

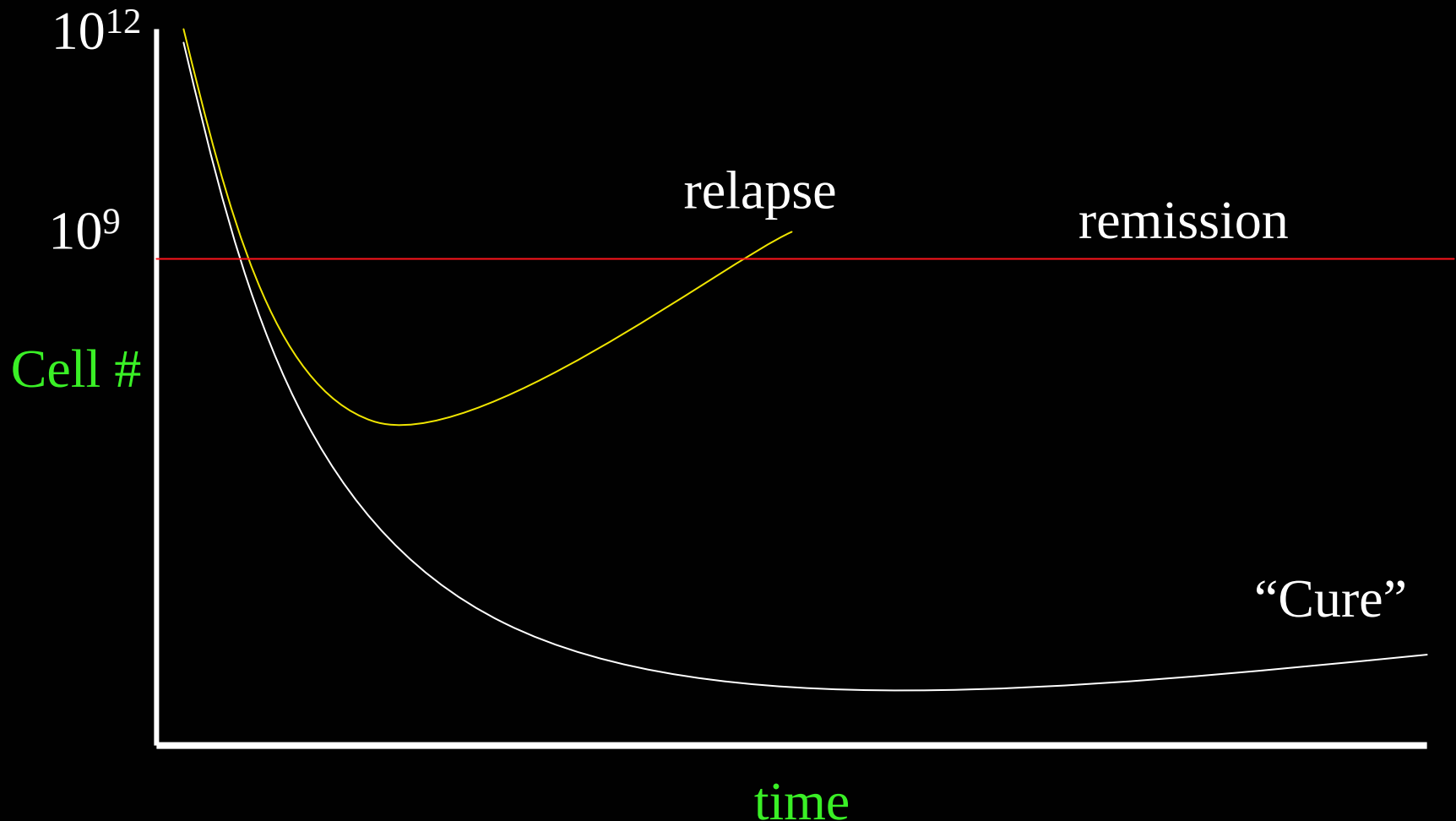
Monitoring residual tumor burden



Jerry Radich
FHCRC
Nov. 2005

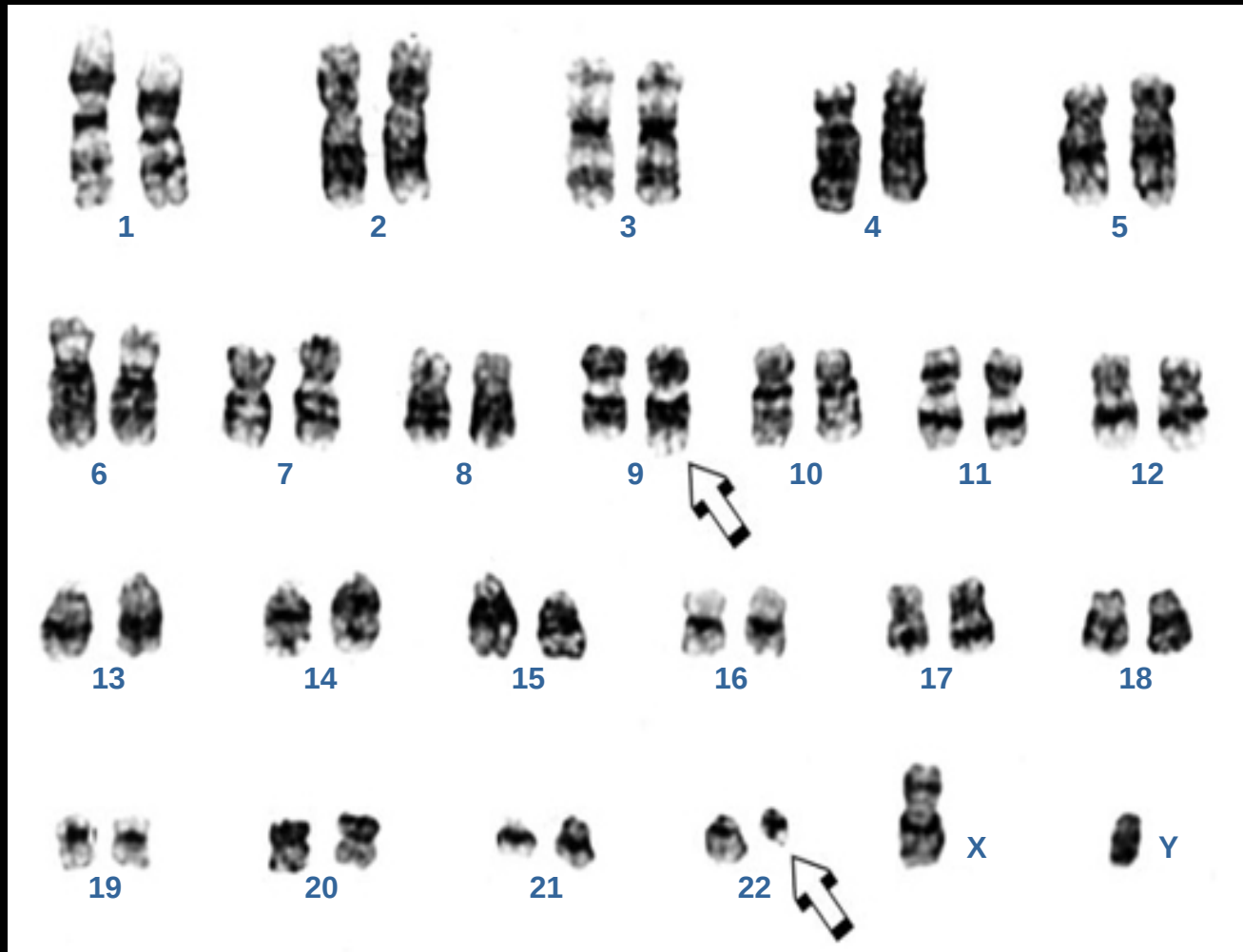
Treating cancer

the problem of disease detection

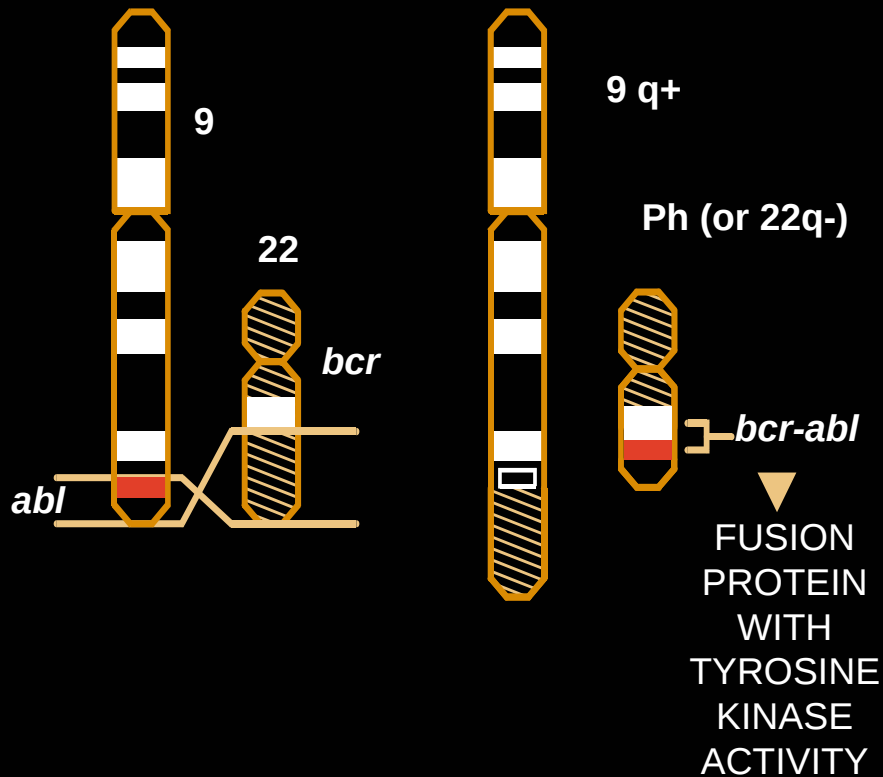


Cytogenetic Abnormality of CML

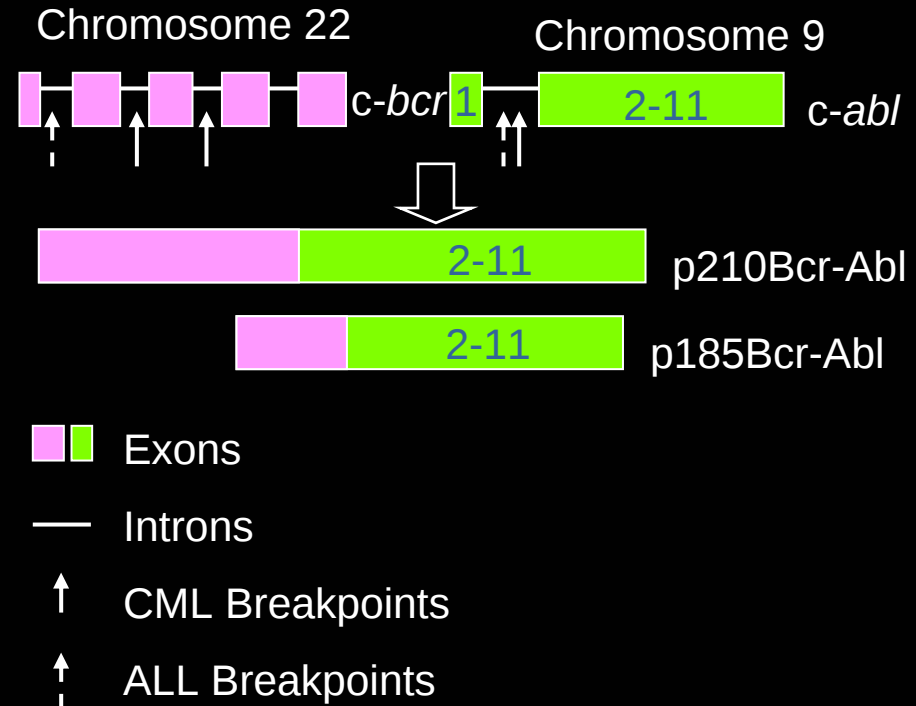
The Philadelphia Chromosome



The Ph Chromosome and *Bcr-Abl*



t(9;22) translocation



bcr-abl gene structure

Natural history of CML

Chronic phase

Ph+

Median duration
3-5 years

Accelerated phase

Cytogenetic changes

Increasing blasts

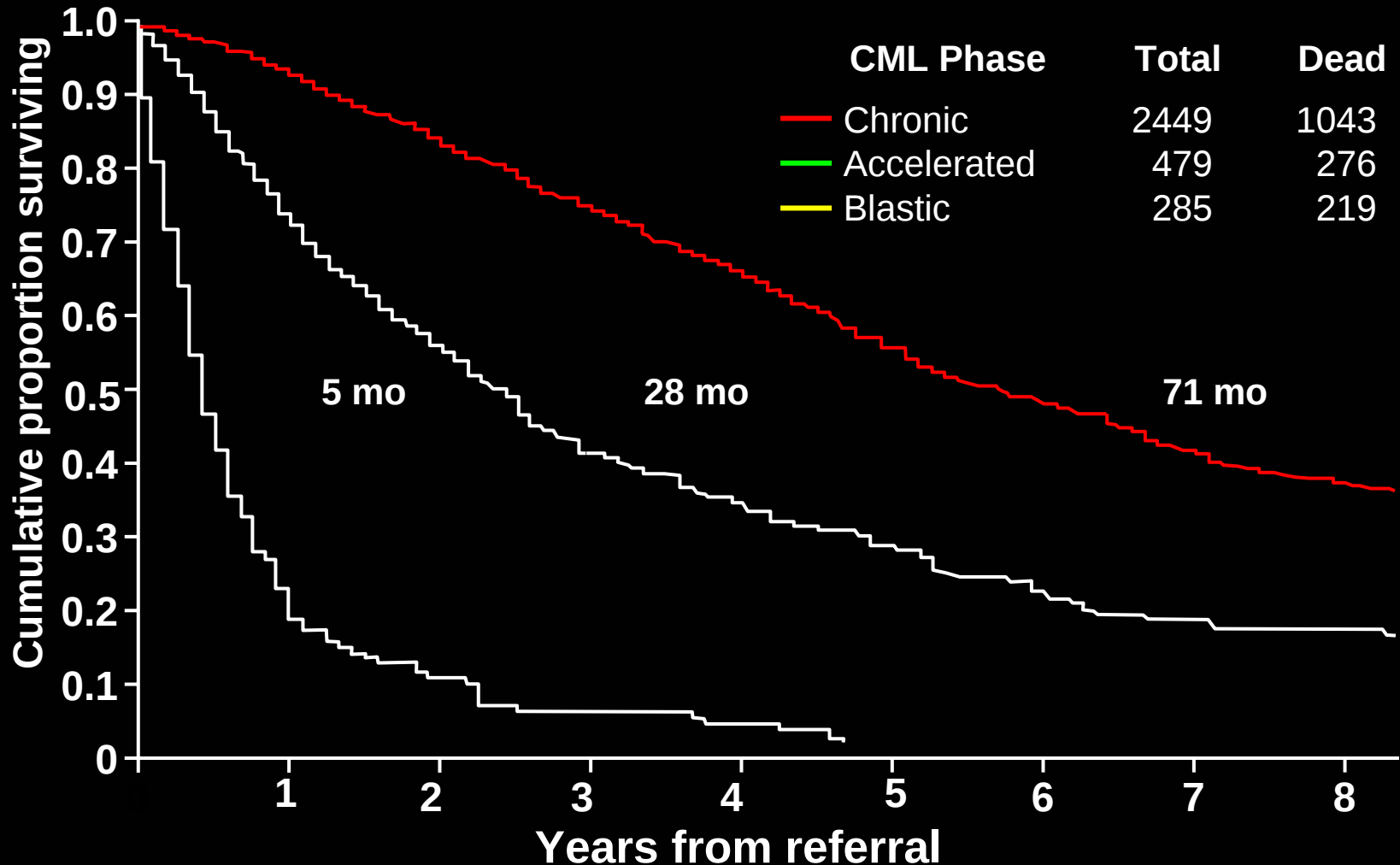
Median duration
6-9 months

Blast crisis

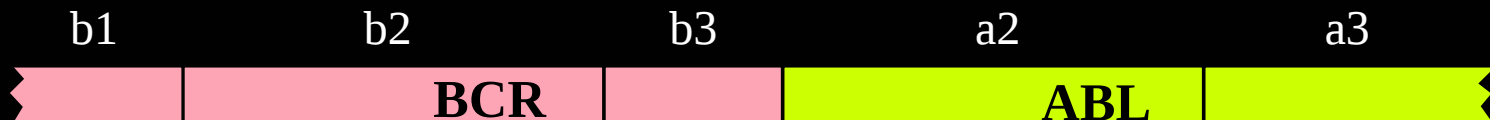
Median survival
3-6 months



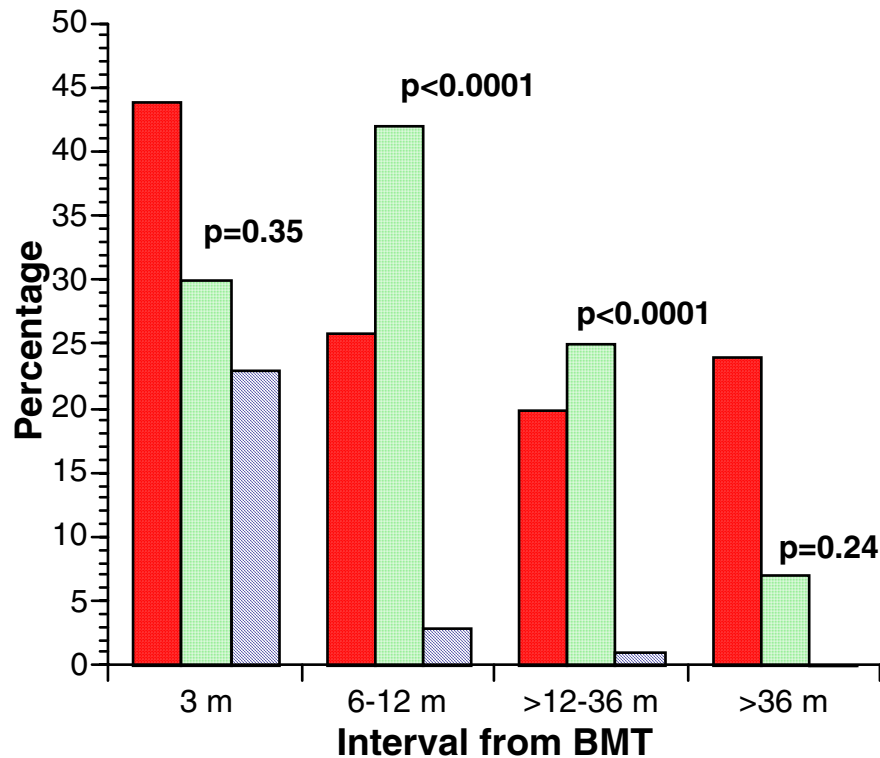
