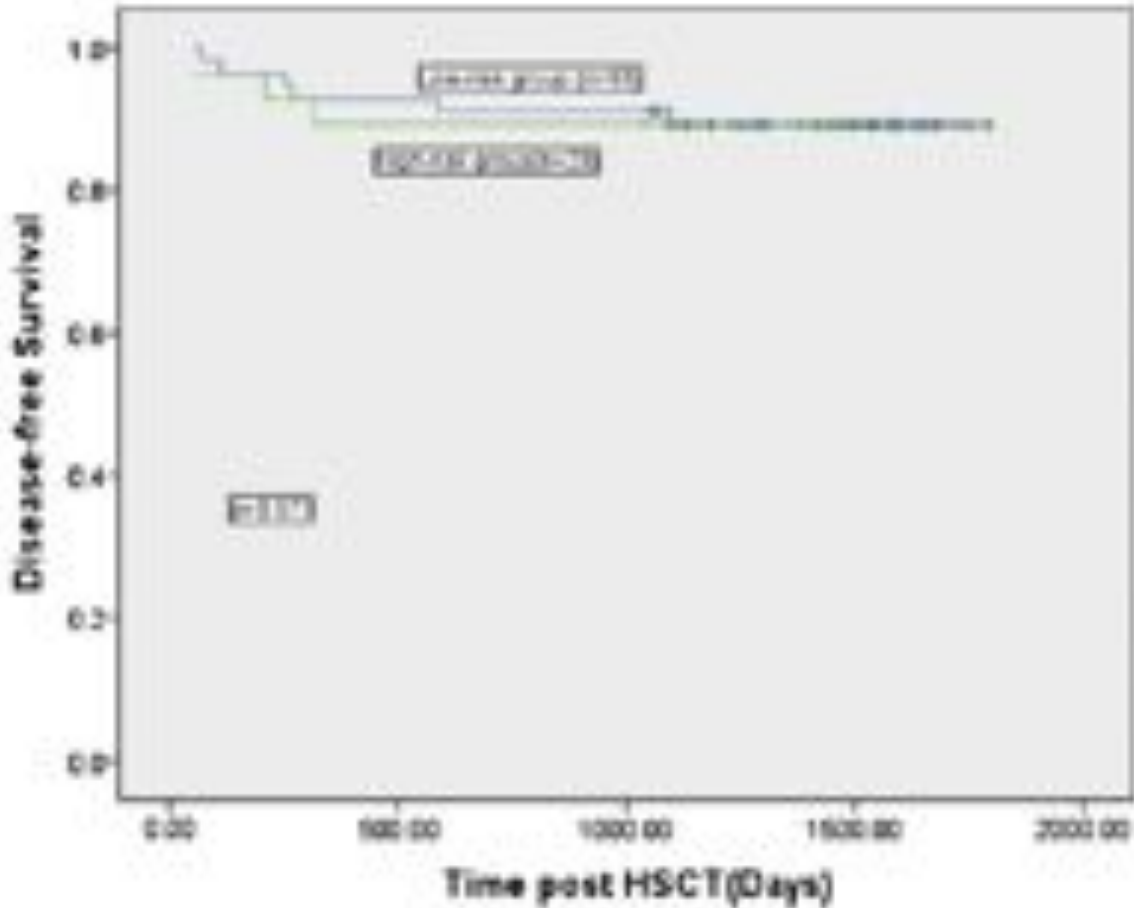
How I treat childhood CML

Jeffrey R. Andolina,¹ Steven M. Neudorf,² and Seth J. Corey³



