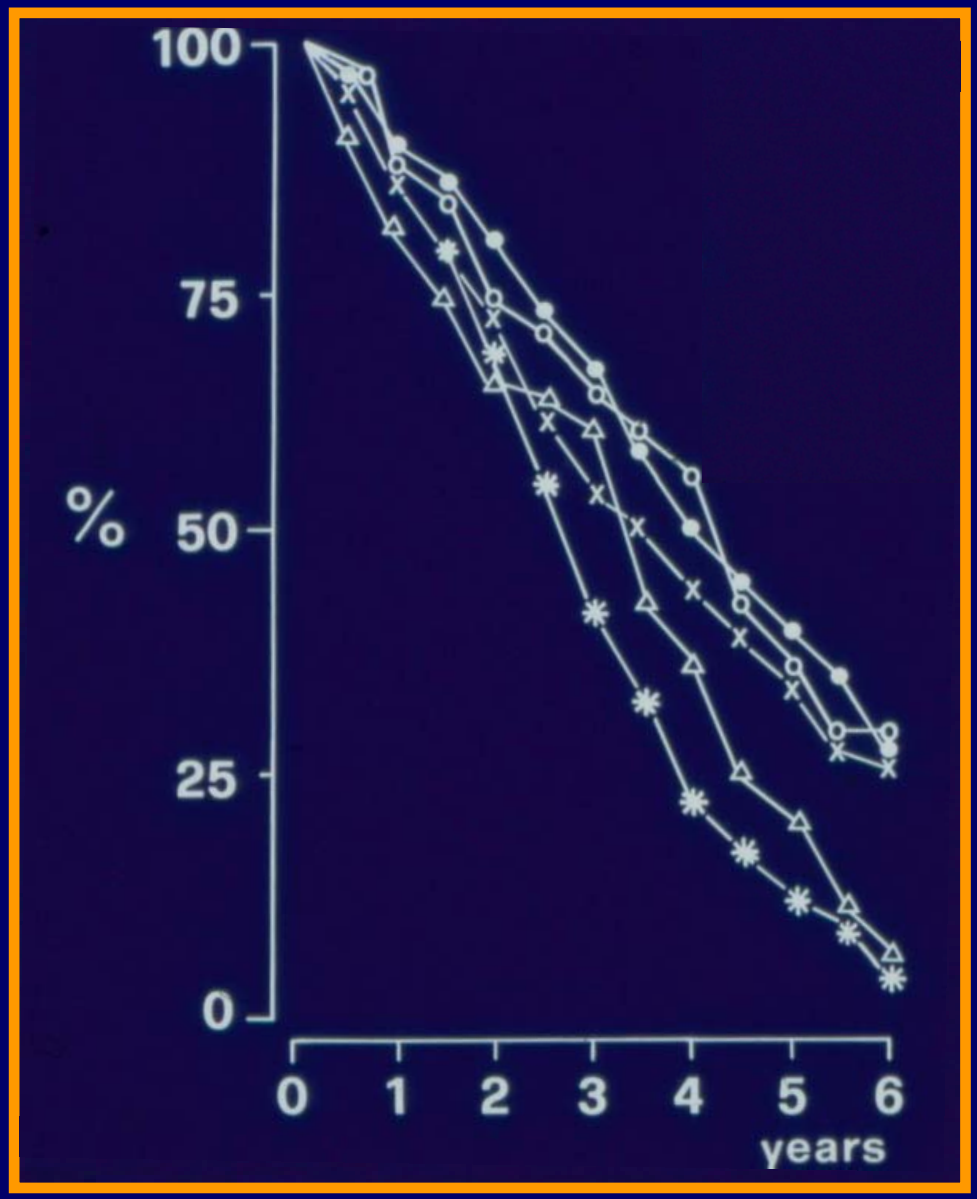
The current standard of care in CML

Gianantonio Rosti, MD
University of Bologna
Bologna, Italy

Ph+ CML: Overall Survival 1898-1977
… just to remember



*	Minot et al.	1898 - 1923	no therapy
△	M.R.C.	1959 - 1963	Busulfan
x	Hop. St. Louis	1957 - 1973	Bus / Hu
o	Sloan Kett.	1970 - 1975	L 5
•	ICSG on CML	1973 - 1977	CML/73+74

Clinical Landmarks in CML

1845 1865 1879 1903 1953 1965 1968 1983 2001

First description of CML

Fowlers's solution -1% arsenic trioxide

Staining methods for blood

Radiotherapy

Busulfan

Hydroxyurea

BMT

Interferon

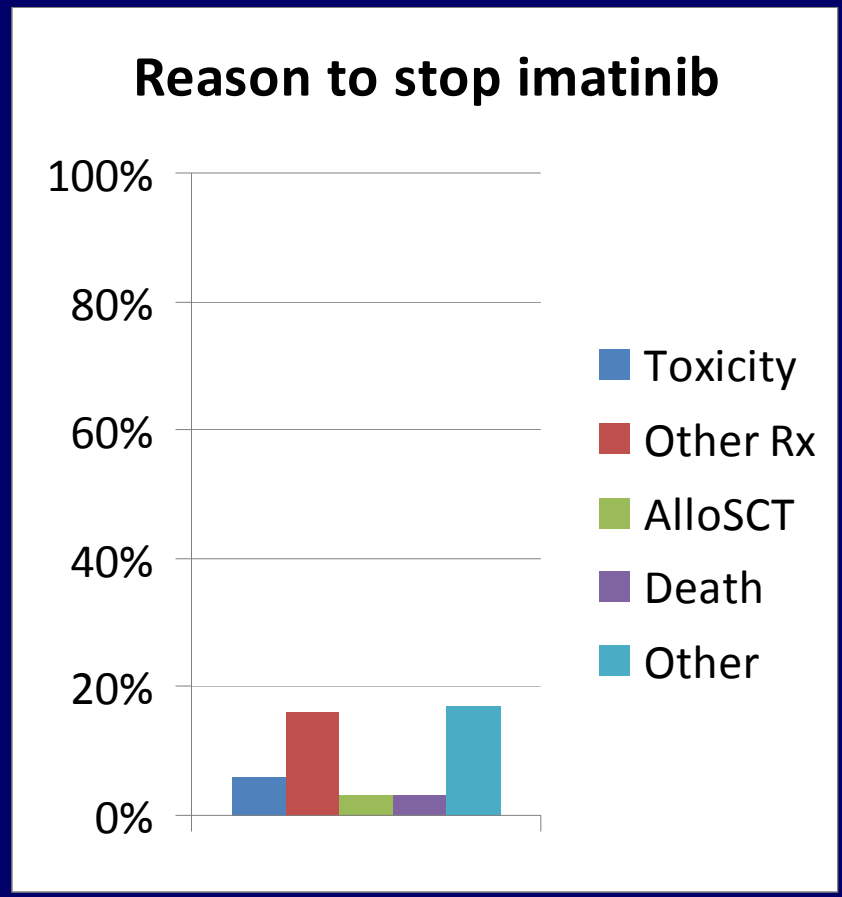
STI571

IRIS trial follow-up: 8 years on imatinib

After 8 years, 55% remain on imatinib.