Survival by Phase of CML



“Nested” RT-PCR for *bcr-abl*



Prevalence and significance of *bcr-abl* + post-BMT (N=346)



- ~ 25% of pts. *bcr-abl* +

- *bcr-abl* + 6-12 m post-BMT associated with a high risk of relapse (RR = 20-30)

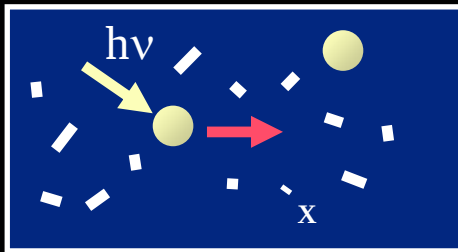
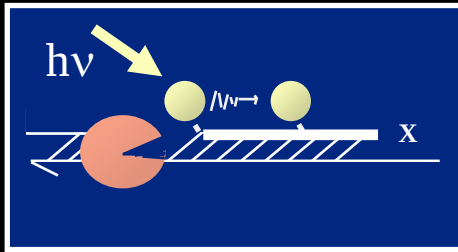
- *bcr-abl* + > 12 m post-BMT may have less risk of relapse

Blood 85:2632, 1995

“Real time” quantitative RT-PCR

I. Hydrolysis Probes

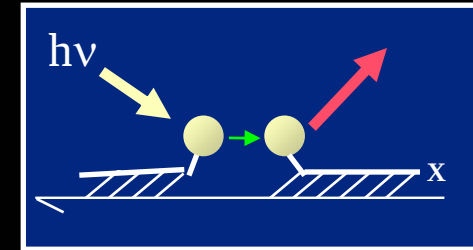
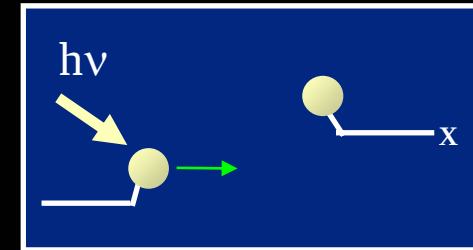
Release from quenching by hydrolysis



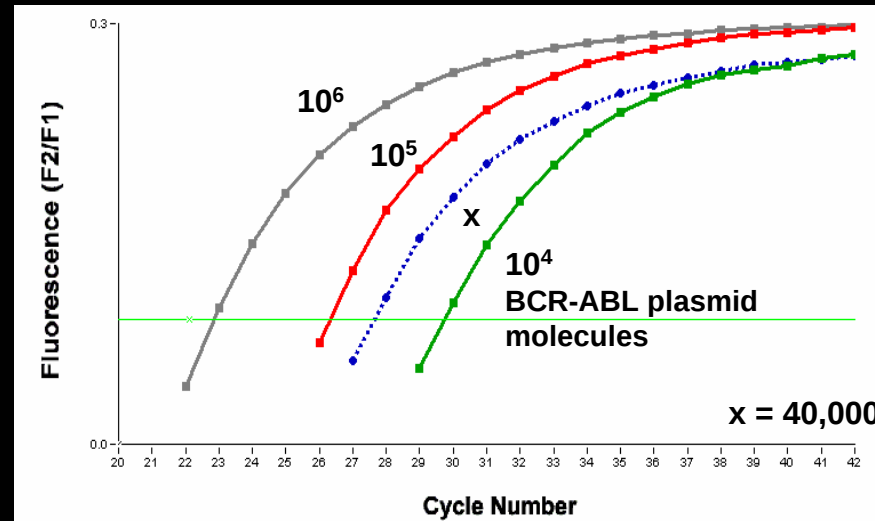
TaqMan™

II. Hybridization Probes

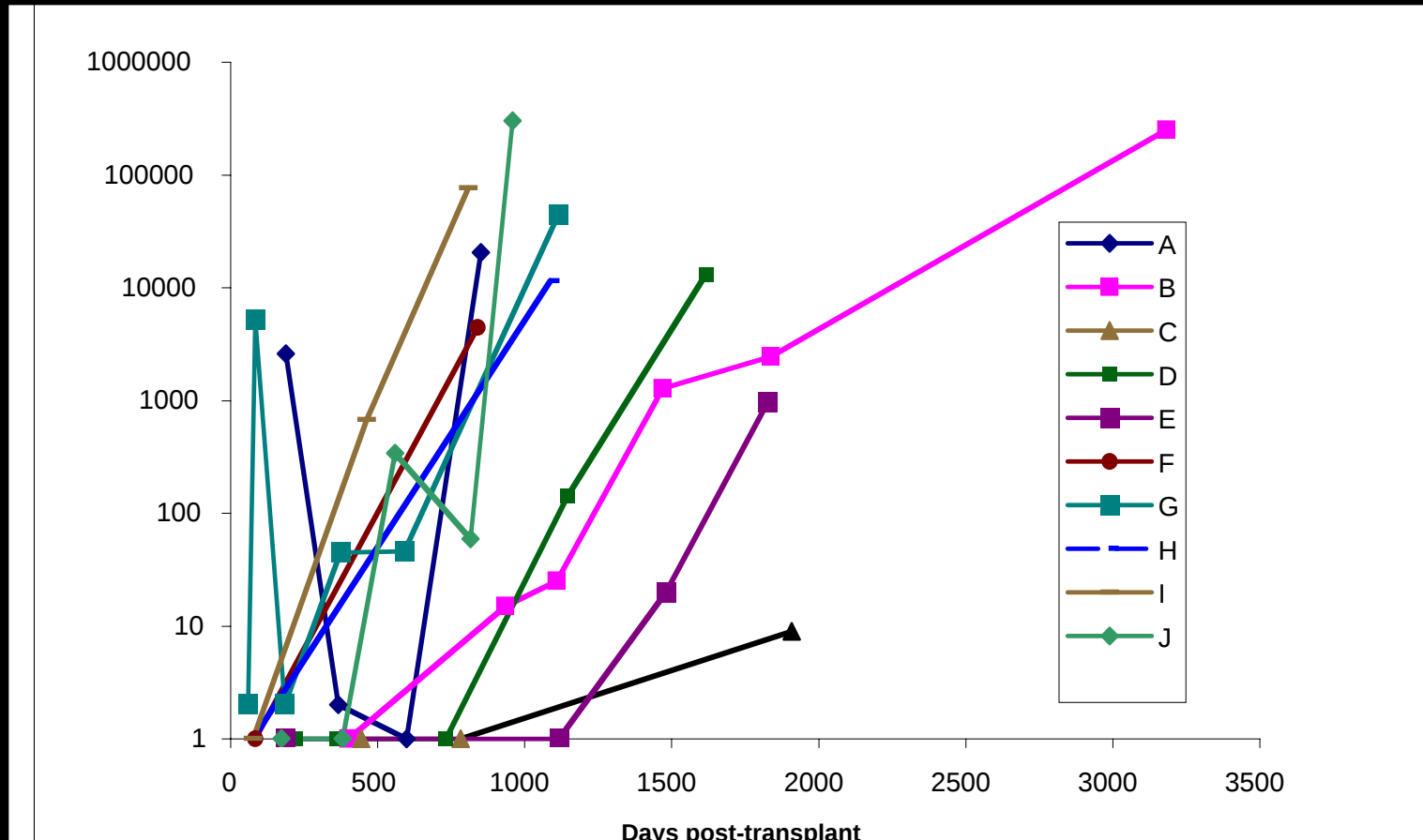
Increased resonance energy transfer by hybridization