Blood. 2012;119:1821-1830

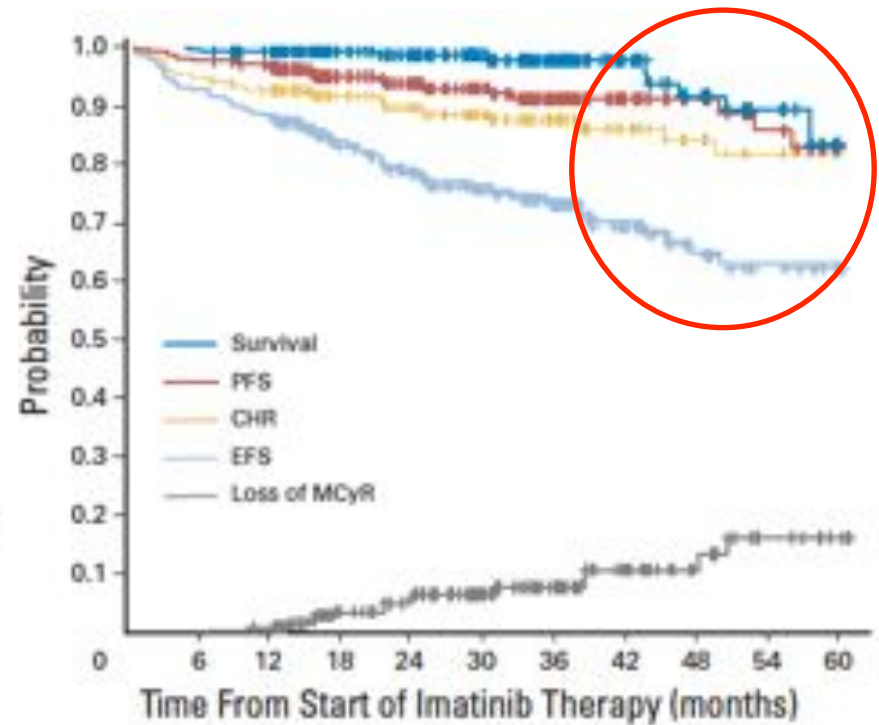
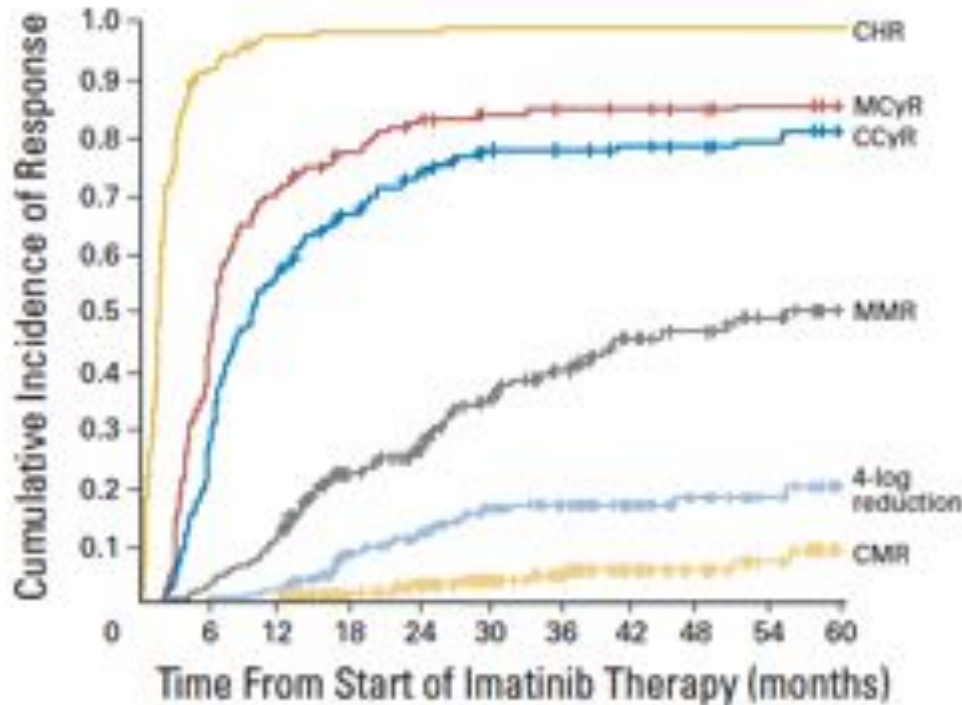
If money becomes the key issue