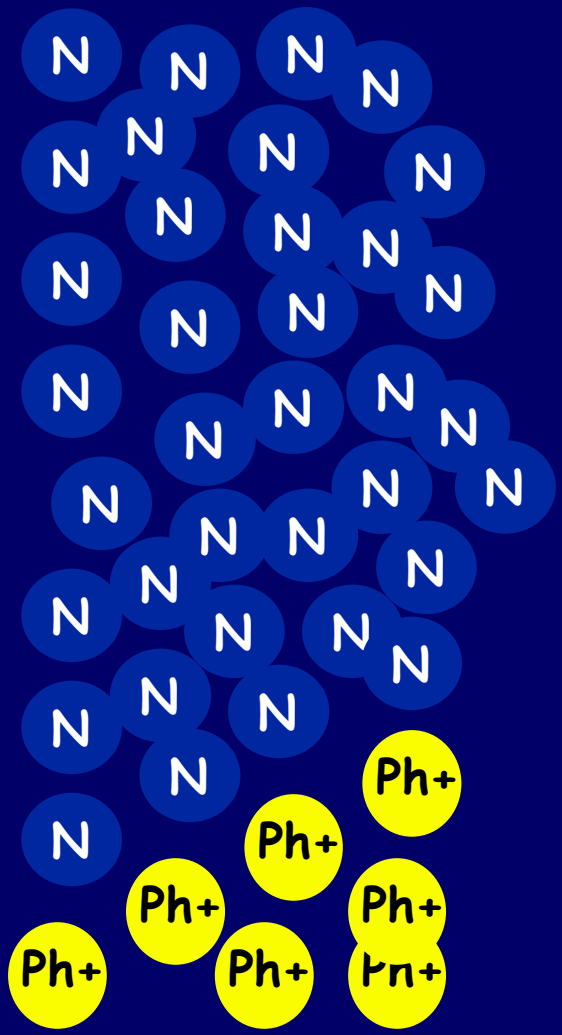
Among the others:

- 6% ceased with toxicity
- 16% moved to other Rx
- 3% proceeded to HSCT
- 3% died while on study
- 17% off study for other reasons: withdrew consent, lost to follow-up



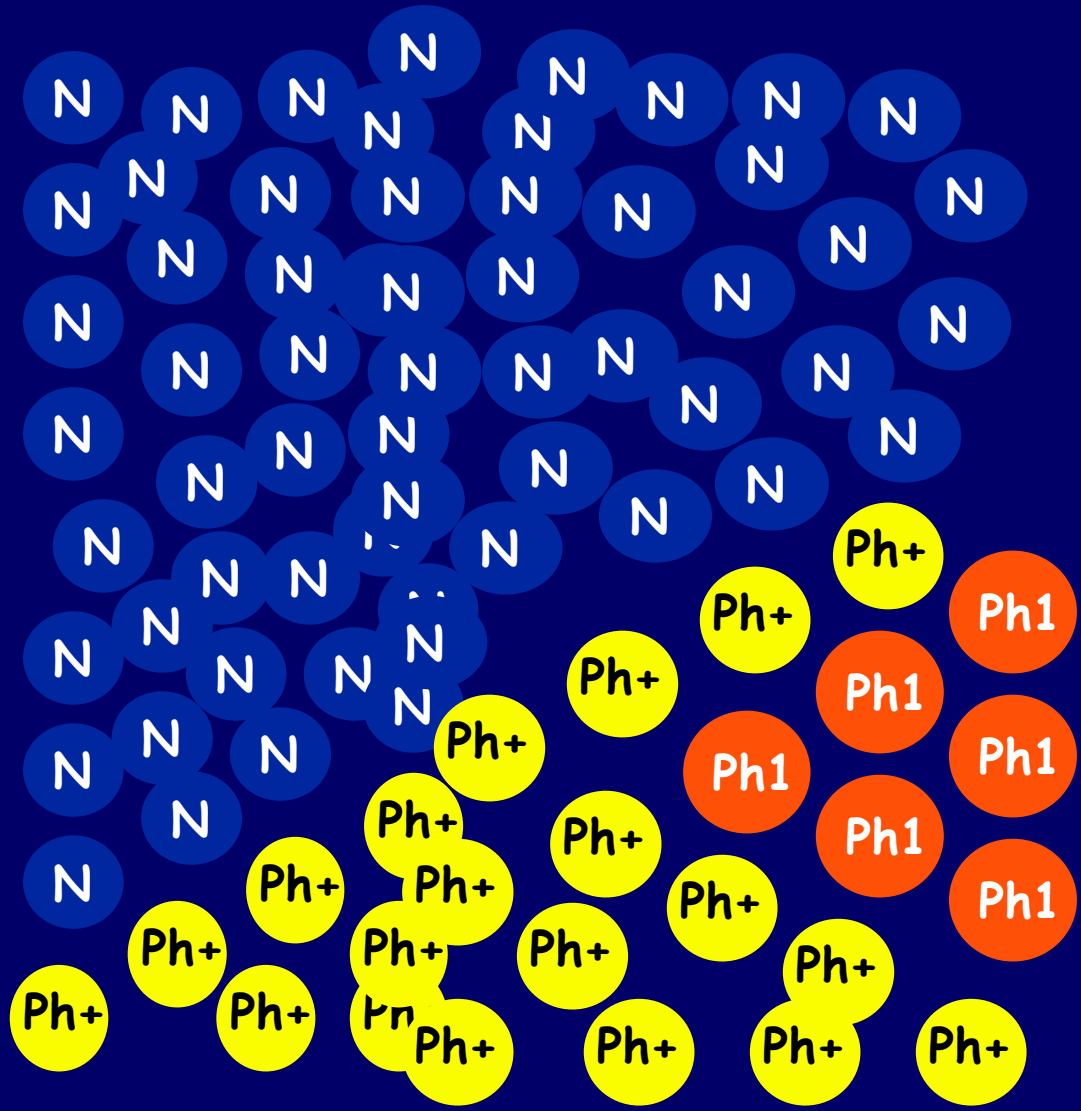
Deininger M et al. ASH 2009;#1126.