LightCycler™



bcr-abl kinetics and relapse



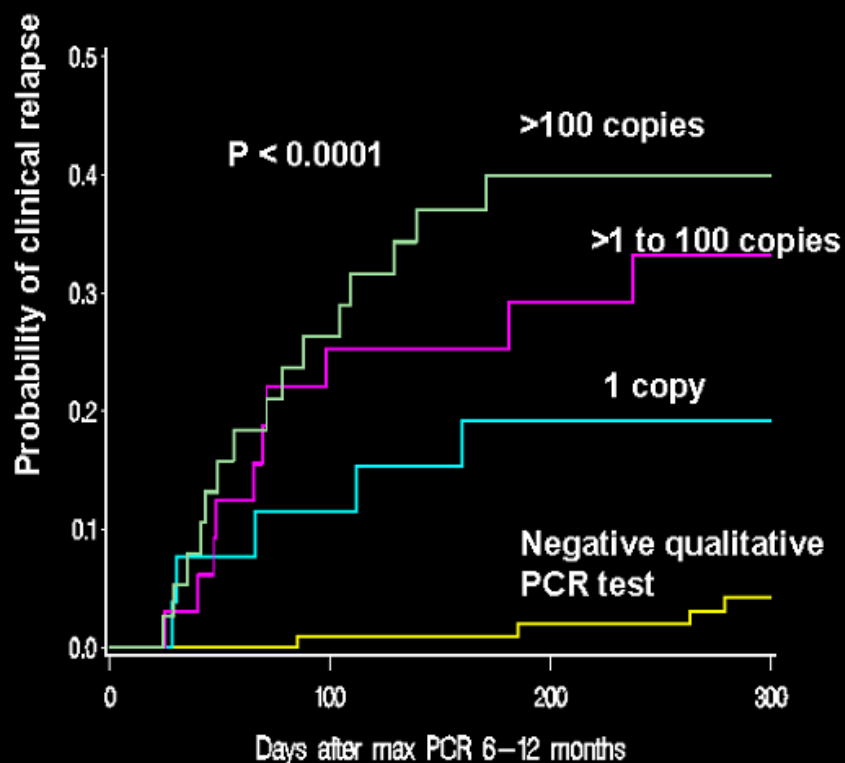
Median *bcr-abl* in relapsed patients = 40,000 copies/ug RNA
Median in *bcr-abl* + patients without relapse = < 100 copies/ug RNA

Risk of relapse associated with achieving a specific quantitative PCR level

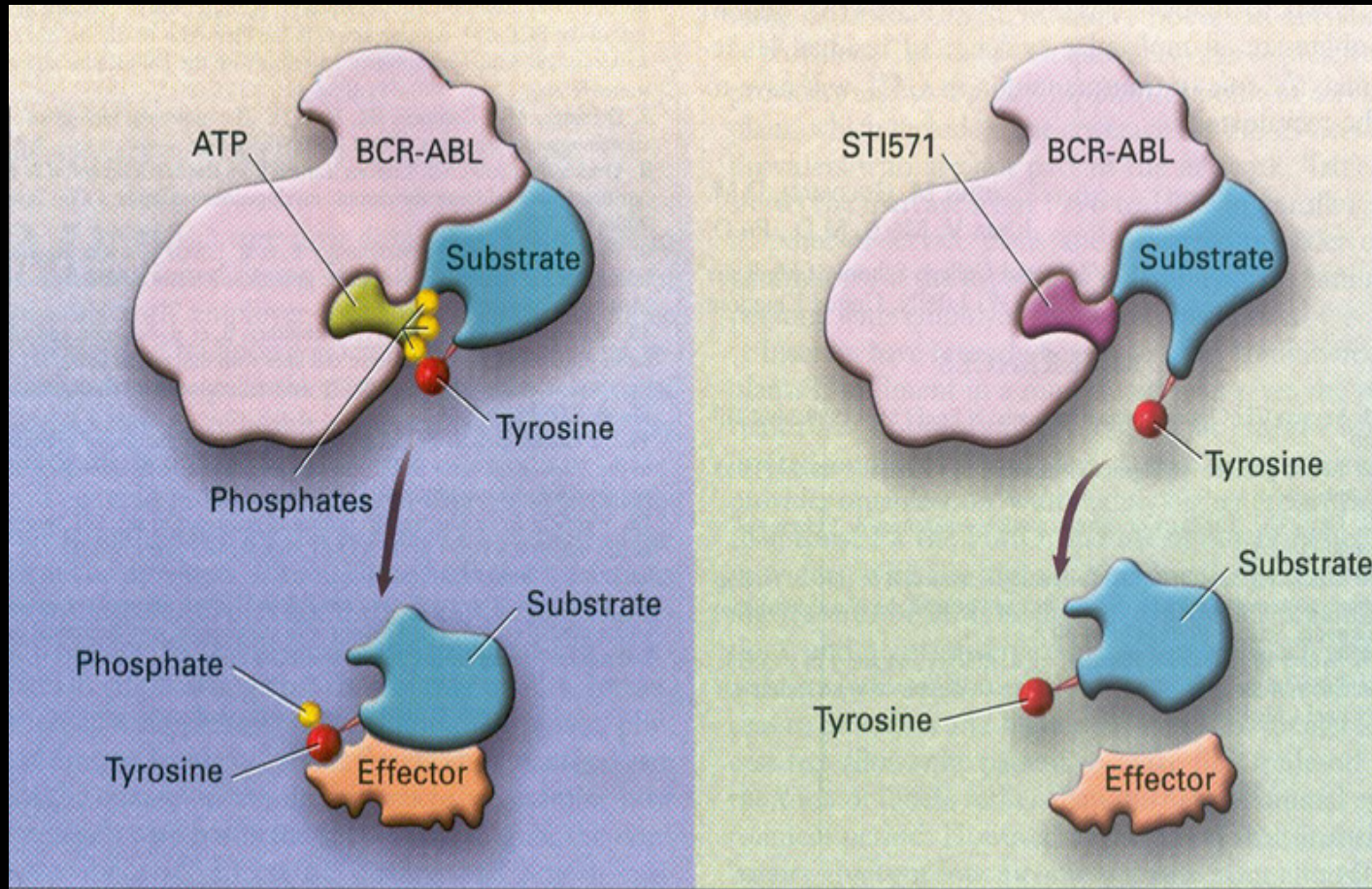
Hazard ratio associated with attaining a maximum PCR value within a specific interval

Copy number	3-6 mo.	6-12 mo.	12-18 mo.	>18 mo.
Negative	1.0	1.0	1.0	1.0
1	1.0	2.5 *	----	3.2
>1 to 100	0.7	3.6 *	1.9	3.4
>100	1.9 *	5.1 *	3.2 *	3.9 *

* Indicates statistical significance



Mechanism of Action of Imatinib Mesylate (a.k.a., STI571, Gleevec, Glivec)

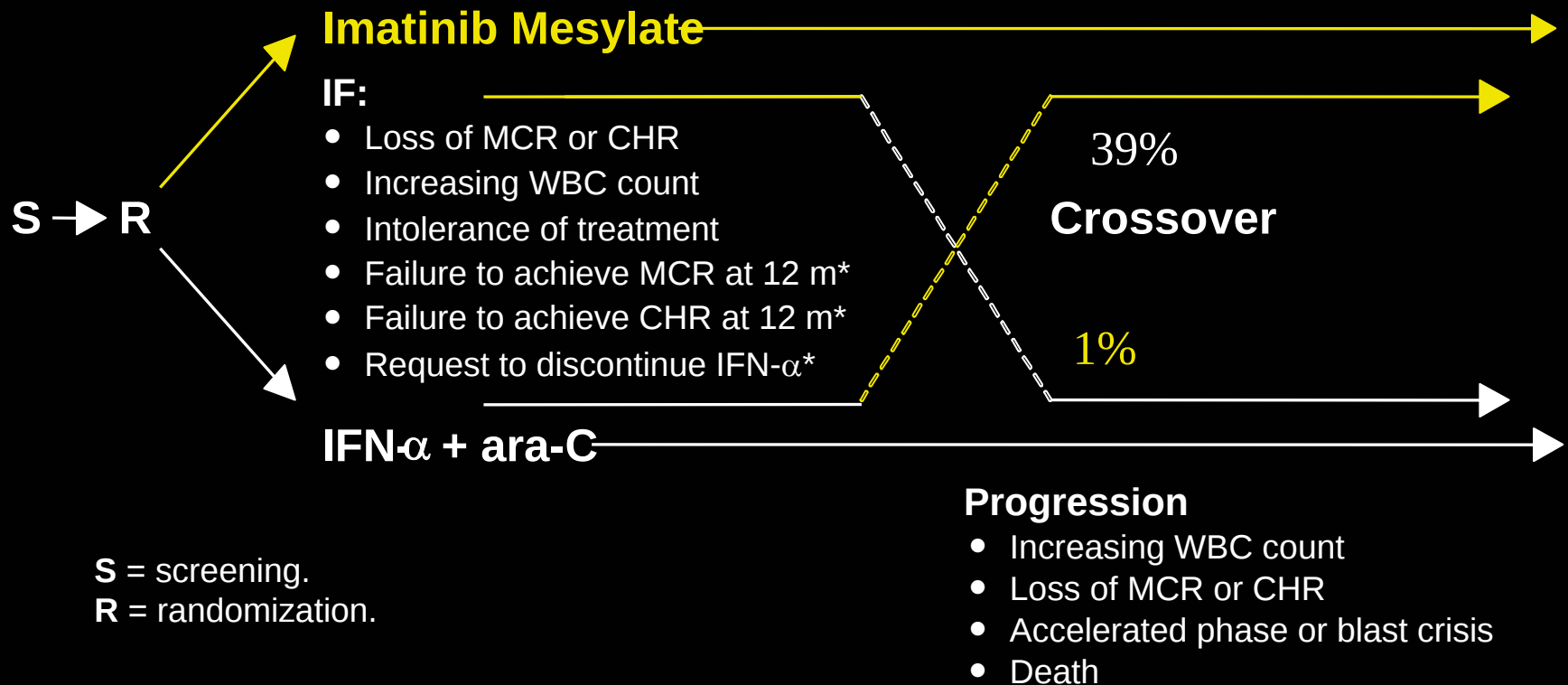


Summary of Phase II results

% of Patients (CI_{95%})	Study 0110 Chronic Phase IFN-α Failure (n=532)	Study 0109 Accelerated Phase (n=235)	Study 0102 Blast Crisis (n=260)
Hematologic response	88% (84.9–90.6)	63% (56.5–69.2)	26% (20.9–31.9)
Complete response	88%	28%	4%
No evidence of leukemia	—	11%	3%
Return to chronic phase (RTC)	—	24%	19%
Major cytogenetic response (MCR)	49% (45.1–53.8)	21% (16.2–27.1)	13.5% (9.6–18.2)
Complete	30%	14%	5%
Partial	19%	7%	8.5%

International Randomized trial of Interferon/Ara-C versus STI571 (IRIS)