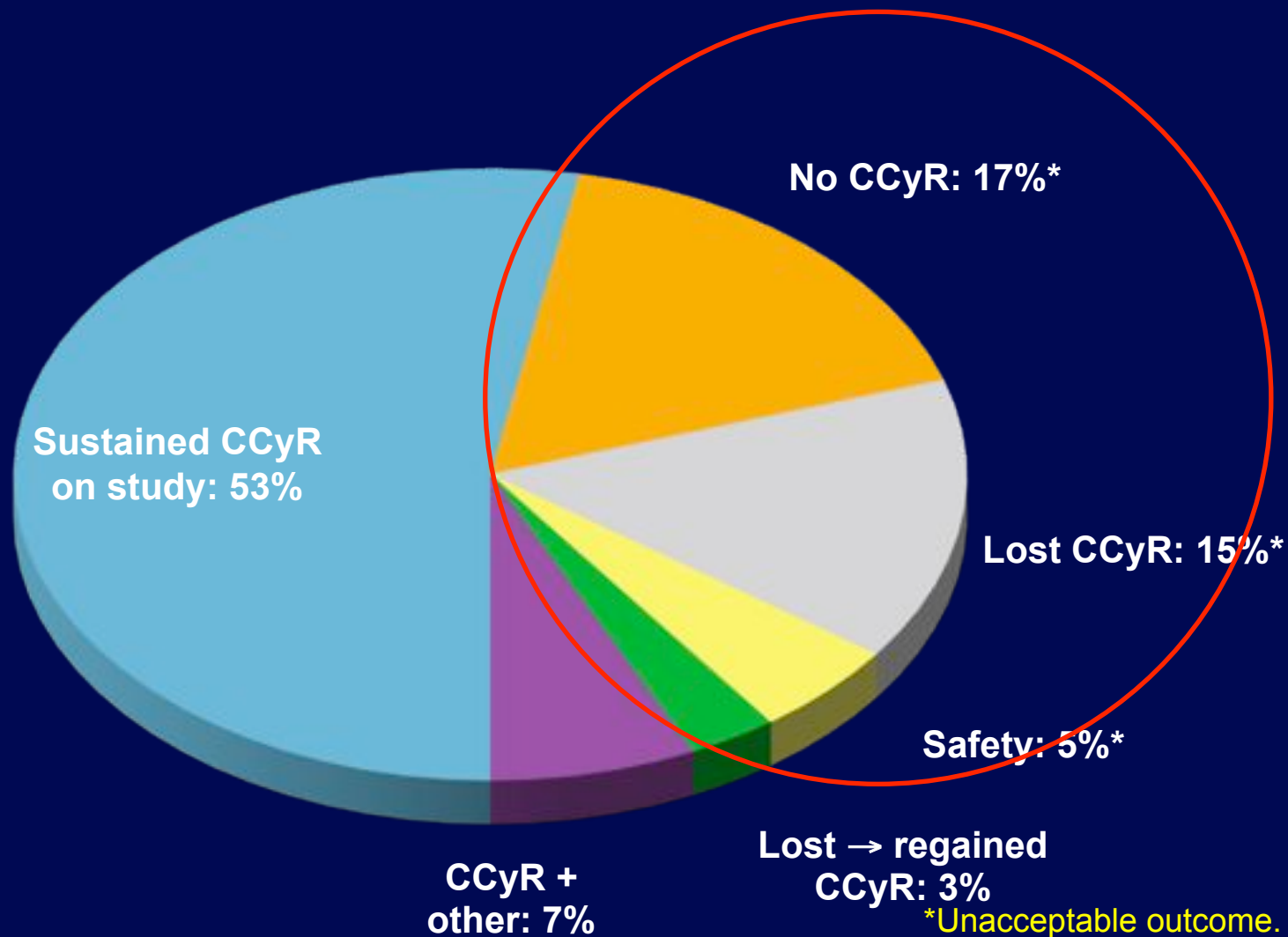
Biol Blood Marrow Transplant 17:649-656, 2011

One concern: Late events in a real world

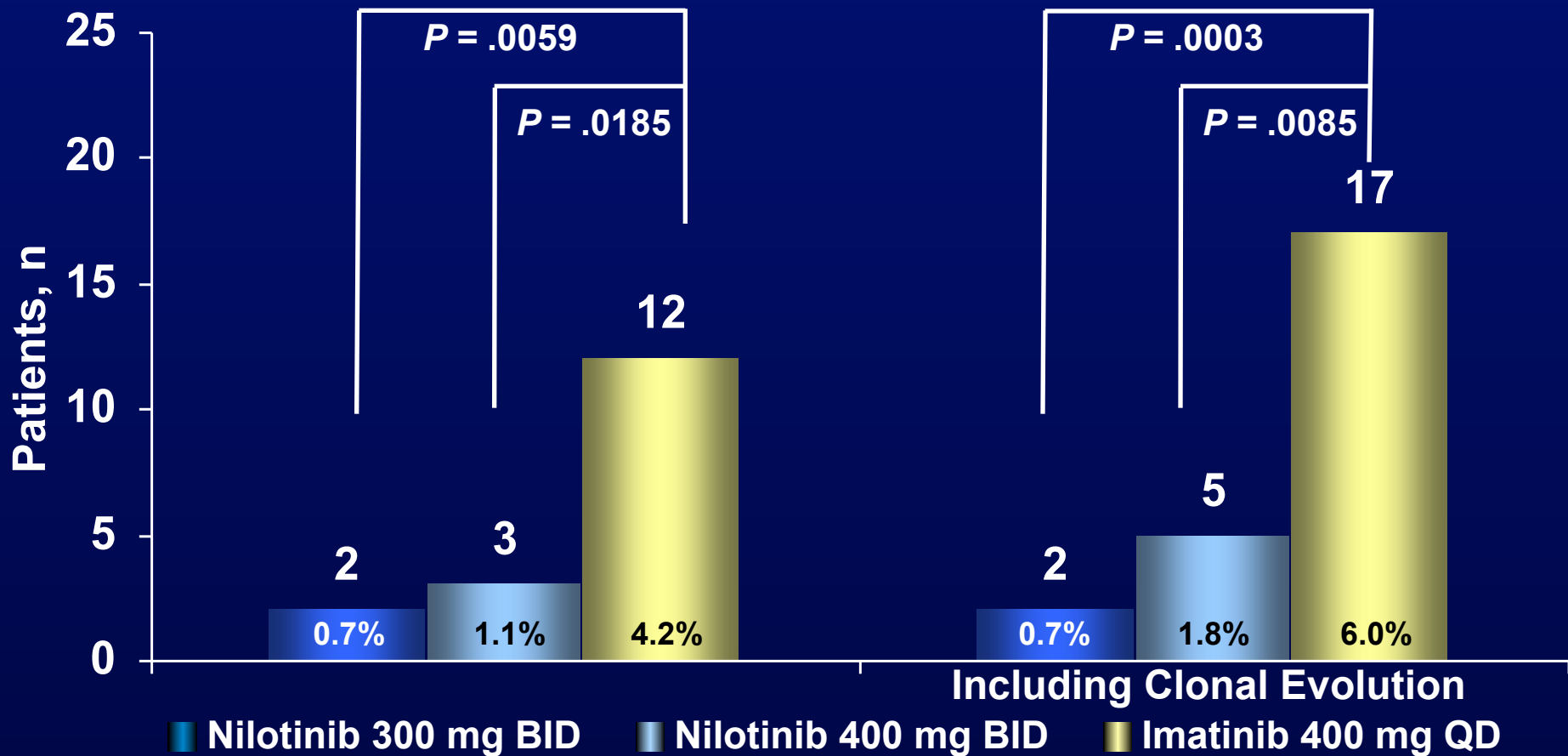
Hammersmith H, 2000-2006, N=204, ITT analysis