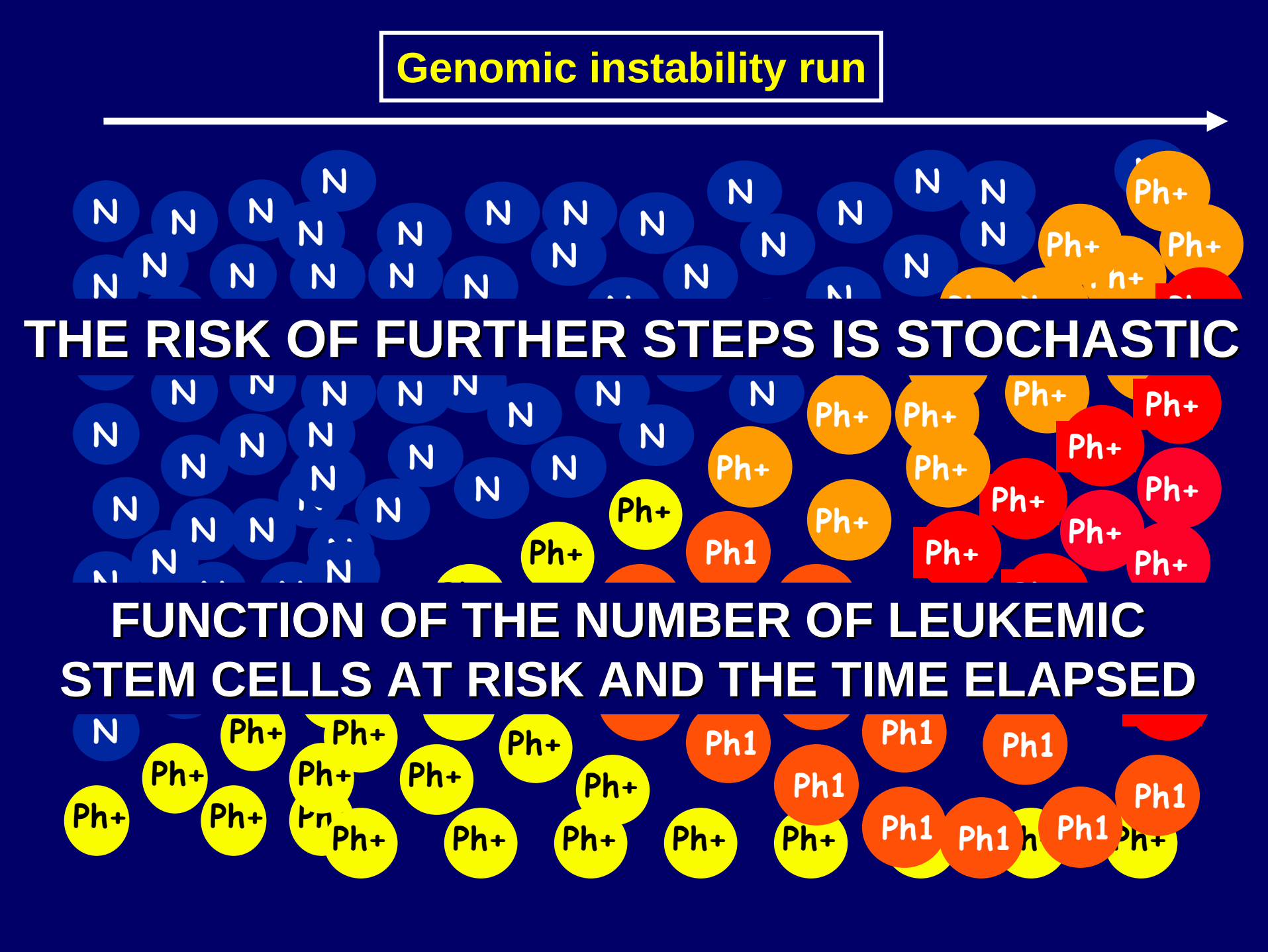
Genomic instability run

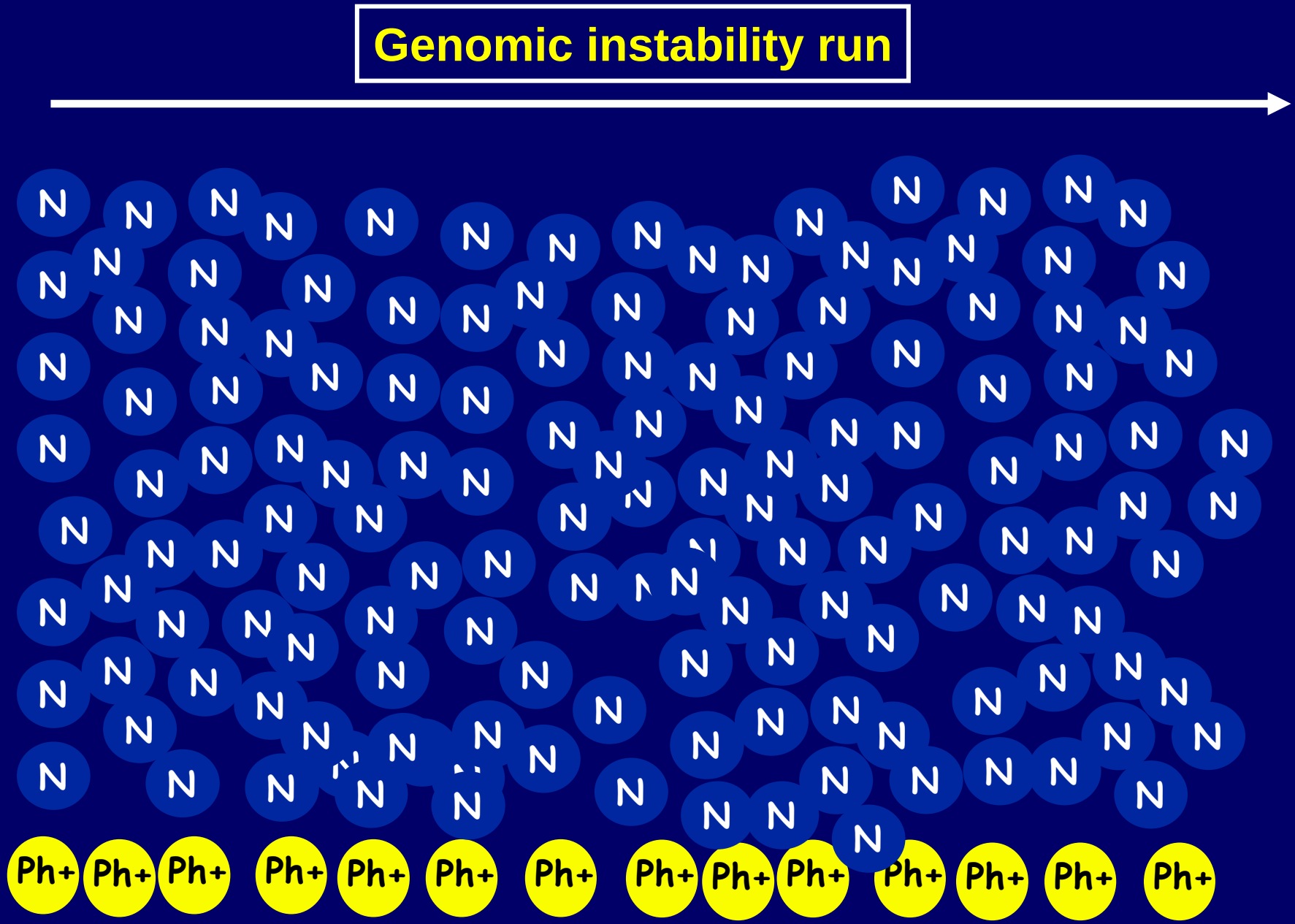


BONE MARROW
Stem Cell Compartment

Genomic instability run

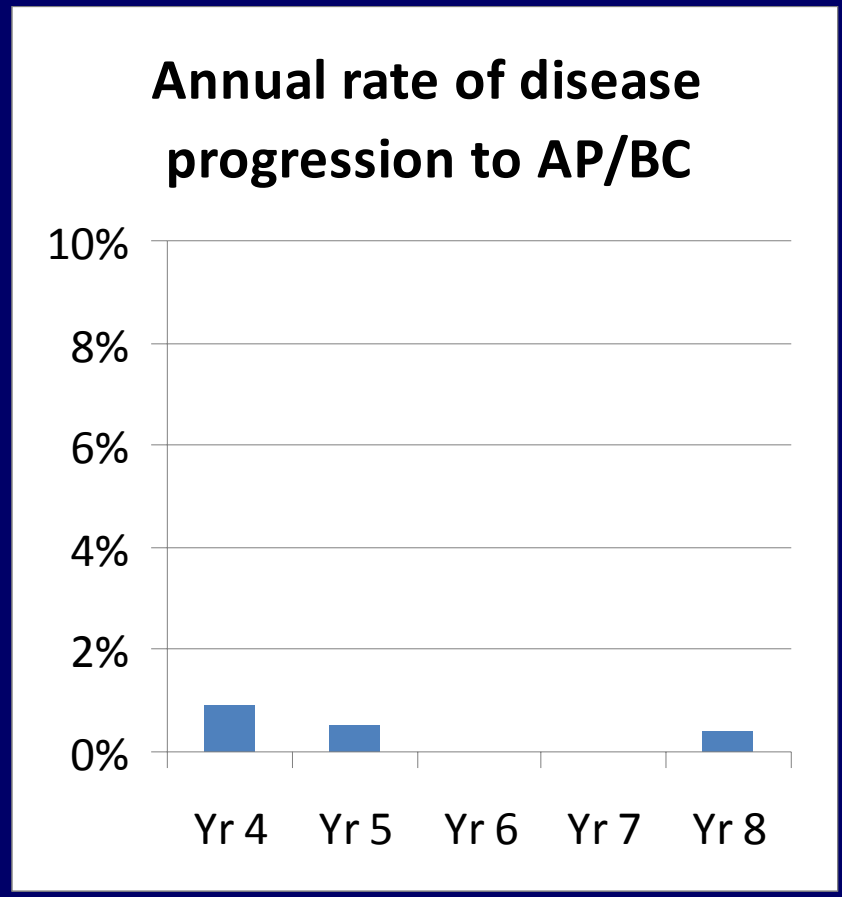



Genomic instability run
N
Ph+
Ph1
THE RISK OF FURTHER STEPS IS STOCHASTIC
FUNCTION OF THE NUMBER OF LEUKEMIC STEM CELLS AT RISK AND THE TIME ELAPSED


Genomic instability run
N
Ph+

IRIS trial follow-up: 8 years on imatinib

- Among patients randomized to imatinib, after 8 years:
  - 81% event-free survival
  - 85% overall survival
  - 86% had achieved MMR
  - 92% not progressed to AP/BC
- Annual rate of progression to AP/BC in years 4 to 8 was:
  - 0.9%, 0.5%, 0%, 0%, 0.4%.
- **No patient in MMR at 12m subsequently progressed.**



Deininger M et al. ASH 2009;#1126.