1106 CML-cp patients enrolled from June 2000 to January 2001



*Independent Data Monitoring Board Recommended Protocol Amendments

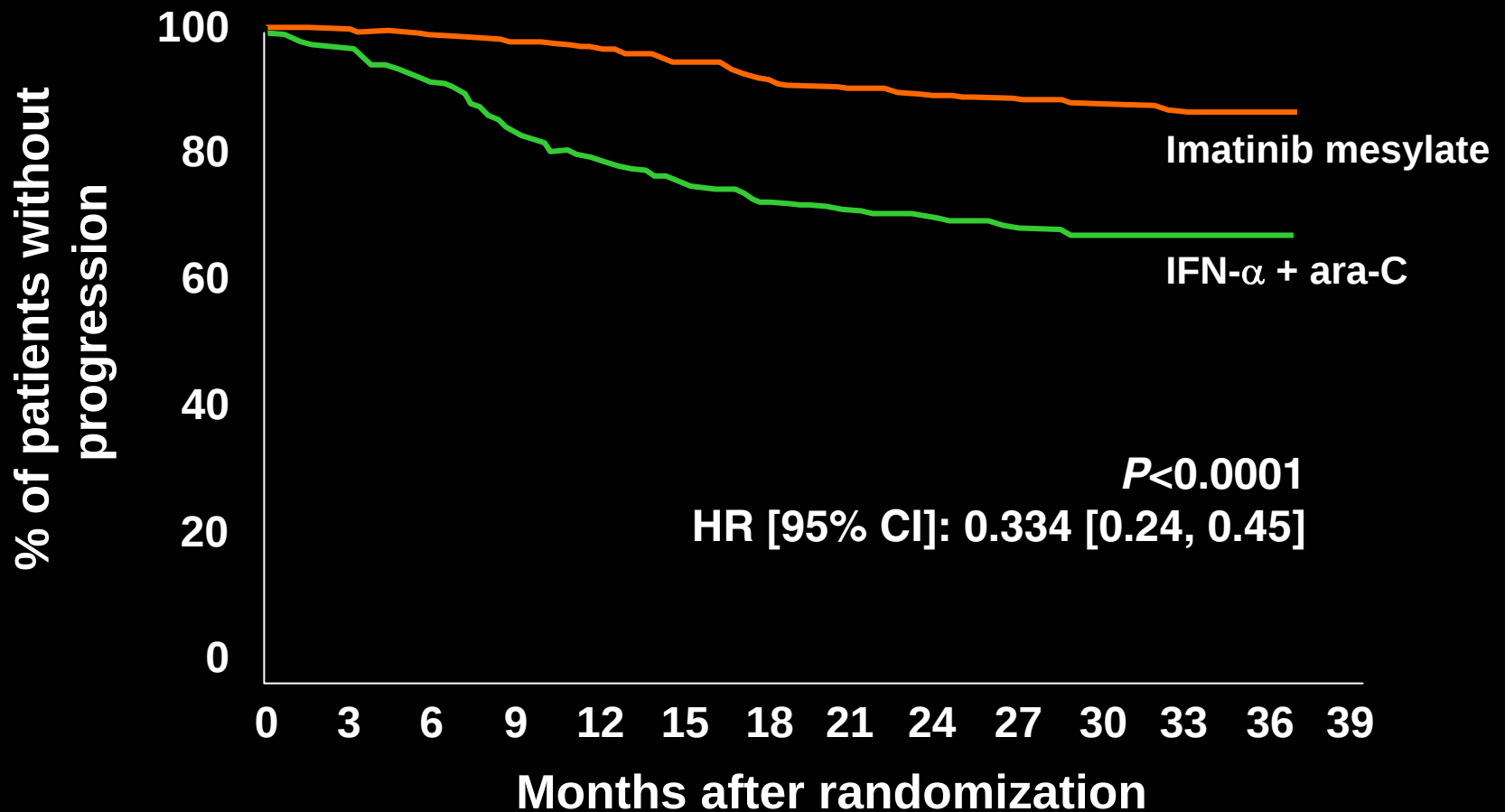
Cytogenetic responses

Imatinib v. IFN/Ara-C

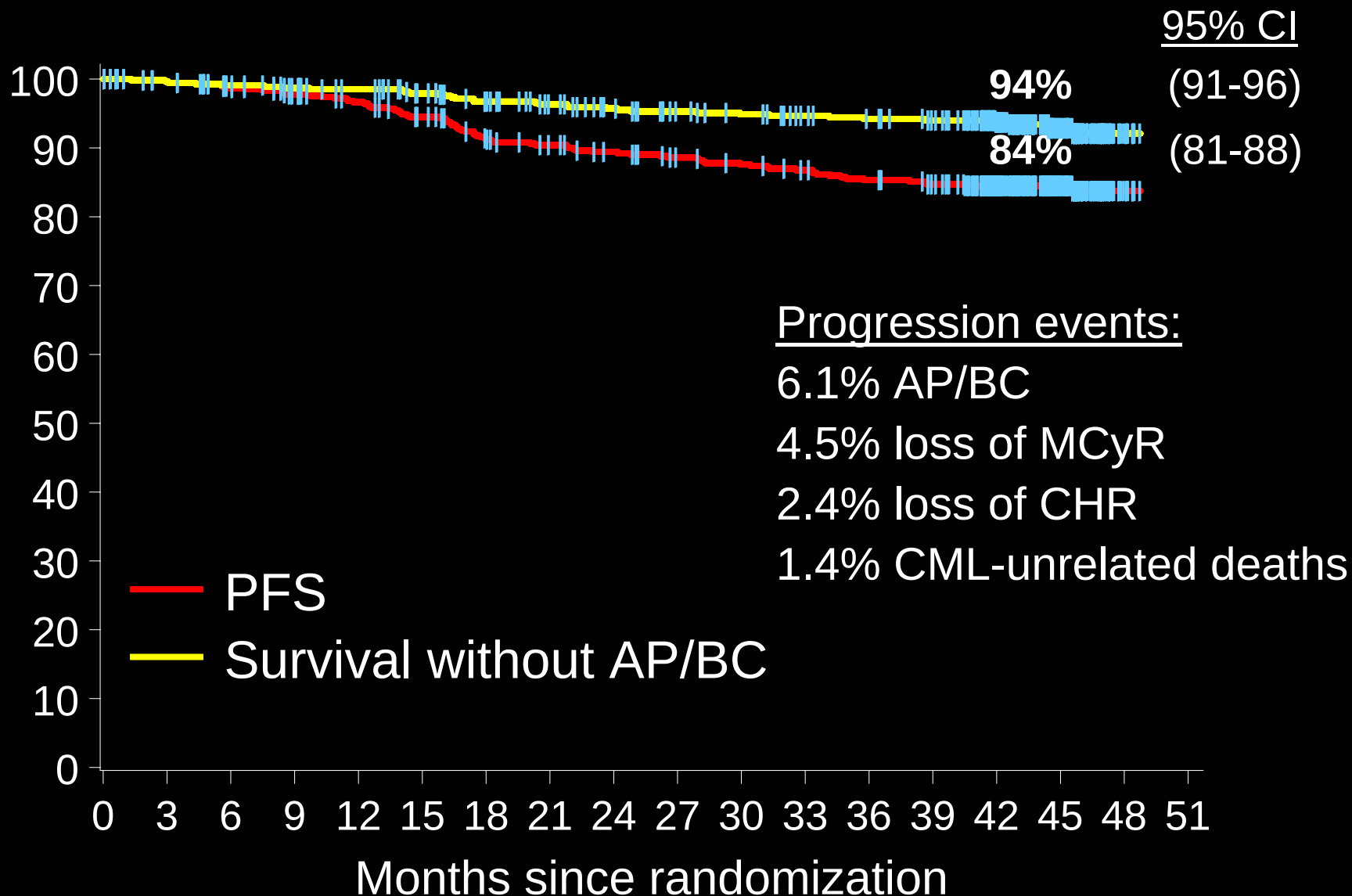
Cytogenetic Response	Imatinib Mesylate (n=553)	IFN- α + ara-C (n=553)
Major (35% Ph+, MCR)*	457 (83%)	112 (20%)
Complete (0% Ph+)*	375 (68%)	41 (7%)
Partial (1%–35% Ph+)	32 (6%)	71 (13%)

*P<0.001.

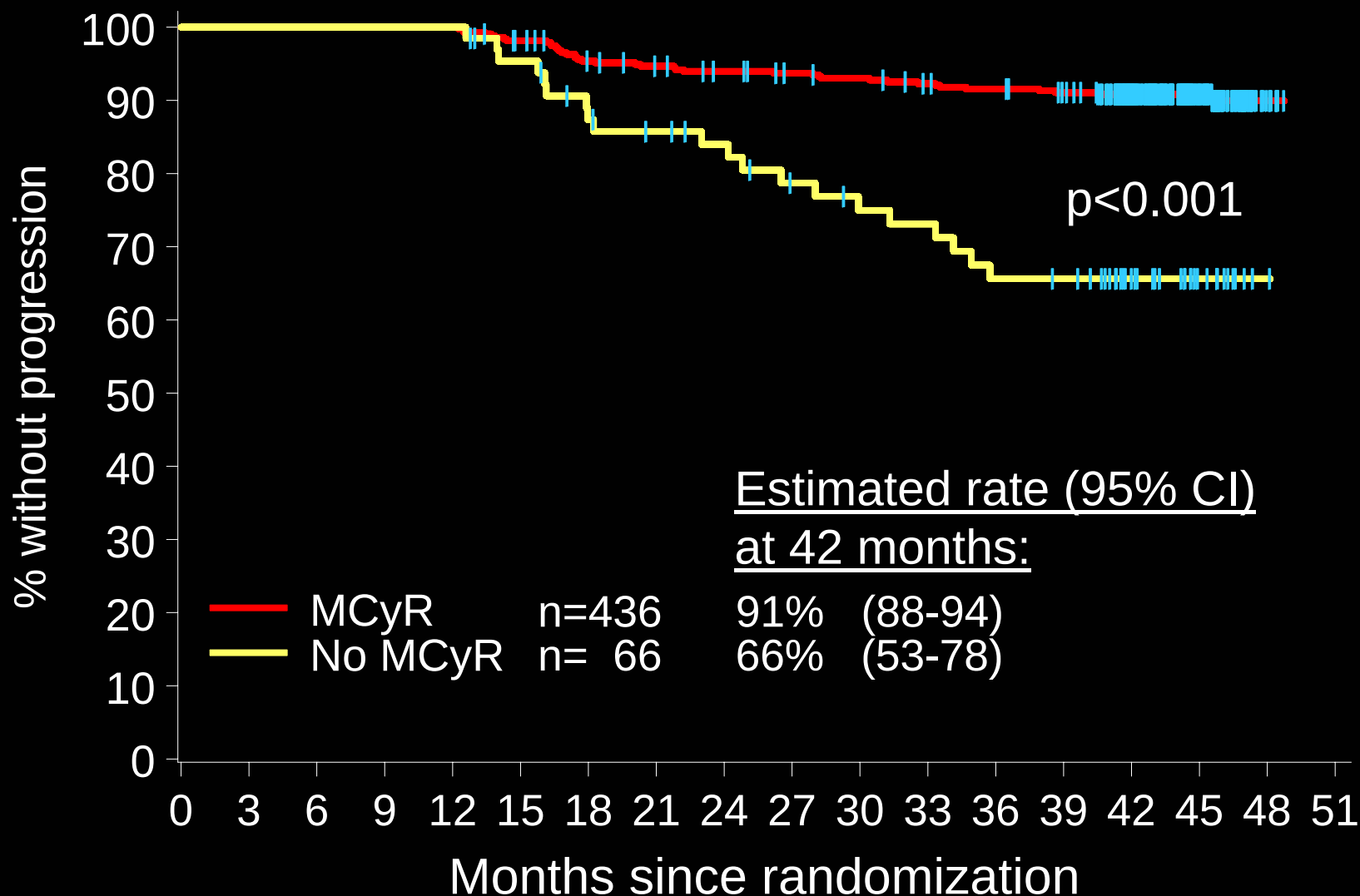
International Randomized Interferon vs Imatinib Mesylate (IRIS) Study: Time to progression*