IRIS 8-Yr update: 37% unacceptable outcome

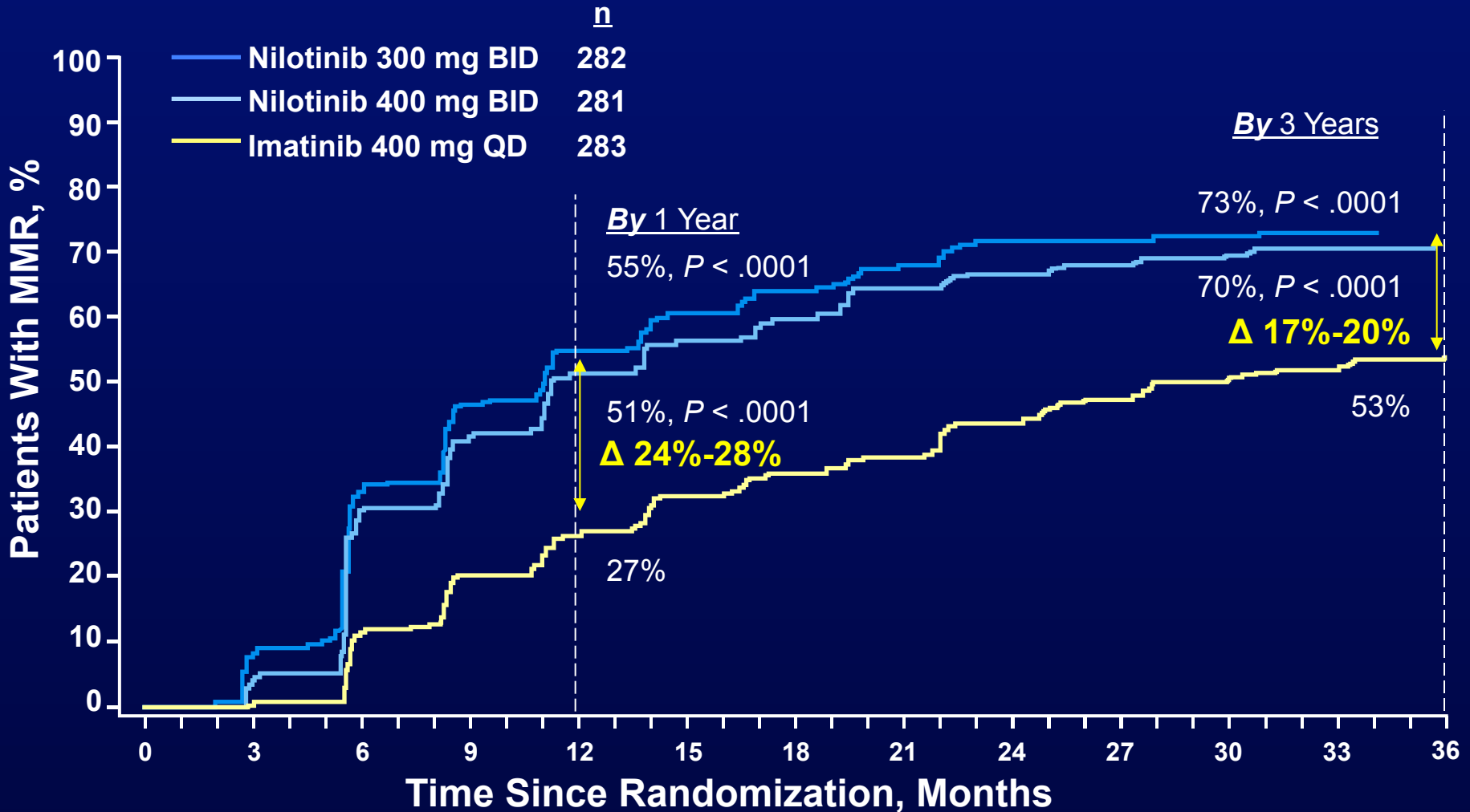


Progression to AP/BC on Treatment



- No new progressions on treatment were observed since the 2-year analysis