It appears to me a most excellent thing for a physician to cultivate prognosis … by seeing and announcing beforehand those who will live and those who will die, he will thus escape censure

Hippocrates, Aphorisms II.19

Which factors predict success on imatinib?

"Predictors" of success

- Trough imatinib level >1000
  - But more AE's if trough >2000
- Patient adherence to therapy
  - Higher if on imatinib only
- MMR achieved by 1 year
  - No patient with MMR at 1yr later had CML progression

"Predictors" of failure

- High Sokal score
  - But effect partly overcome if trough imatinib level >1000
- Frequent dose interruptions
  - Particularly if prolonged >2wk
- Inability to maintain 400mg
  - Especially if myelosuppression

Larson RA et al. ASH 2009; Deininger M et al. ASH 2009; St Charles M et al. ASH 2009;#2209

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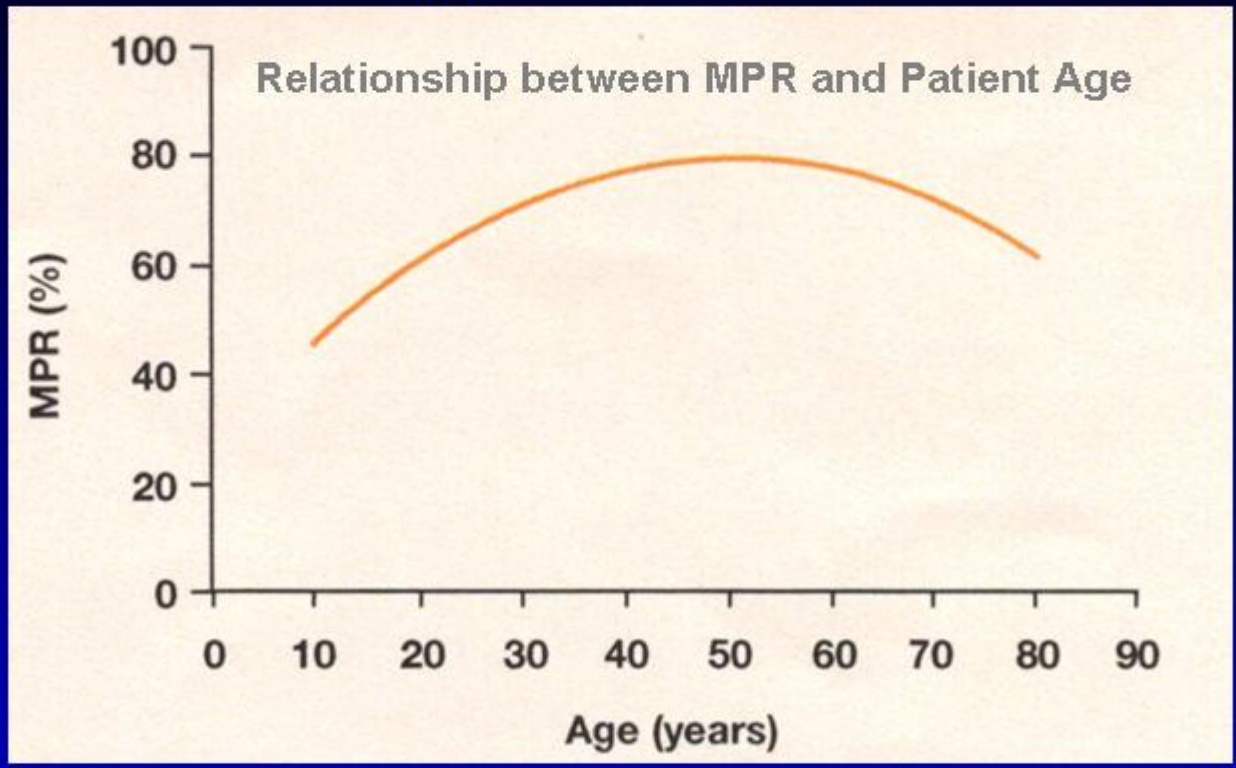
Compliance and persistency with imatinib