Progression-free Survival and Survival Without AP/BC on First-line Imatinib

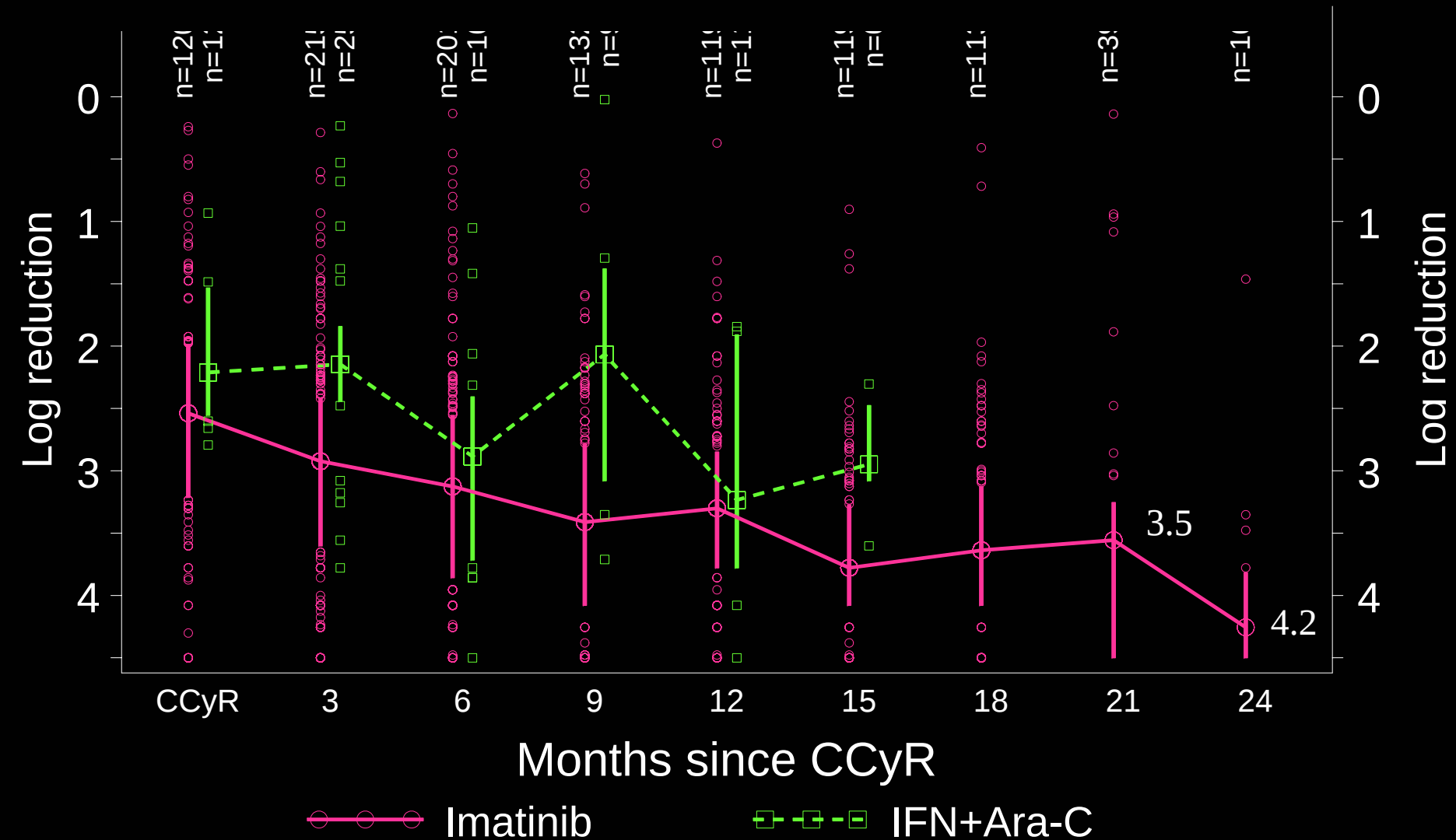


Time to Progression on First-line Imatinib by MCyR within 12 months

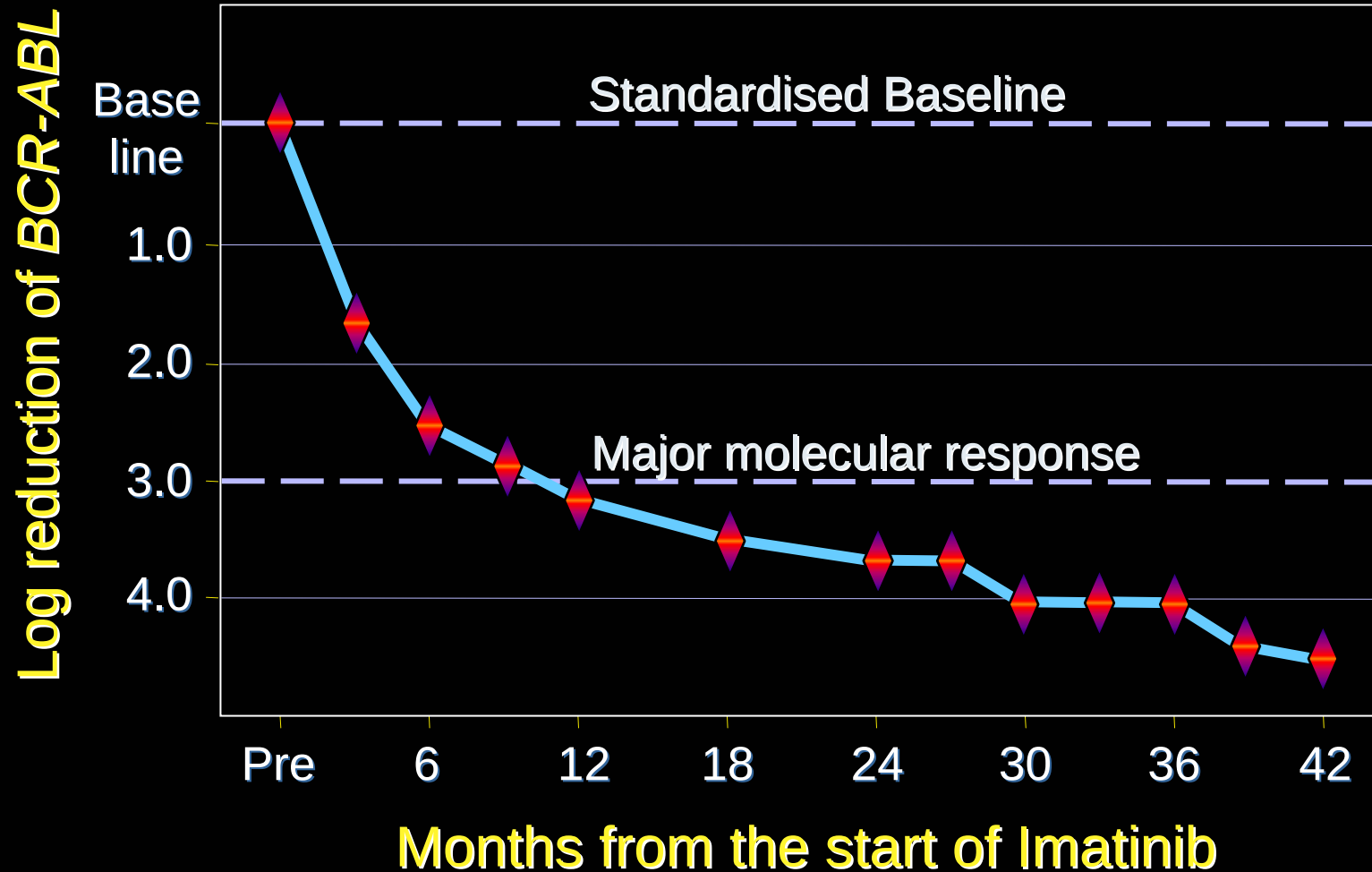


Molecular response of Bcr-Abl

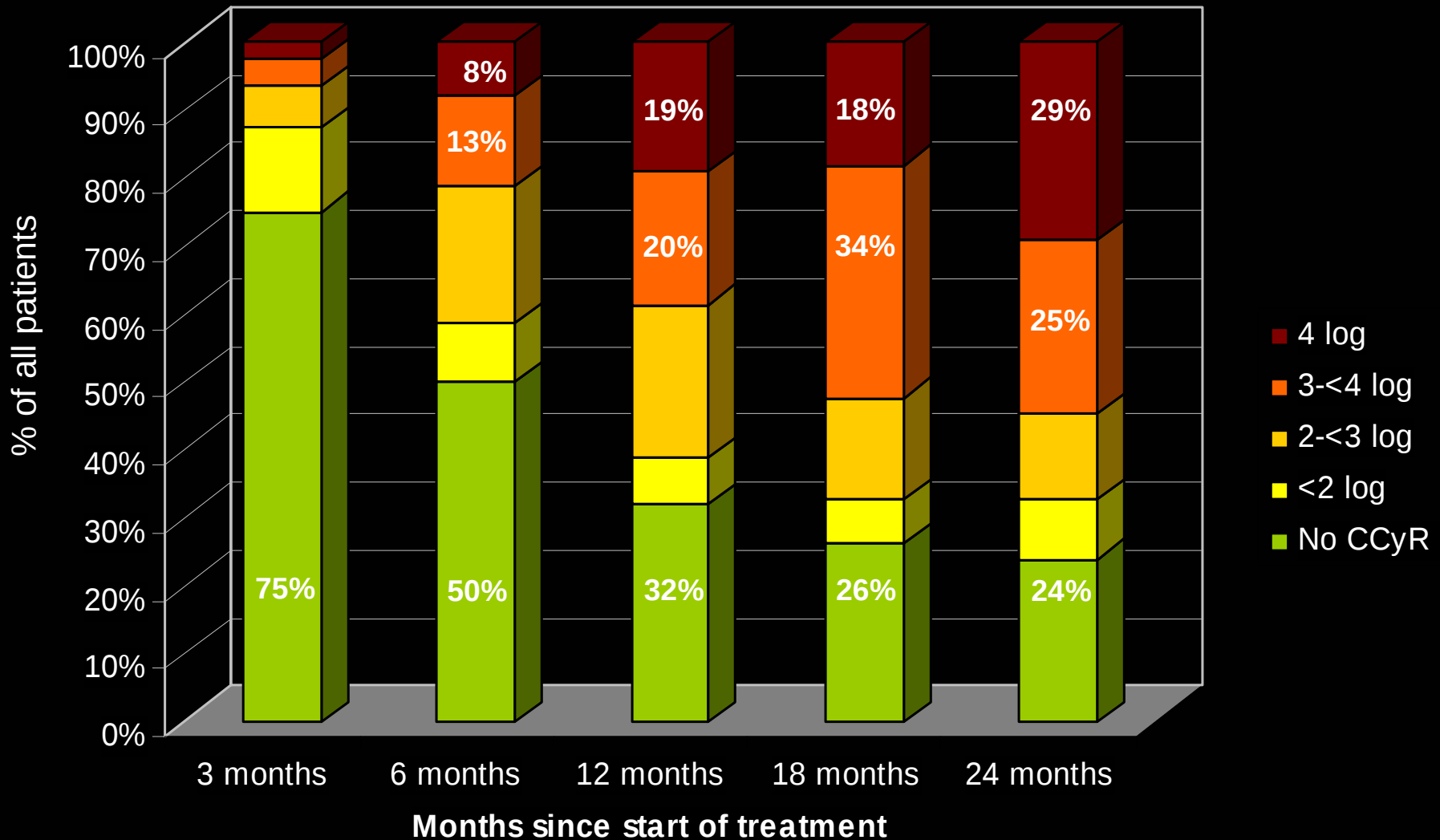
IRIS trial for CCyR



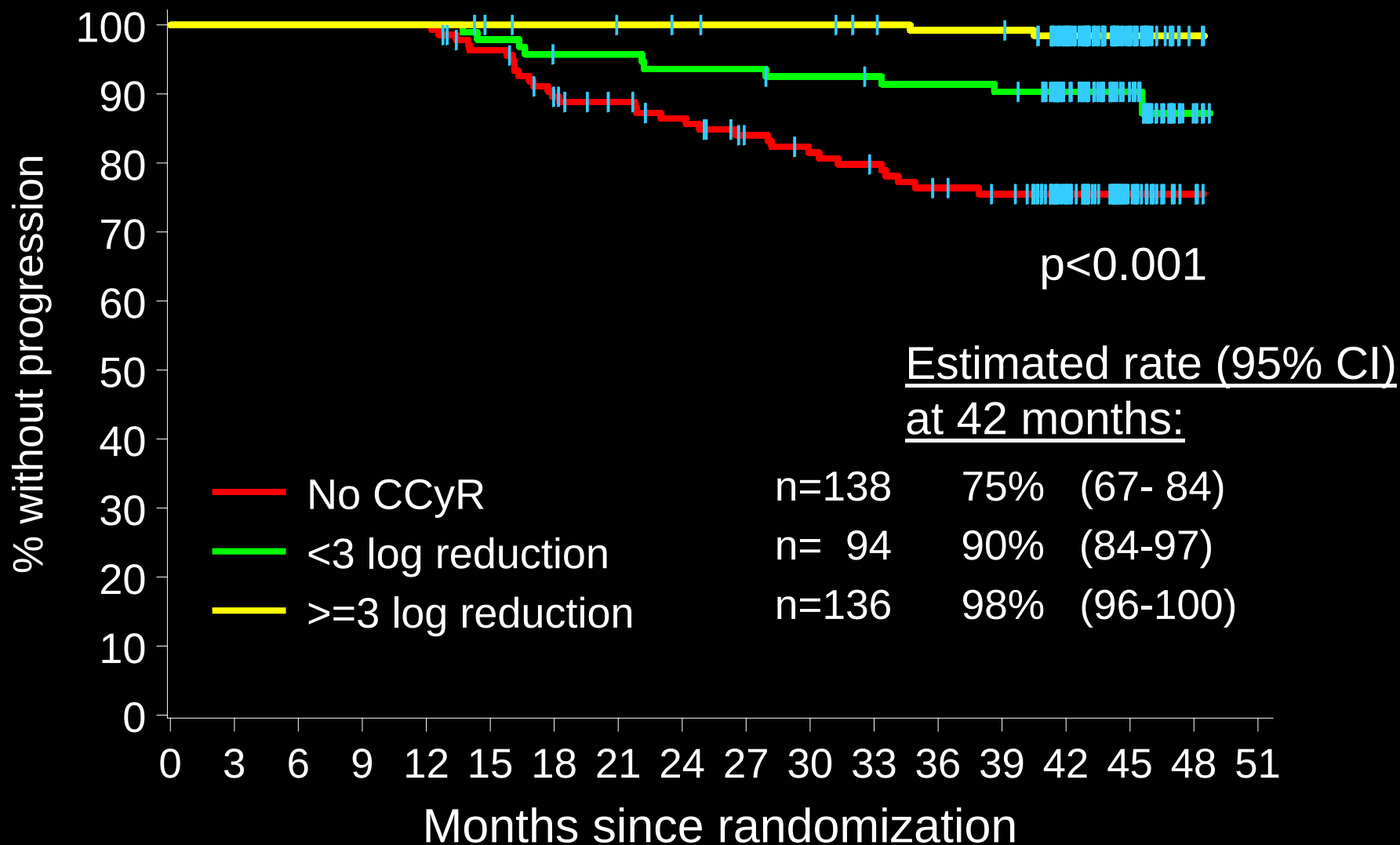
IRIS molecular response



IRIS trial: Overall estimated log reduction of *BCR-ABL* after IM treatment

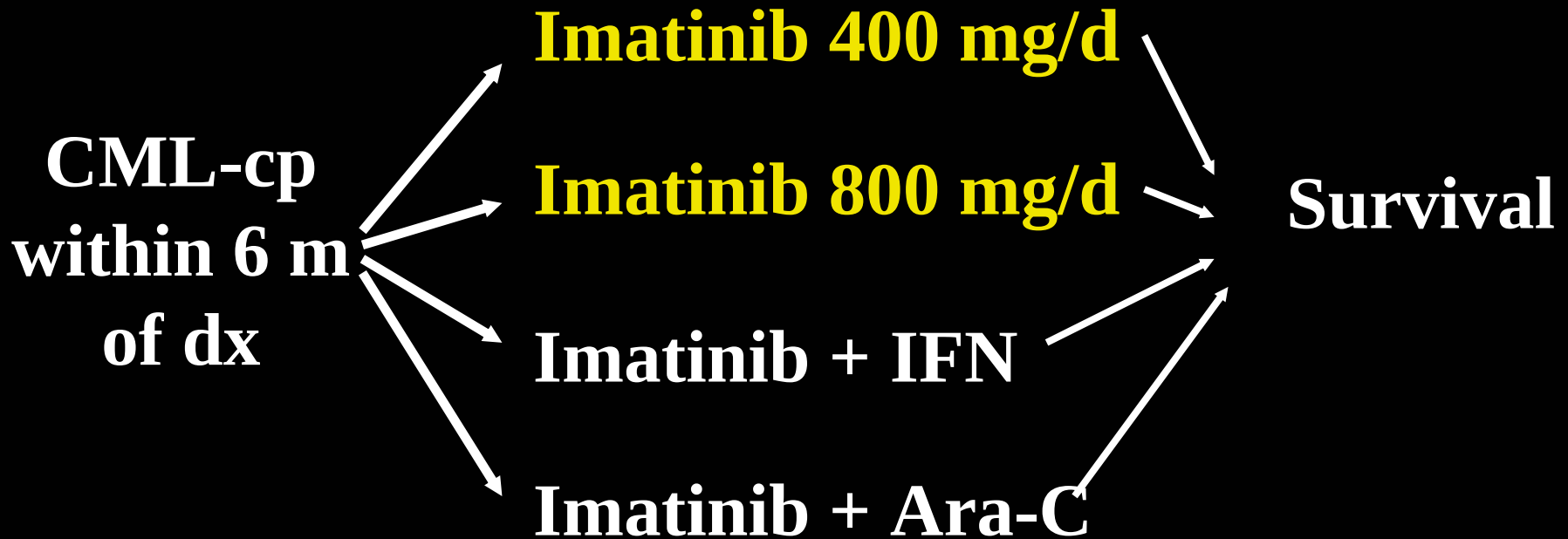