- Nilotinib has a significantly lower risk of progression than imatinib

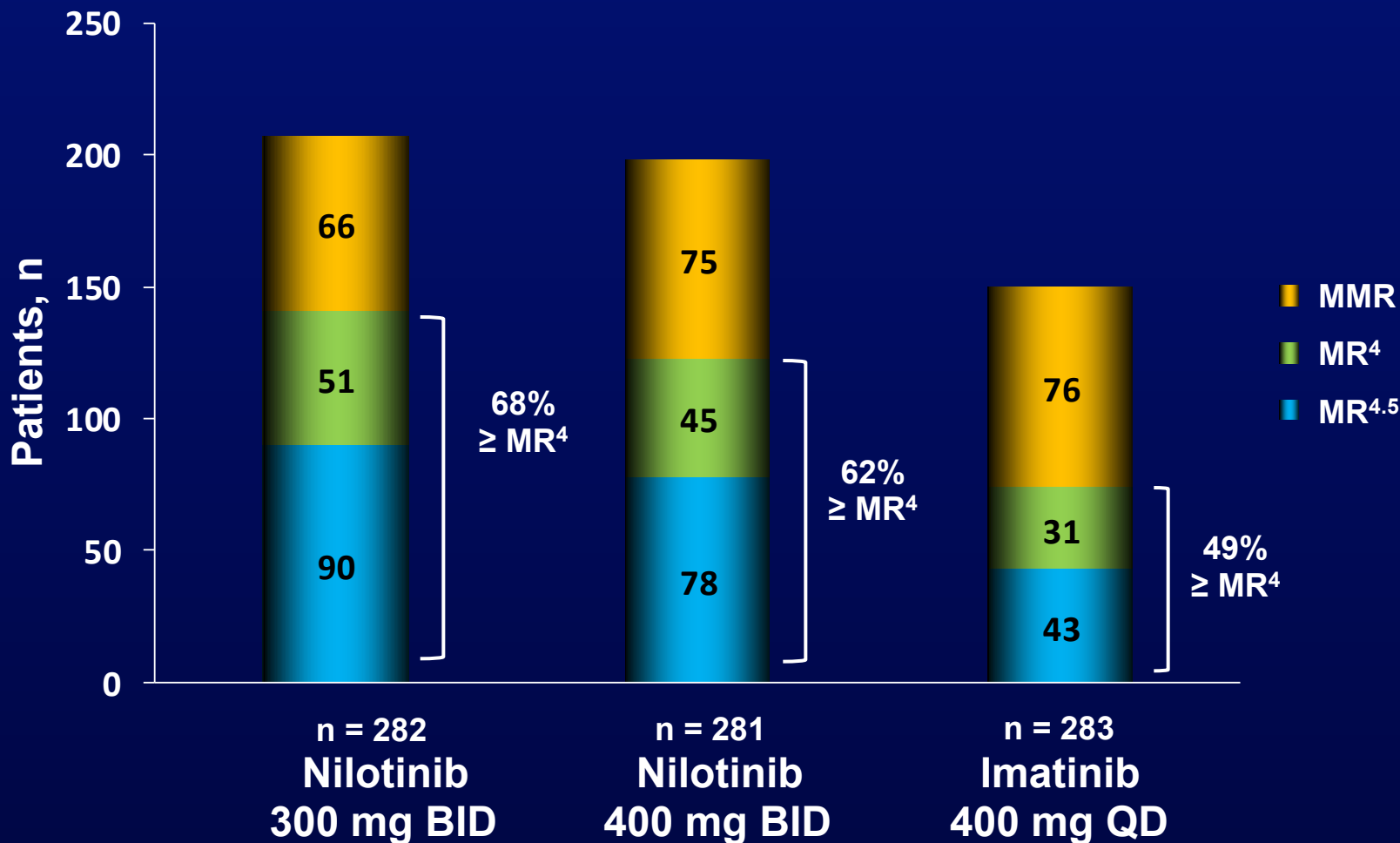
Cumulative Incidence of MMR*



* Equivalent to BCR-ABL transcript levels of $\leq 0.1\%$ (International Scale, IS). 20