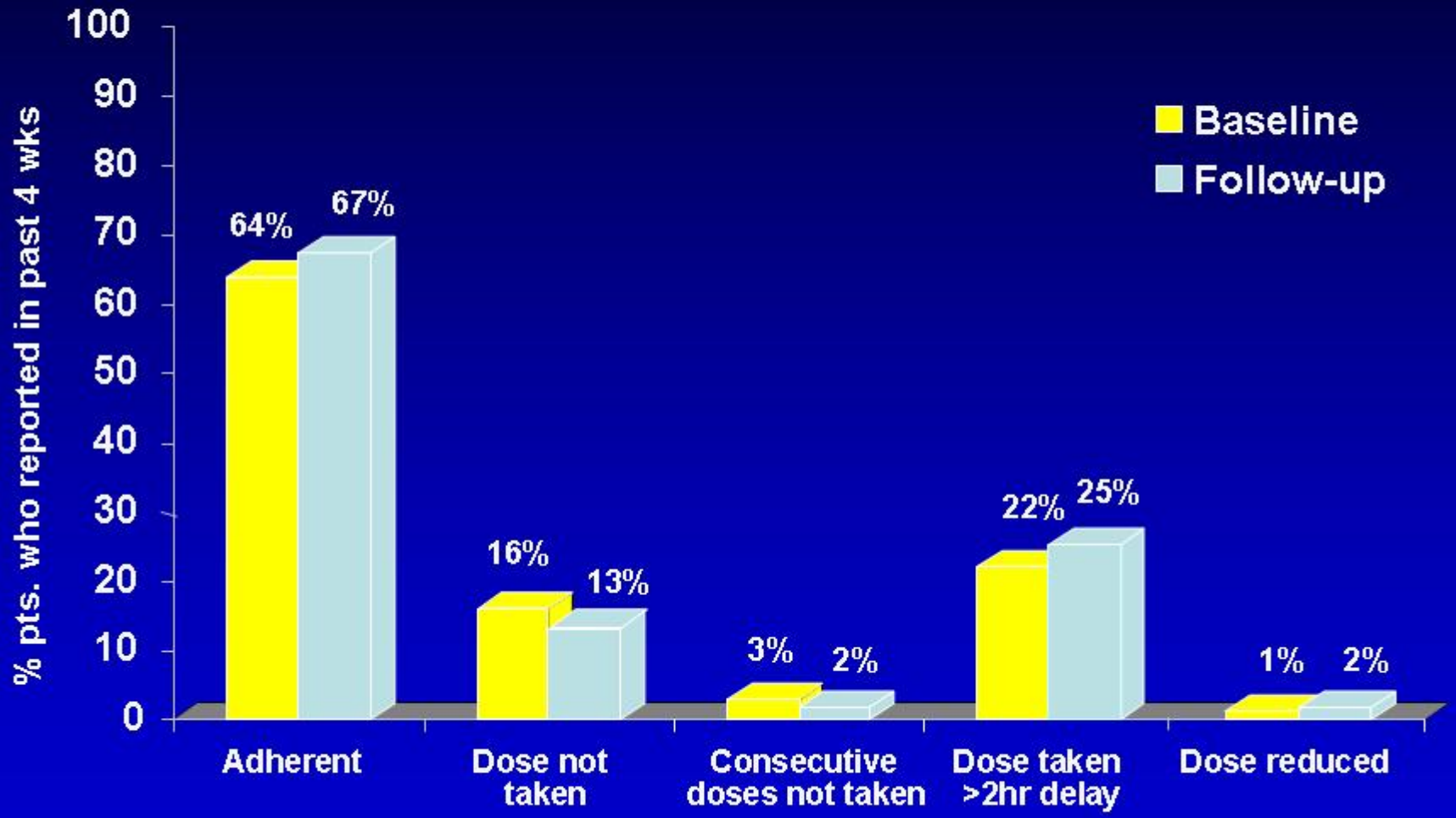


Compliance and persistency with imatinib	CML (n=286)	GIST (n=34)
Medication possession ratio (MPR), mean (SD)	76.3 (28.3)	74.5 (30.7)
Discontinued imatinib for >30 consecutive days n (%)	90 (31.5%)	8 (23.5%)

MPR = total days supply of imatinib in the first year divided by 365

Darkow et al. Pharmacoeconomics 2007, 25:481-96.

Patient reported adherence and non-adherence (Adagio study)



Overall adherence and non-adherence by behavior, self-reported

Noens L. et. al. Blood 2009 113:5401-5411

Variables associated with level of adherence Multivariate canonical correlational model

- Factors correlated with better adherence include:
  - Patient: knowledge, education, self-efficacy, and number of meds taken
  - Physician: specialty and university affiliation, CML practice and time spent on initial visit at diagnosis
- Factors correlated with poor adherence include:
  - Patient: older age, poorer functional status / quality of life, longer disease history & time on imatinib, lower rating of chronic care and males living alone
  - Physician: years in practice and duration of follow-up visits

Noens L et al. Blood 2009 113:5401-11.

Adagio Study conclusions

1. Adherence is associated with higher rates of optimal response and CCyR
2. Non-adherence is more prevalent than patients, physicians and family members believe
3. Several determinants may serve as alert signals, many of which are clinically modifiable
4. Non-adherence must be ruled out as a possible reason for suboptimal response or relapse before switching therapy

Noens L et al. Blood 2009 113:5401-11.