Progression-free Survival on First-line Imatinib by Molecular Response at 12 months



'SPIRIT'

**STI571 (Imatinib) Prospective International
Randomized Trial**

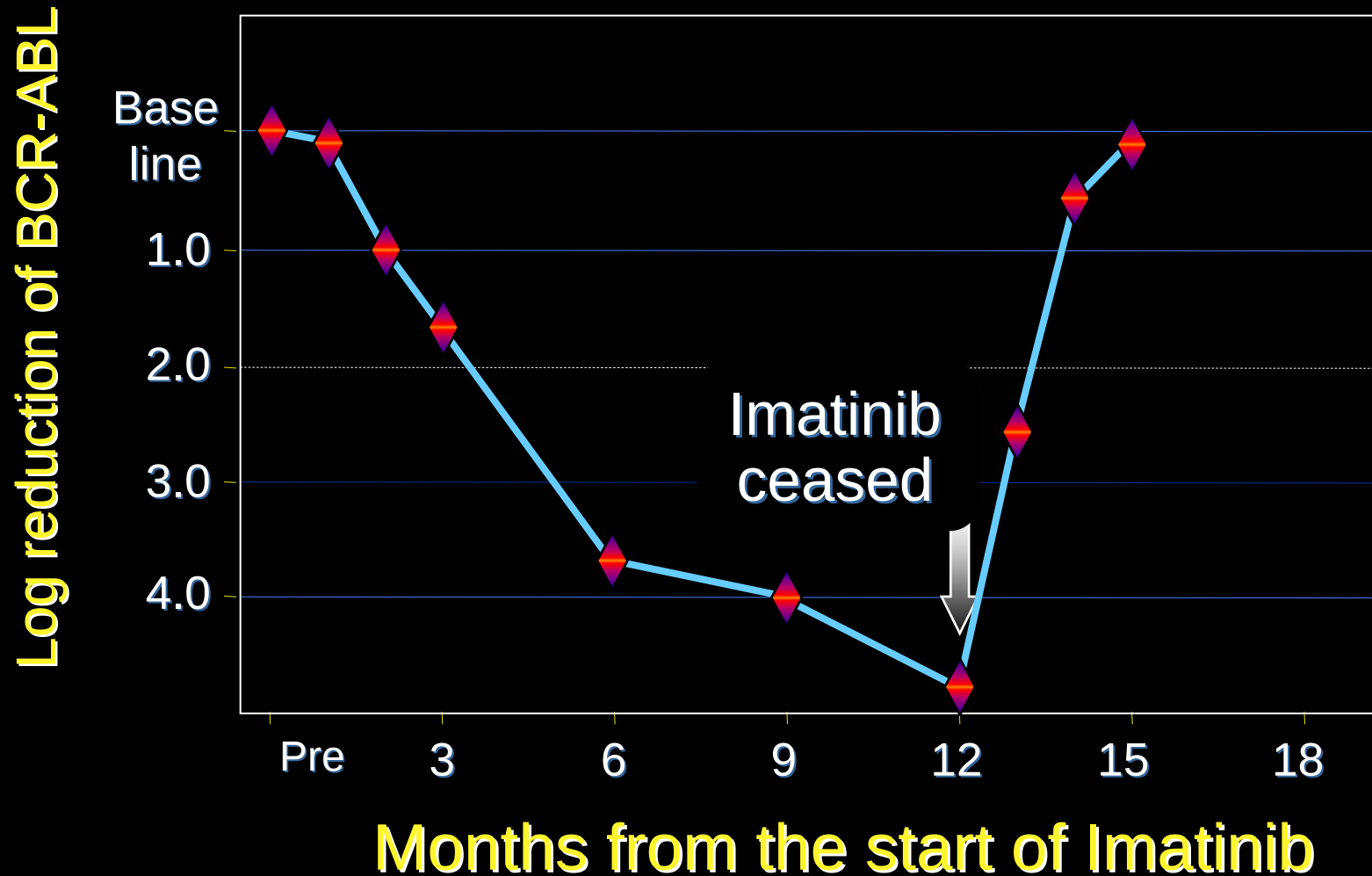


***SWOG:** depth of MRD burden (log reduction in bcr-abl at 12 months) as a surrogate outcome variable*

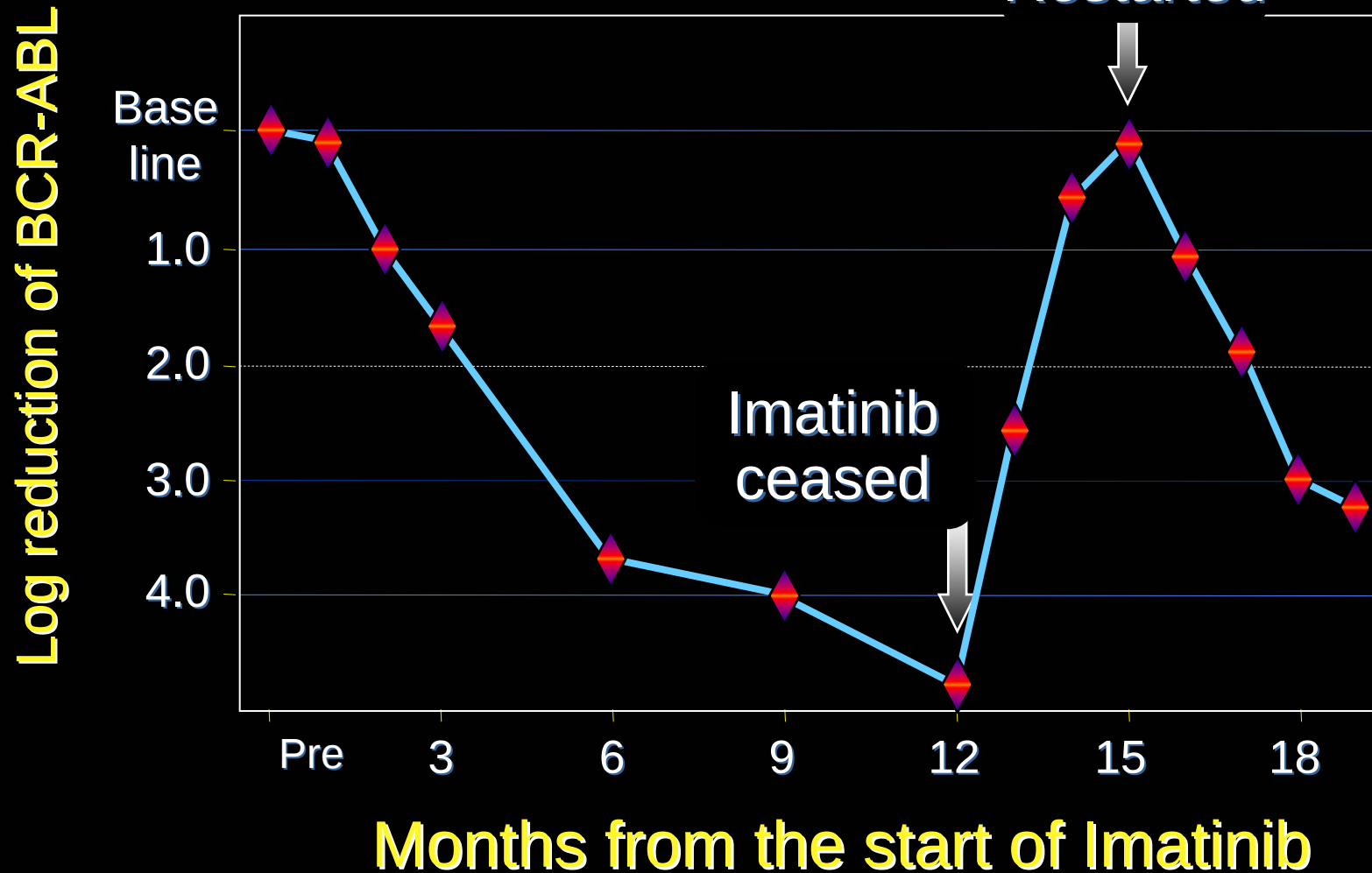
Intergroup CML trial

- Chronic phase CML
- IM 400 v. 800 v. dasatinib
- Endpoint-4 log bcr-abl reduction at 12 m
 - N= $\sim$ 100 each arm
 - First trial to use molecular endpoint