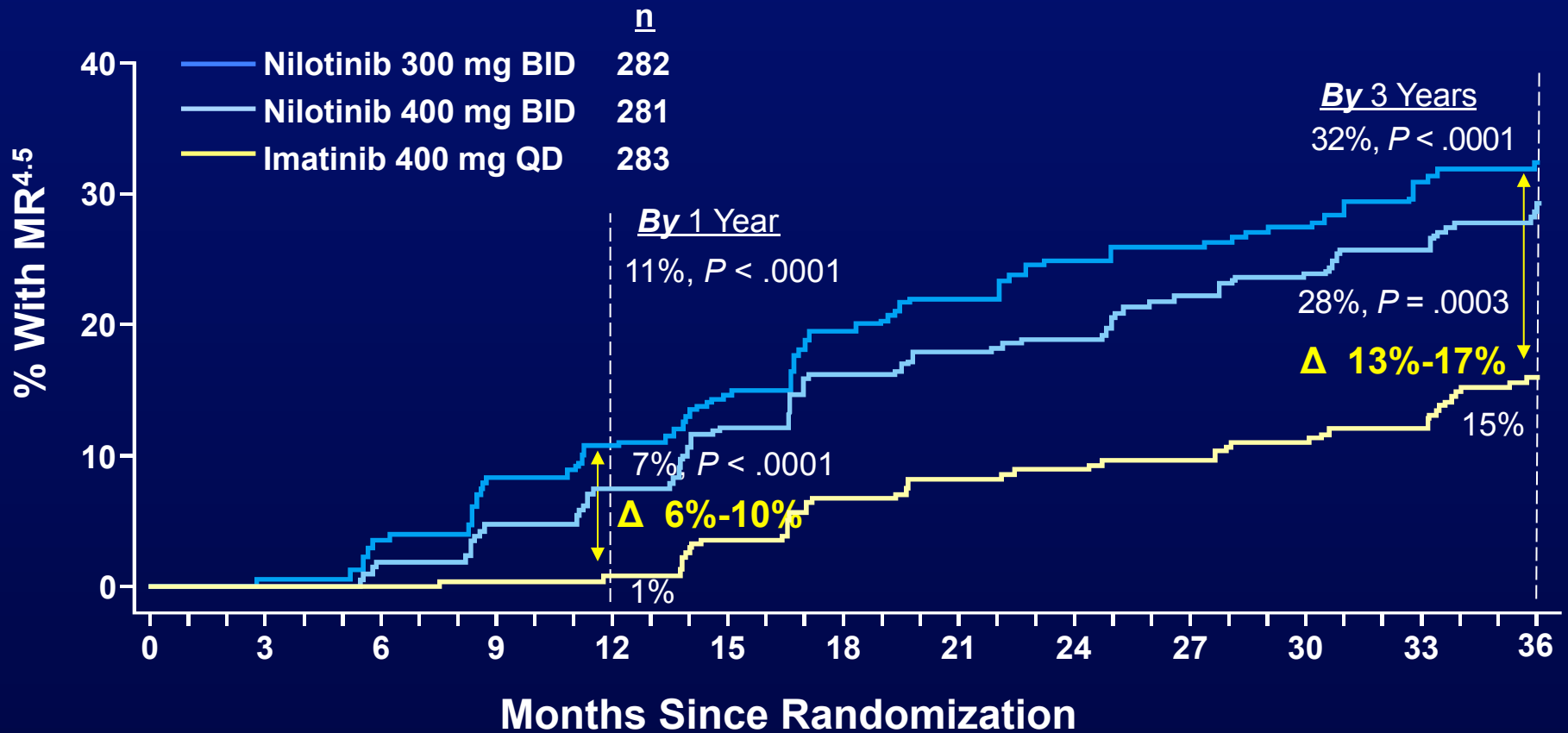
Data cutoff: 27Jul2011.