How health professionals can help patients meet the challenges of taking oral TKIs

- **Work with Patient Advocates and Support Groups in devising comprehensive and easy-to-understand information about:**
  - **WHY** dosage instructions need to be followed
  - **WHY** there is a need to take the drug regularly
  - The degrees of **flexibility** in a given schedule
  - **Potential interactions –** drugs/foods/natural supplements
  - **Simple remedies** for managing side effects

  - **HOW THE DRUG WORKS!**

Which genetic factors influence response?

Genes linked to lower imatinib response:

- hOCT1
  - Pumps imatinib into CML cells
- HNF4A
  - Regulates expression of hOCT1
- MDR1
  - Pumps imatinib out of CML cells and out of liver/gut
- CYP1A2
  - Minor metabolizing enzyme in liver
- ERCC5
  - Enzyme involved in nucleotide base excision repair of DNA damage
- XRCC4
  - Enzyme involved in repair of double-stranded DNA breaks

Soverini S et al. ASH 2009;#3283; Kim JA et al. ASH 2009;#3284;
Van Erp N et al. Clin Cancer Res. 2008 Dec 15;14(24):8308-13.

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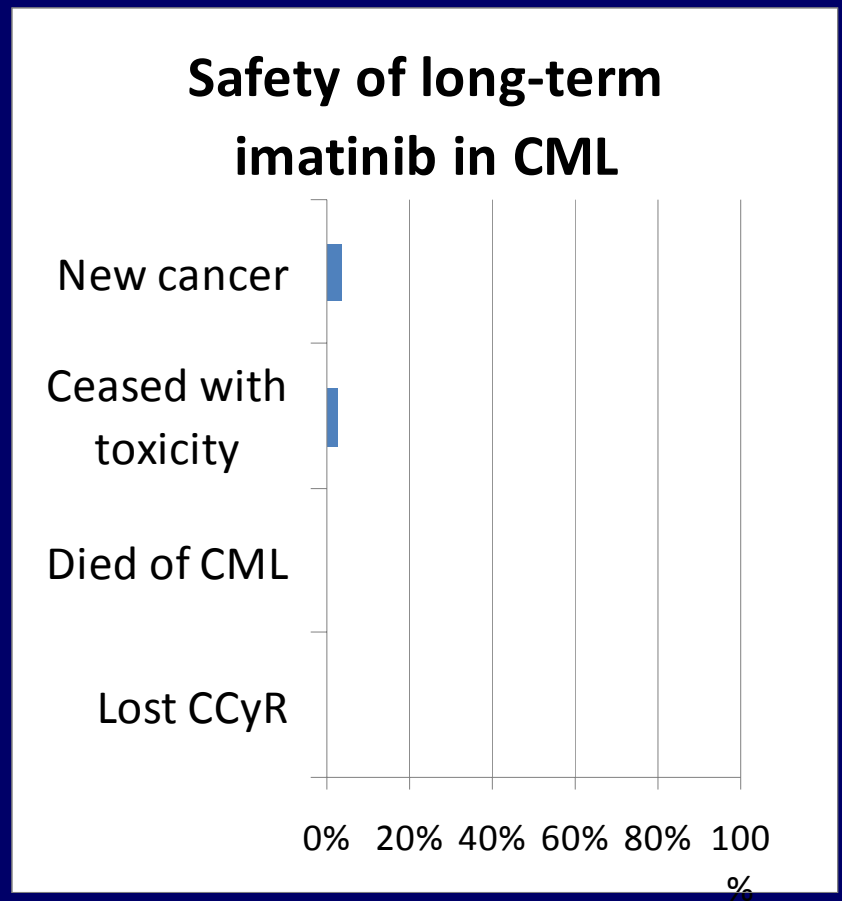
Long-term safety of imatinib in CML patients

- Global study of long-term imatinib
  - 834 CML patients already in CCyR,
  - followed for median 4 years
- Common adverse events:
  - Muscle cramps, fatigue, oedema, skin fragility, diarrhoea.
- Efficacy results:
  - 36% achieved CMR
  - 0.6% lost CCyR
  - 0.7% died of CML
- Safety results
  - 2% discontinued due to toxicity
  - 3.5% developed another cancer



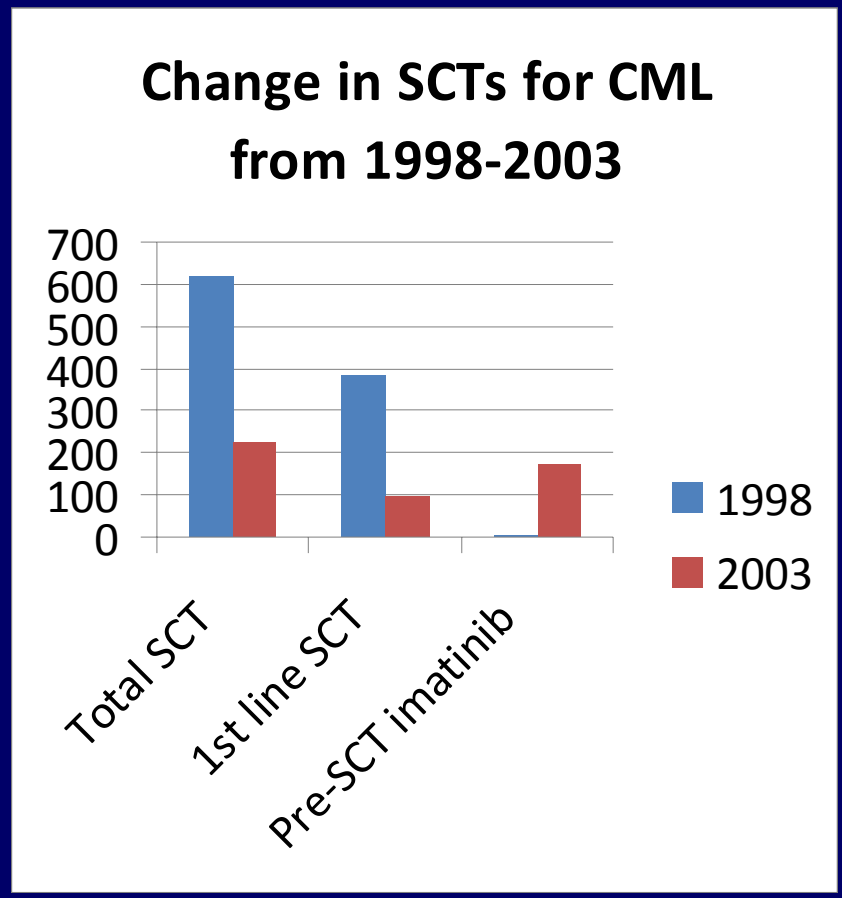
Kim DW et al. ASH 2009;#2199.