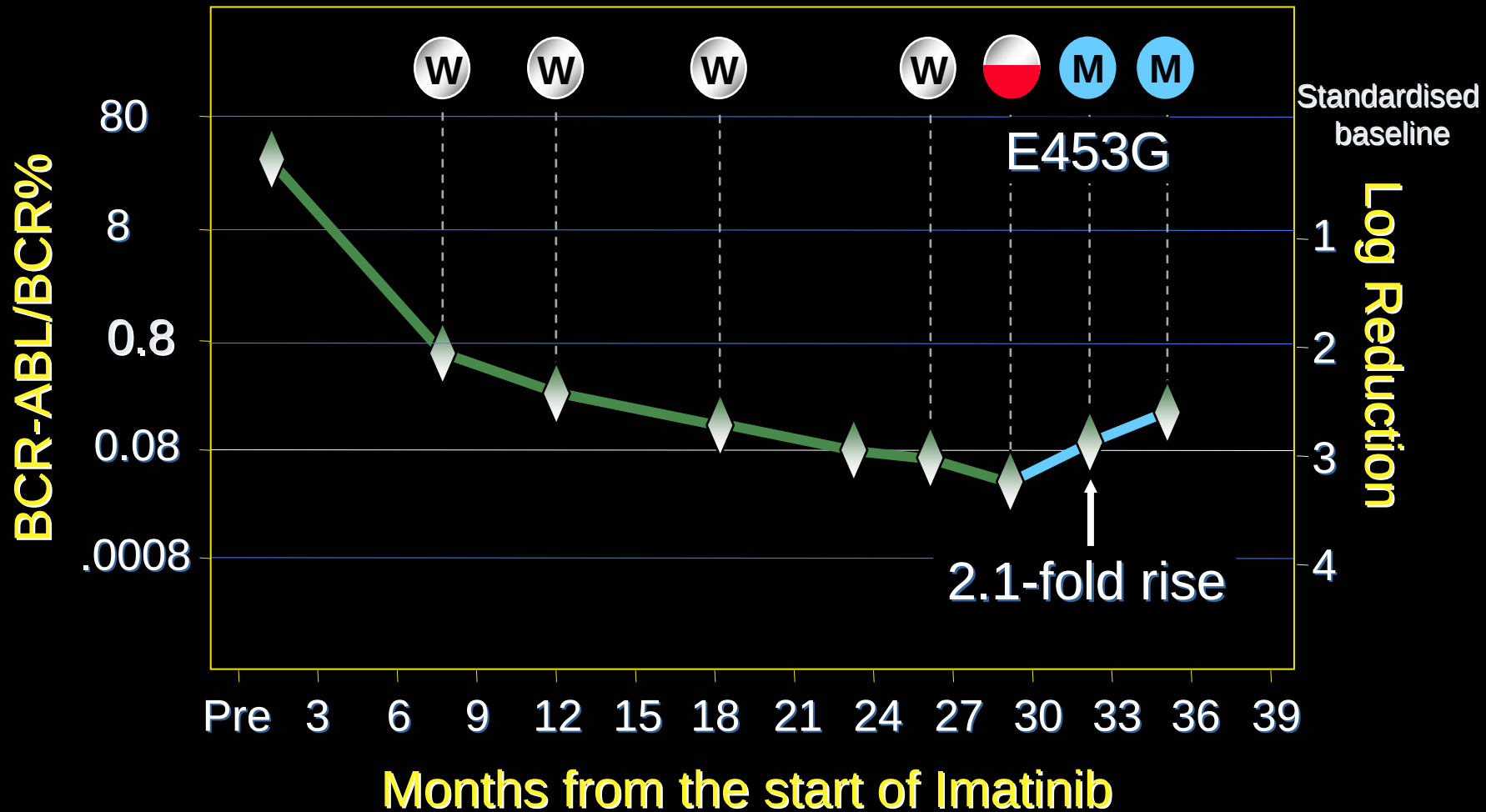
Track Individual Response



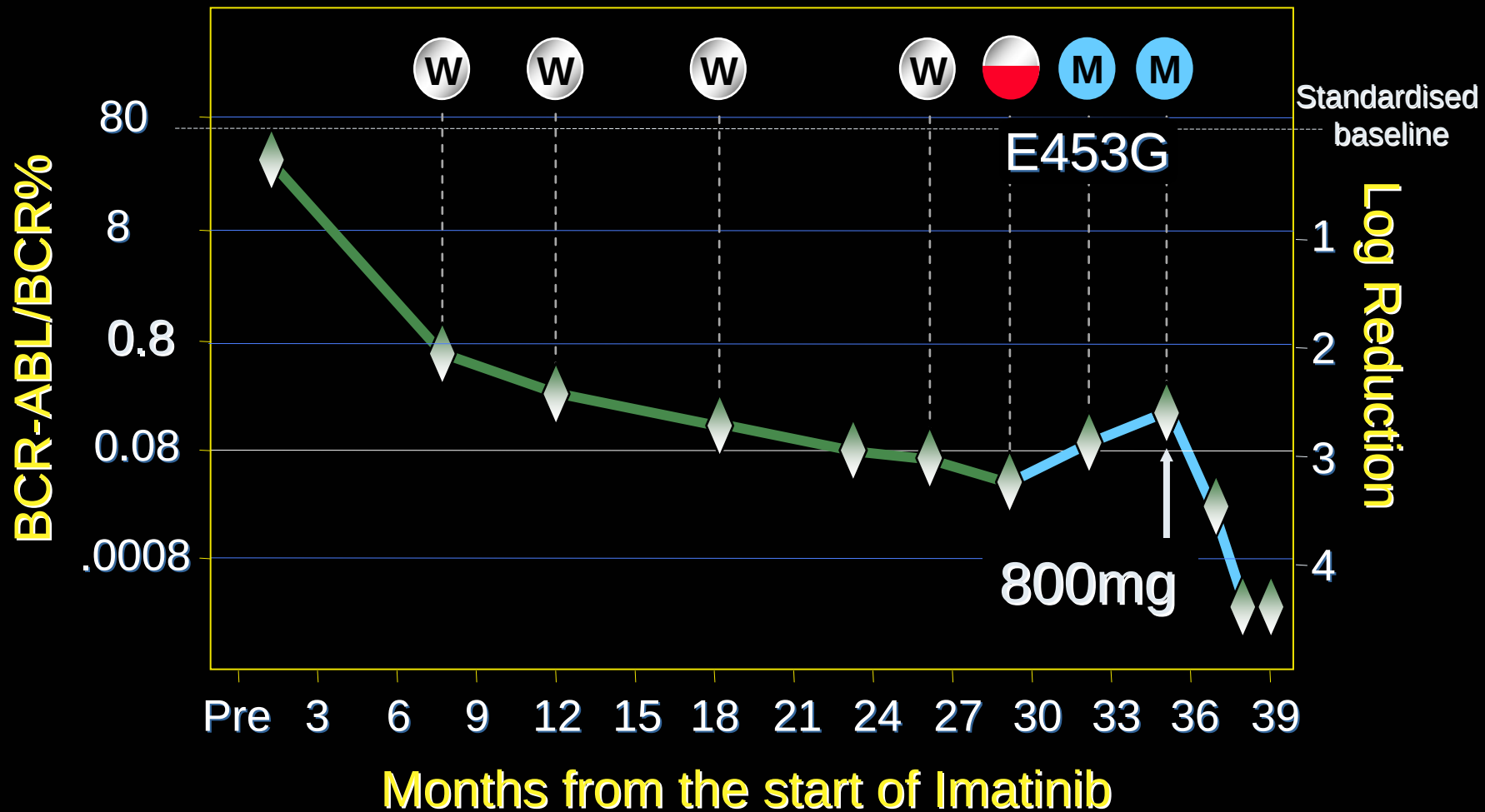
Track Individual Response



Track Individual Response

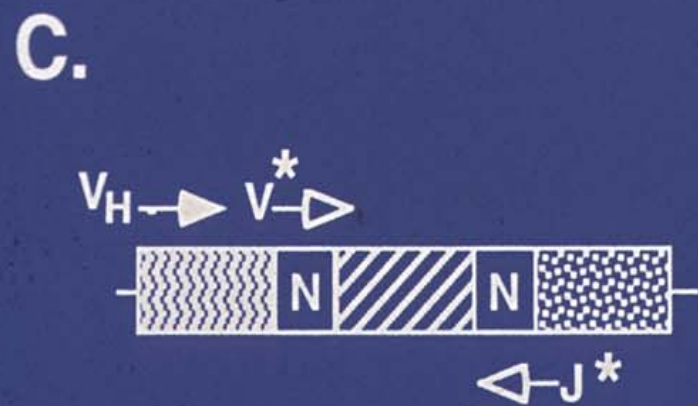
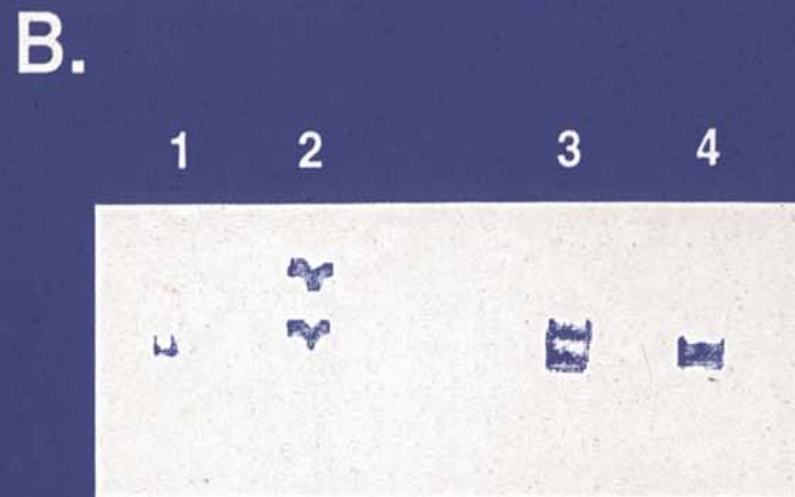
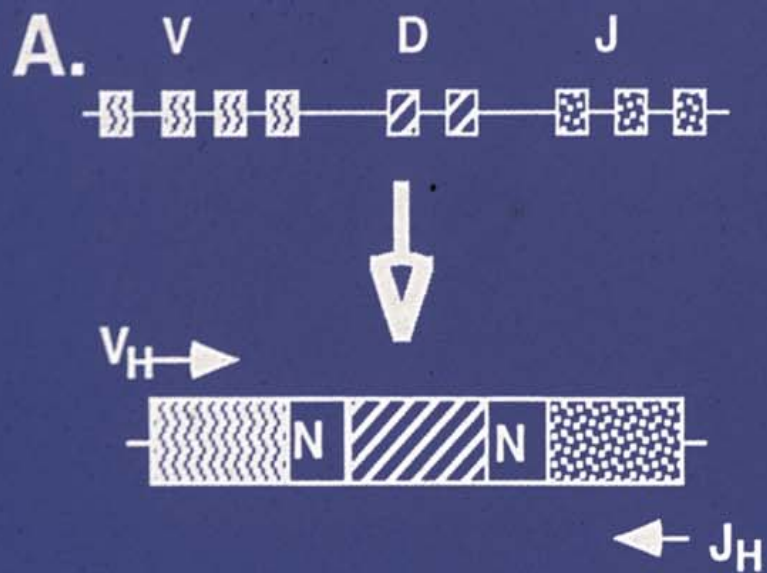


Track Individual Response



MRD detection in ALL predicts relapse after chemo or BMT

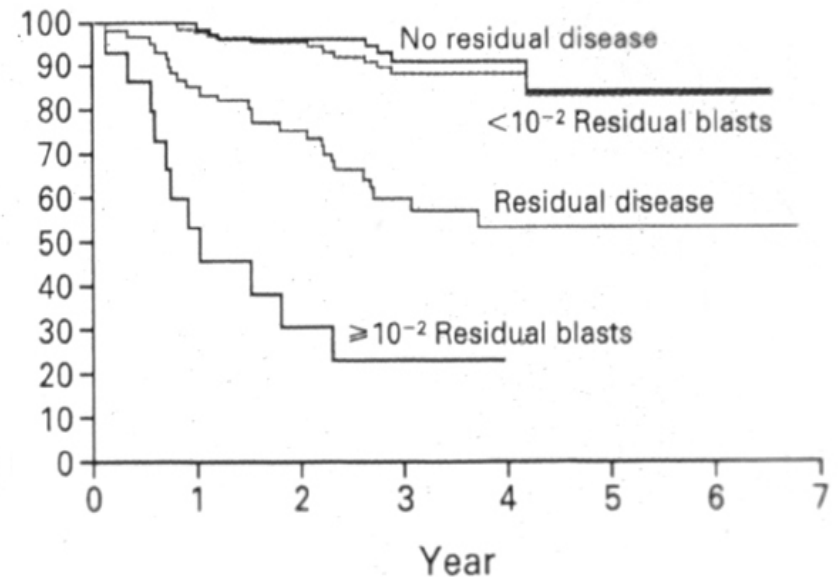
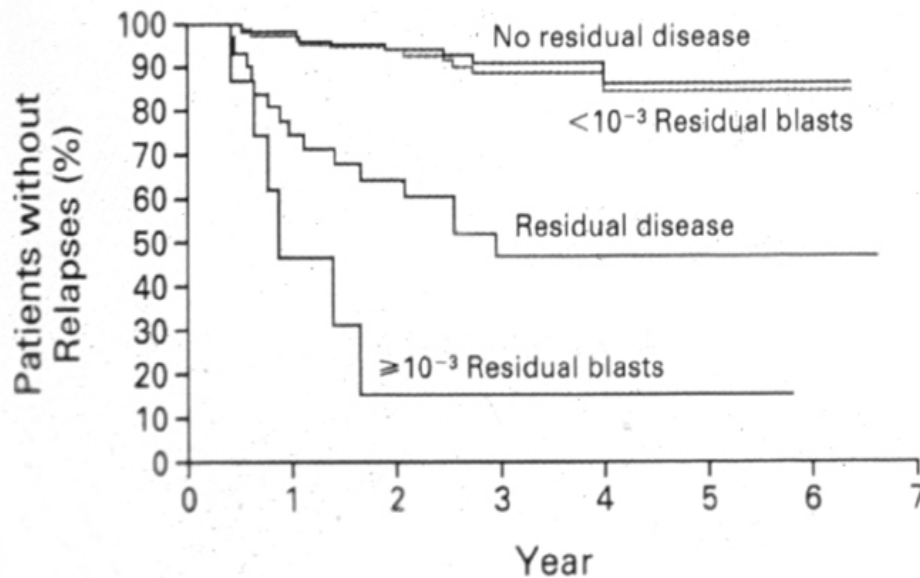
- Chemotherapy-MRD after induction or consolidation predicts relapse.
 - RR of relapse ~ 5-15
- Transplantation-MRD pre- or post-BMT predicts relapse and outcome.
 - MRD pre-BMT has worse outcome
 - MRD post-BMT -> RR relapse 5-10



MDR in Pediatric ALL

TABLE 3. RELATIVE RISK OF RELAPSE ACCORDING TO THE PRESENCE OR ABSENCE OF RESIDUAL DISEASE AT TWO TIME POINTS.