Depth of Molecular Response in Patients With MMR by 3 Years



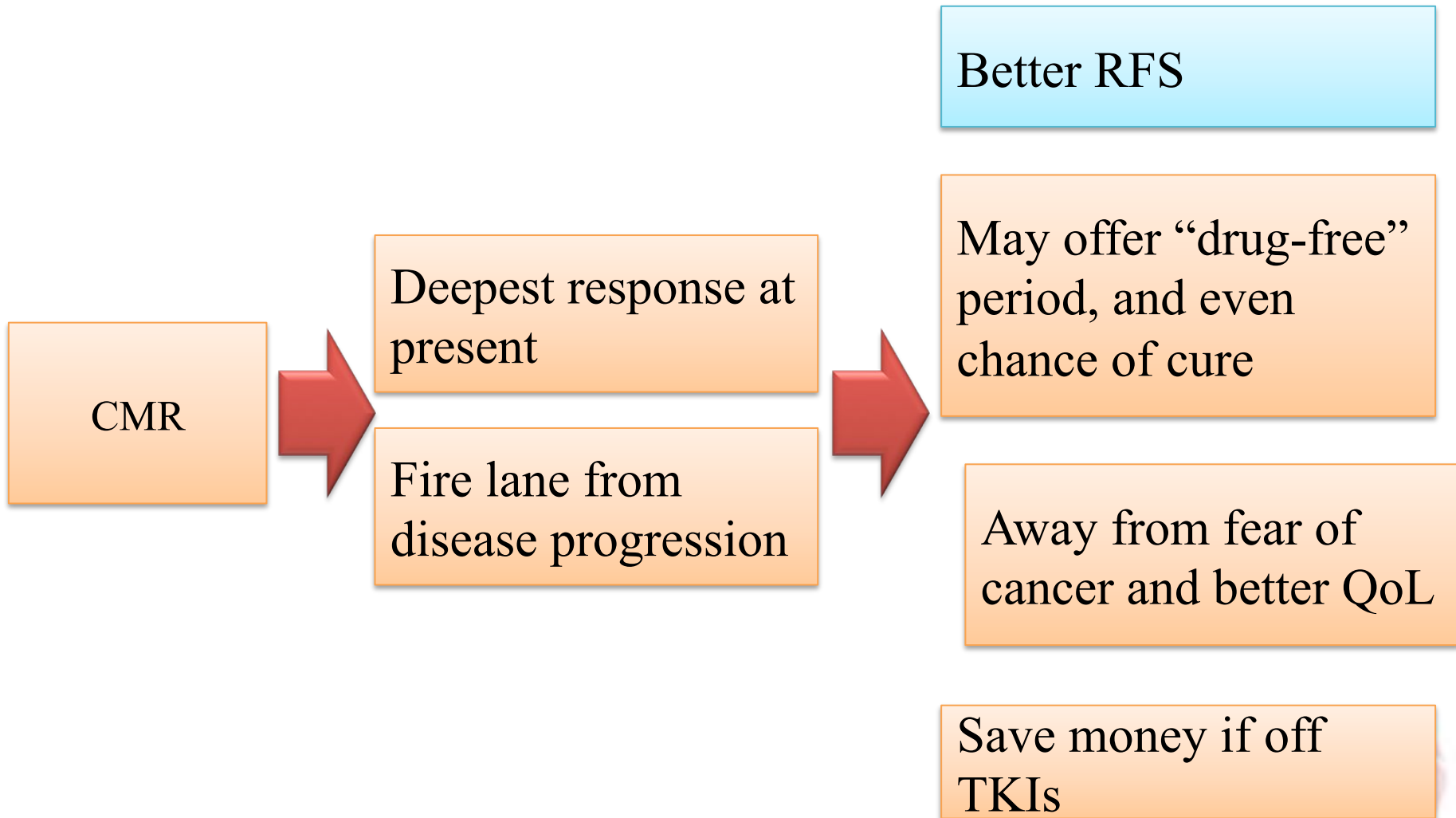
- 68% of patients who achieved MMR by 3 years on nilotinib 300 mg BID achieved an MR⁴ or greater vs 49% on imatinib