Evolving strategies in 1st line CML

- 2000: IRIS study
  - imatinib 400mg; escalate if lack of response
- 2002: TIDEL 1 study
  - imatinib 600mg; escalate if sub-optimal response
- 2004: TOPS study
  - imatinib 800mg; de-escalate for toxicity
- 2006: TIDEL 2 study
  - imatinib 600mg; adjust for trough level and response;
  - switch to nilotinib if needed

Rapid impact of imatinib on BMTs

- US study of numbers of stem cell transplants (SCTs) in CML patients from 1998 to 2003
- SCTs for CML fell by 64%:
  - 617 in 1998; 223 in 2003
- 1st-line SCTs fell by 74%
  - 383 in 1998; 98 in 2003
- Pre-SCT imatinib therapy increased from 1% to 77%



Giralt SA et al. Br J Haematol. 2007 Jun;137(5):461-7

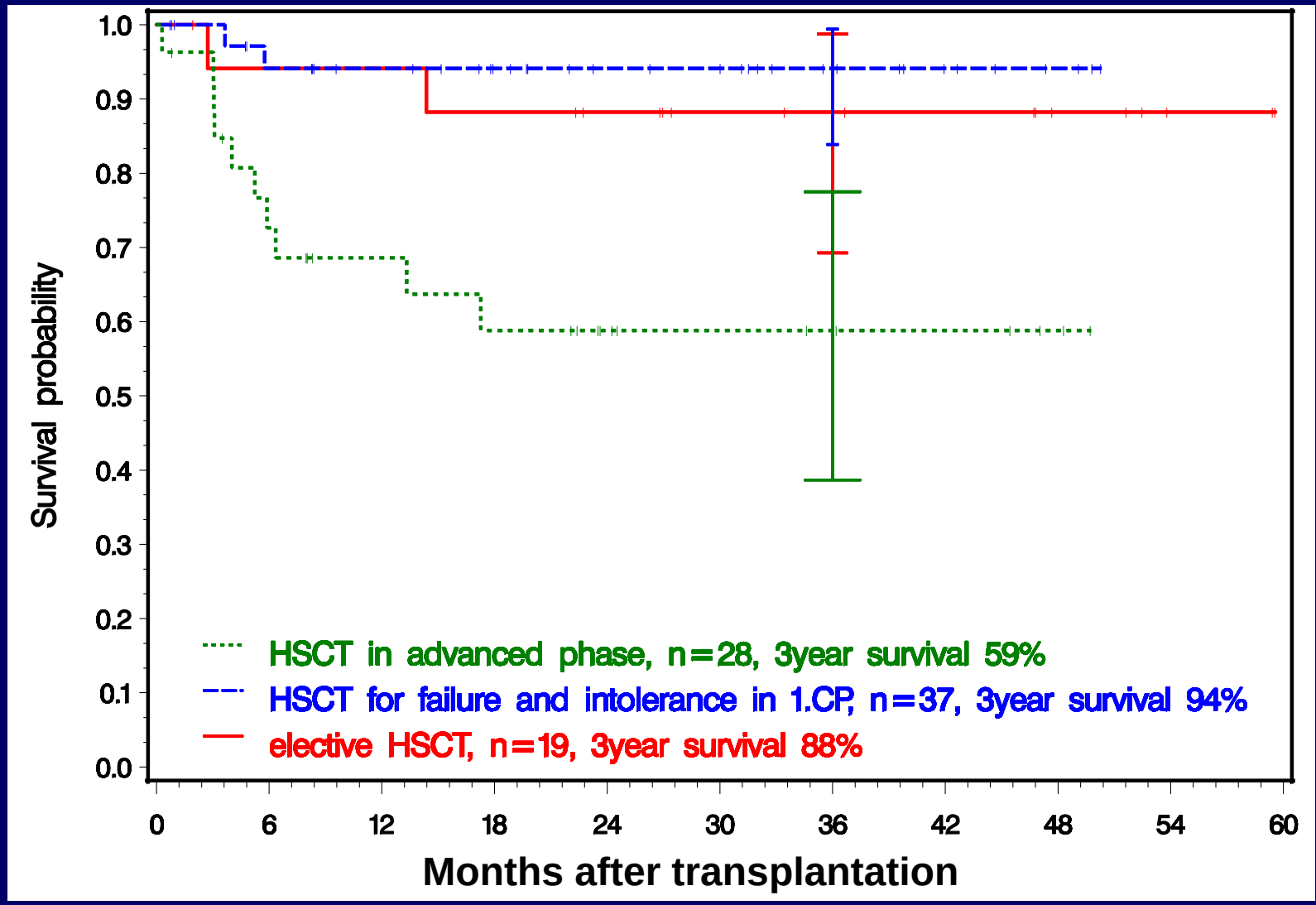
CHRONIC MYELOID LEUKEMIA
PERFORMING ALLOGENEIC STEM CELL TRANSPLANTATION*

- AT DIAGNOSIS (front-line)	- In pts presenting in AP or BP. Pretreatment with a TKIs recommended
- IN CASE OF IM-FAILURE	- In pts who have already progressed to AP or BP; pretreatment with a 2nd generation TKI is recommended - In patients carrying the T315I mutation
- IN CASE OF FAILURE OR SUBOPTIMAL RESPONSE TO 2nd GENERATION TKIs (3rd line)	- In all eligible patients, depending on response (suboptimal or failure) and on EBMT risk score

*STANDARD (MYELOABLATIVE), FROM HLA-ID SIBS OR MATCHED UNRELATED DONORS (8/8 or 7/8 A,B,C,D, high resolution)

ELN, JCO 2009

Allo-SCT for CML in the imatinib era



Saussele et al. Blood. 2010 Mar 11;115(10):1880-5.