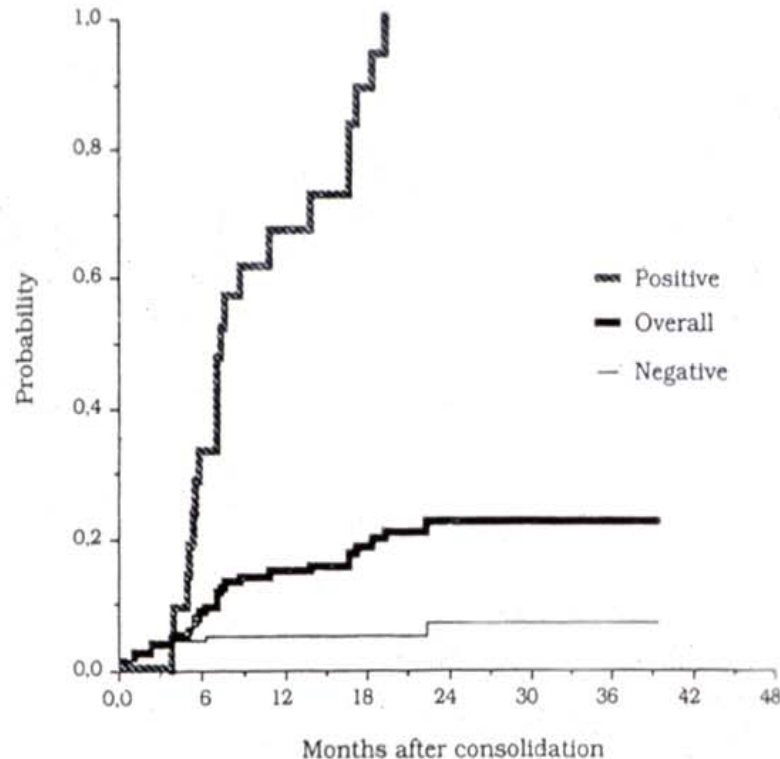
RESIDUAL DISEASE*	AFTER INDUCTION THERAPY, AFTER CONSOLIDATION THERAPY			AFTER INDUCTION THERAPY, AFTER INTERVAL THERAPY			AFTER CONSOLIDATION THERAPY, AFTER INTERVAL THERAPY		
	NO. OF PATIENTS	NO. WITH RELAPSES	RELATIVE RISK†	NO. OF PATIENTS	NO. WITH RELAPSES	RELATIVE RISK†	NO. OF PATIENTS	NO. WITH RELAPSES	RELATIVE RISK†
Absent, absent	73	3	1.0	78	4	1.0	91	7	1.0
Present, absent	15	3	4.9	23	5	4.1	8	2	3.0
Present, present	32	15	15.0	22	11	14.0	22	11	9.6



MRD in t(15;17) AML (APL)

- MRD detection of PML/RARA is strongly associated with relapse (Diverio, Blood, 1998).
- 163 APL patients studied after consolidation.
 - All in molecular remission after consolidation
 - 21 converted to PML/RARA +; 20/21 relapsed
 - 8/142 PML/RARA - patients relapsed

MRD in t(15;17) AML (APL)



~ N=163 patients who were PCR- after consolidation,
≥ 6 months f/u post-consolidation, and ≥ 2 PCR assays

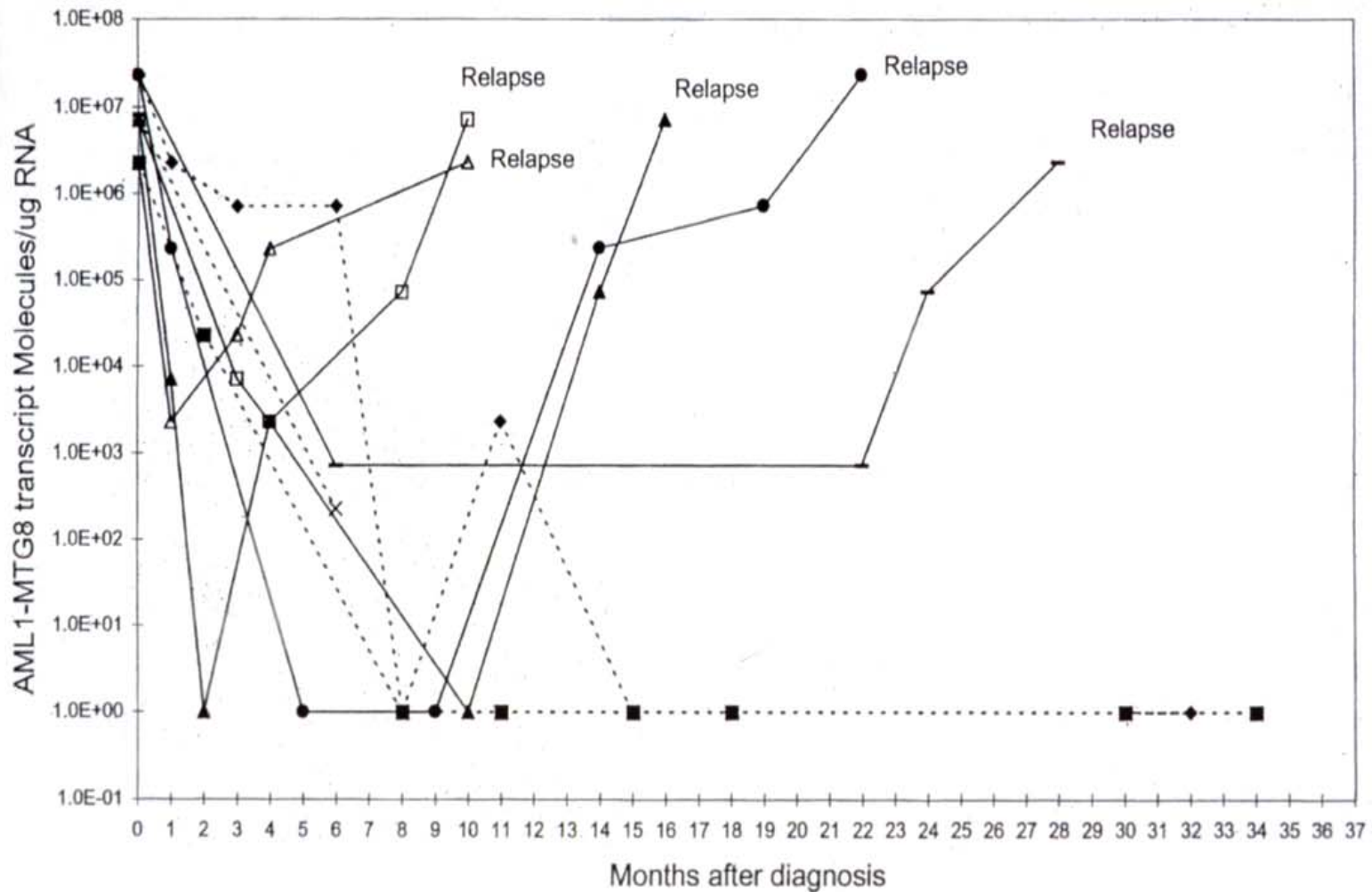
~ 21 pts. became PCR+; 20/21 relapsed

~ 8/142 PCR- pts. relapsed (RR=32)

MRD in t(8;21) AML

- MRD variably associated with relapse.
 - Most (all?) survivors are AML1/ETO +!
 - “Dormancy”
 - AML1/ETO found in erythroid, lymphoid cells
 - Is this a stem cell disease?
 - Quantitative RT-PCR helps in picking patients at highest risk of relapse.

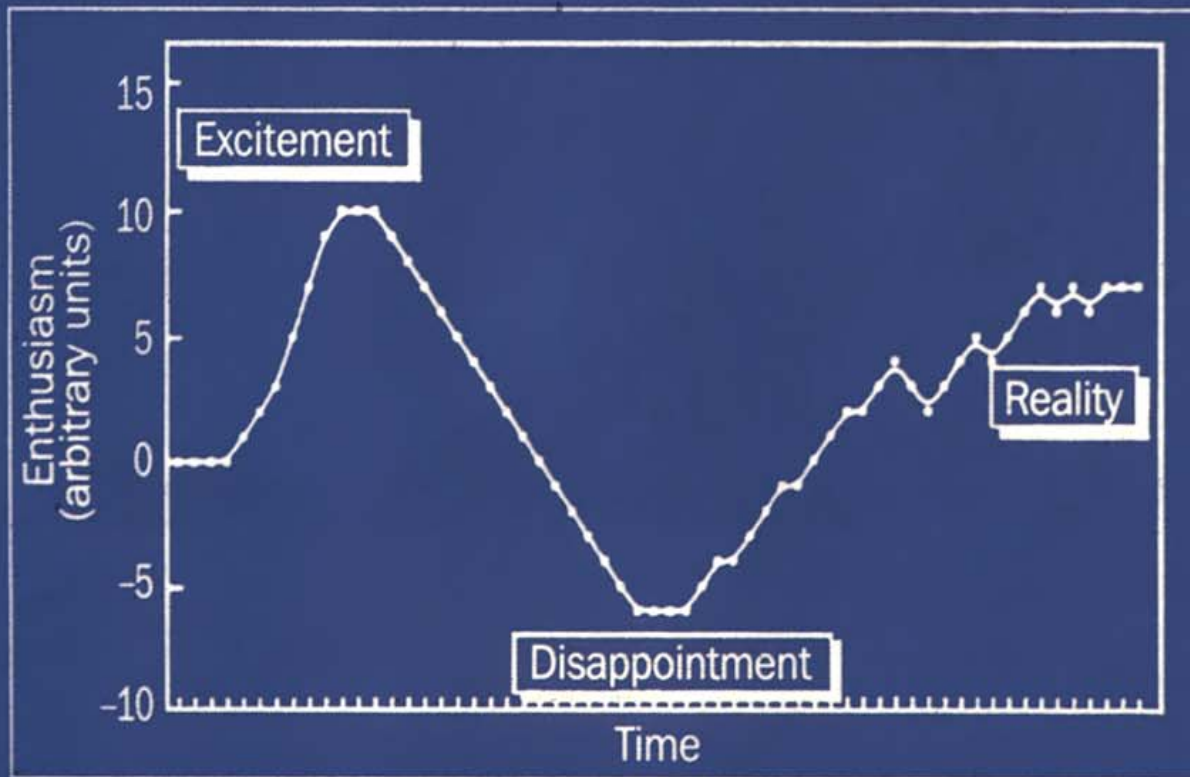
MRD in t(8;21) AML



Targets for monitoring

- Chronic myeloid leukemia
 - BCR/ABL by RT-PCR
- Acute myeloid leukemia
 - PML/RAR
 - AML/ETO
 - MYH11/CBFFB
 - FLT3
- Acute lymphoblastic leukemia
 - BCR/ABL
 - IgH VDJ or TCR rearrangements
- Non-Hodgkins lymphoma
 - IgH-Bcl2

The Natural History of most things





Good night and thanks from...

Radich lab (FHCRC)

Rosetta Inpharmatics

Cheryl Willman (SWOG)

Brian Druker (OHSU)

Wendy Stock (U Chicago)

Charles Sawyers (UCLA)