Cumulative Incidence of MR^{4.5}*



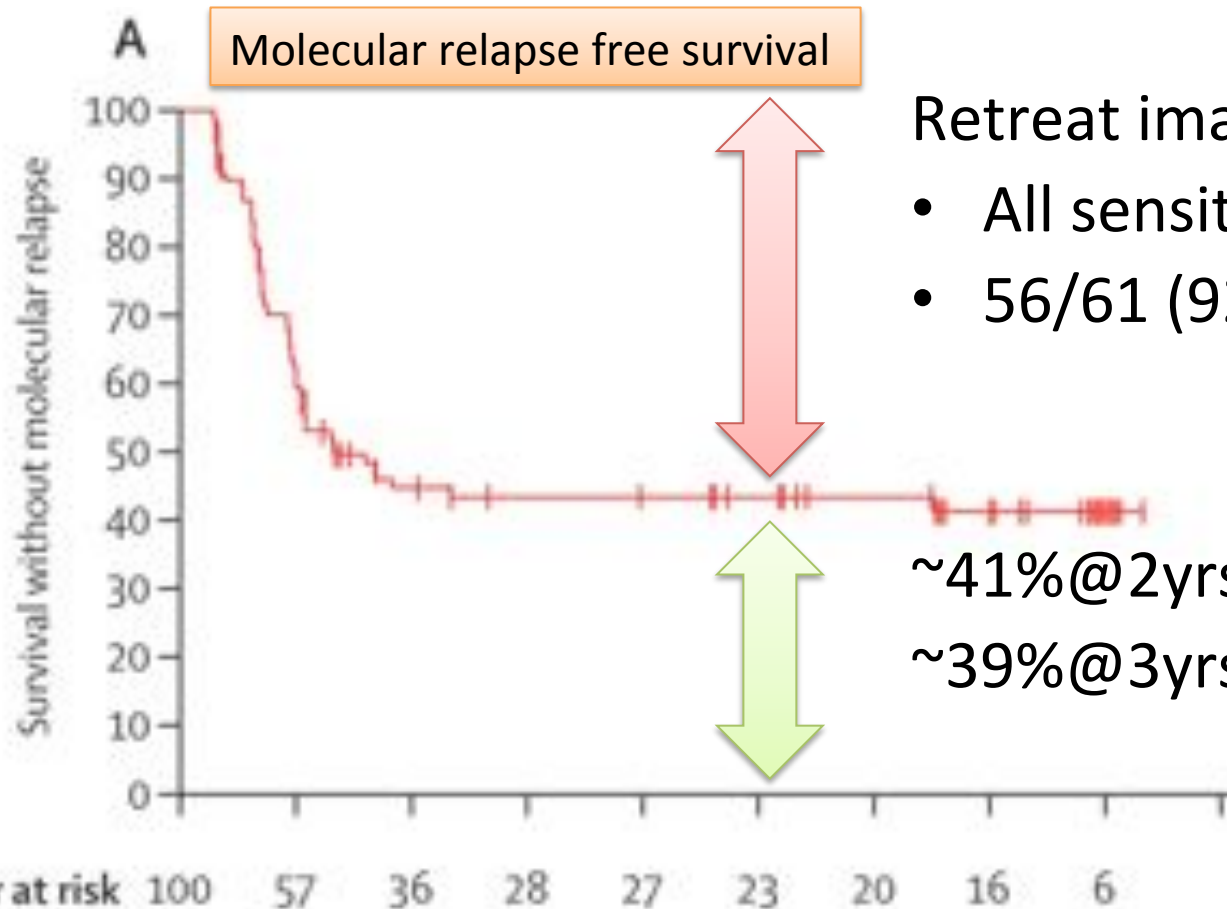
* Equivalent to BCR-ABL transcript levels of ≤ 0.0032% (IS).

CMR Means...



Proof of Concept

Stop Imatinib after Durable CMR STIM Trial



Retreat imatinib:

- All sensitive
- 56/61 (92%) re-gain CMR

~41% @ 2yrs

~39% @ 3yrs

F. Mahon et al, Lancet Oncol 2010; 11: 1029–35

F. Mahon et al. (STIM) Poster 603 @ ASH 2011

Cost Isn't Everything. Value is.



Imatinib	Nilotinib	Dasatinib	Allo-SCT
20 USD 100mg/tab	21 USD 150mg/cap	42 USD 50mg/tab	
400mg/day	600mg/day	100mg/day	
29,200/year	\$30,660/year	\$30,660/year	150K-200K (USA) 35K-100K (TWN) (First year)
233K (8 years)	245K (8 years)	245K (8 years)	200K-400K (USA) 60K-100K (TWN) (8 years)

We Need A Safer Parachute



Feel Like Normal, and Better QoL

Working, dating, married

Pregnancy, having children

Possible drug-free

CML Treatment Paradigm: 2012

CP CML



Complete diagnostic workup
Tumor burden by Q-RT-PCR
Imatinib 400 mg/day
Nilotinib 300 mg BID
Dasatinib 100 mg/day



Goals
Heme CR in 1-2 mos
Cyto response in 3-6 mos
CCyR in 12-15 mos
MMR in ~ 12 mos

No



Advanced-phase CML



CHEMO + TKI vs TKI alone
Imatinib 400 mg BID
Dasatinib 70 mg BID
Nilotinib 400 mg BID

Dasatinib
Nilotinib



Allo-HSCT
@ progression

Allo-HSCT: second or third salvage ?

Thanks for your attention !