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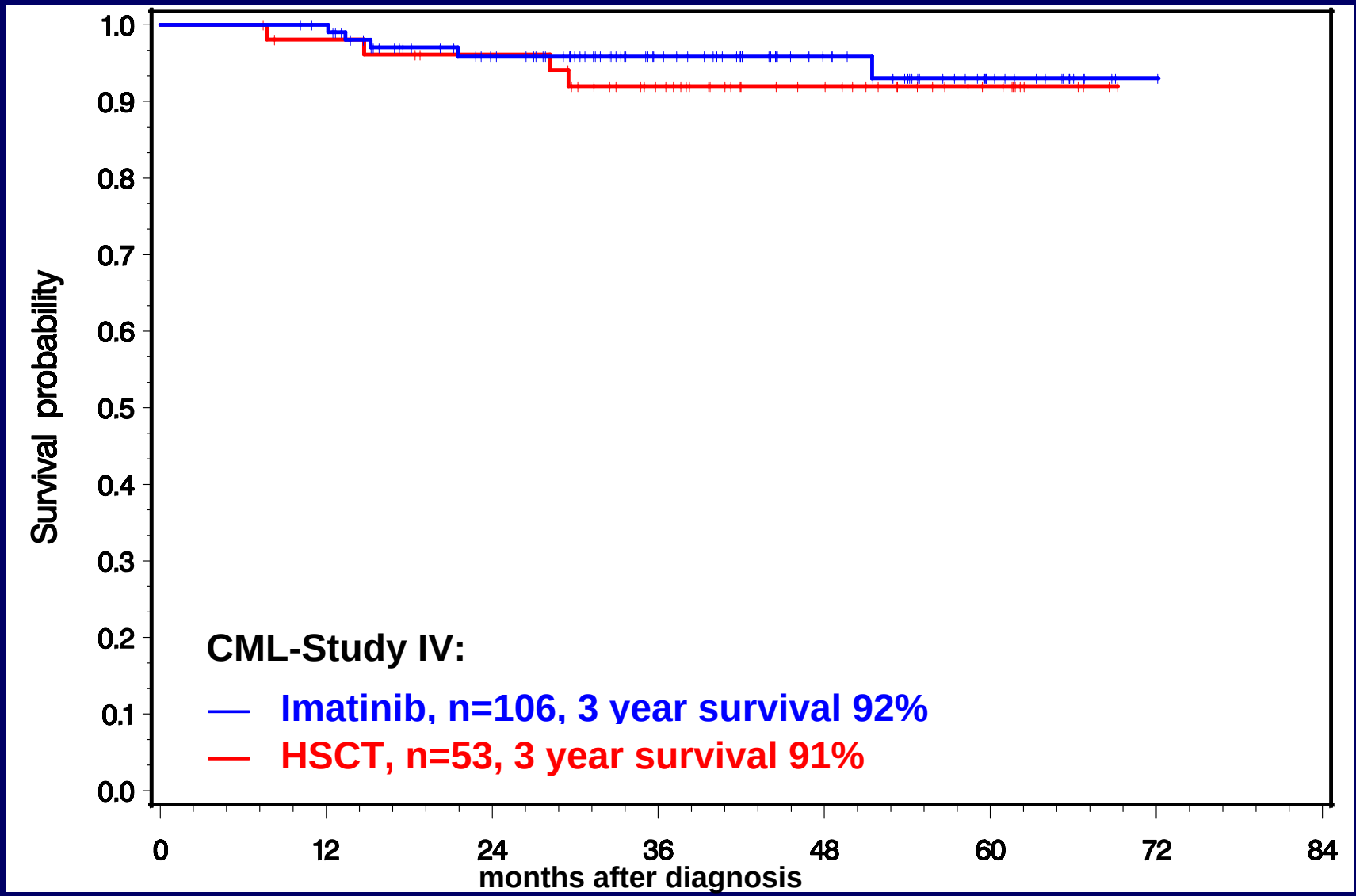
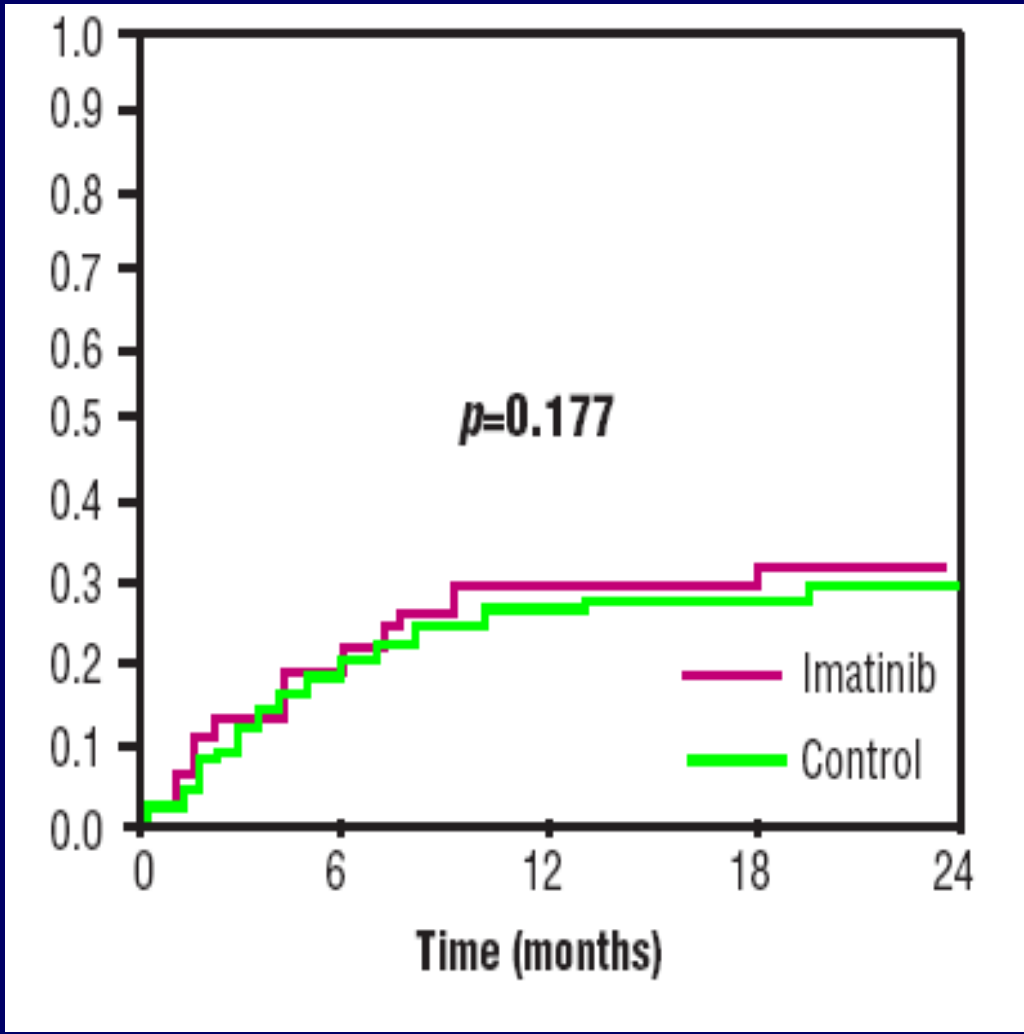


Saussele et al. Blood. 2010 Mar 11;115(10):1880-5.

Imatinib therapy pre-treatment does not adversely affect treatment-related mortality



Deininger et al., Haematologica. 2006 Apr;91(4):452-9

Conclusions on First-line imatinib in chronic-phase CML

Wait a little for 2nd-generation TKIs to grow up!

We are probably NOT quite ready to abandon imatinib as 1st-line therapy, due to its unsurpassed long-term efficacy and safety

Mature results from Phase 3 trials of 2nd-generation TKIs against imatinib as 1st-line therapy need to be reviewed before choosing a new 1st-line drug

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