8th International Conference
for Organizations Representing People
with CML or GIST

NEW HORIZONS
in TREATING CANCER

Vösendorf, Austria
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Sponsored by Novartis

CML 101

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CML – A (very) brief history

- 1960 Peter Nowell & David Hungerford identify the Philadelphia Chromosome
- 1973 Janet D Rowley names the Ph chromosome as a variant of chromosome 22
- 1983 Research concludes that bcr/abl is the cause of CML
- 1990s STI-571 (imatinib mesylate), a good inhibitor of bcr/abl
- 1998 Novartis initiates phase 1 trials led by

Brian J Druker with Charles Sawyers & Moshe Talpaz

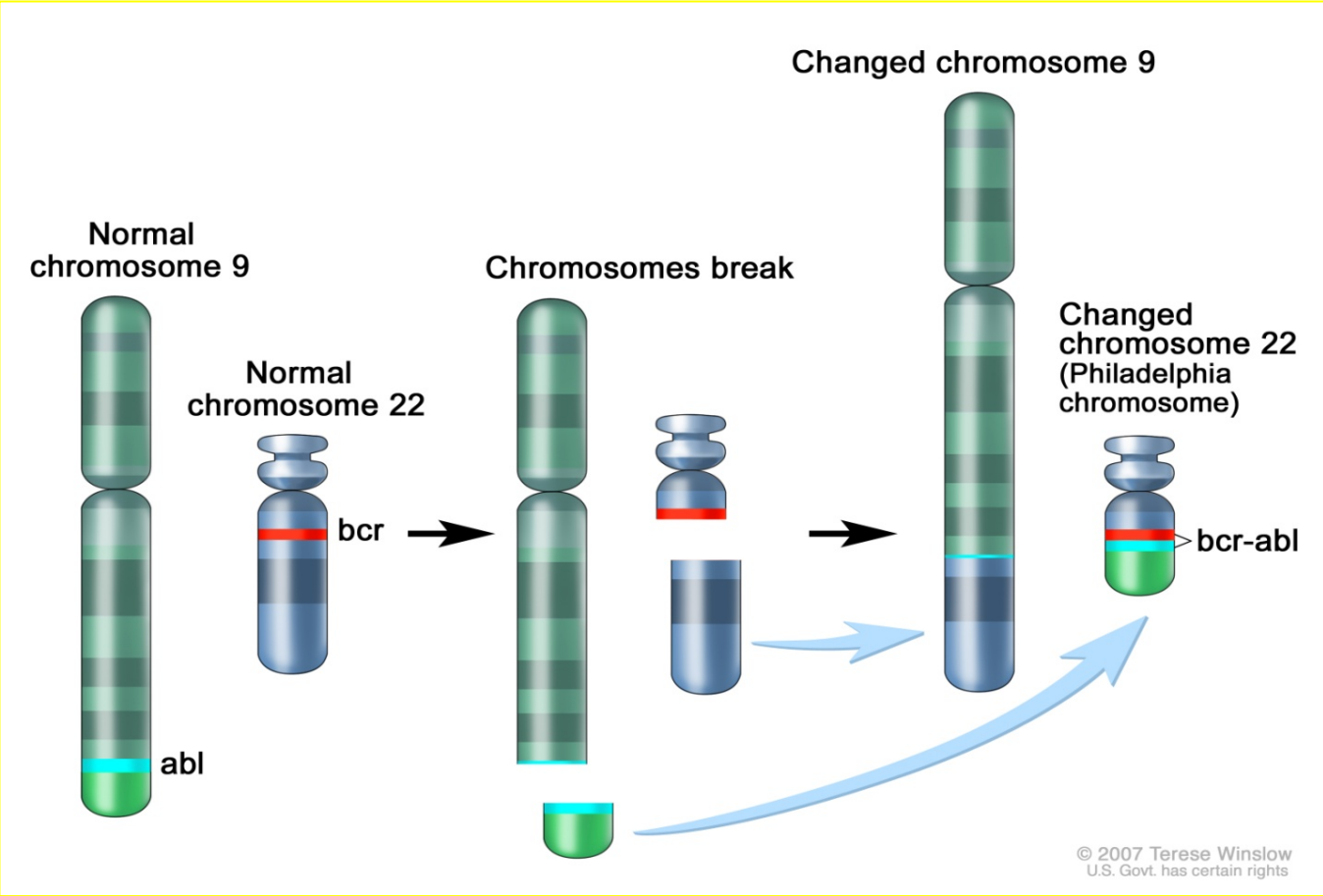
How common is CML?

- 4 main types of leukaemia – all are rare cancers
- 2 acute (develops quickly) – ALL and AML
- 2 chronic (develops slowly) – CLL and CML
- CML is 2nd most common haematological malignancy in western countries ...whereas
- CML is the most common in India and other Eastern countries
- CML occurs in approx. 1 - 1.5 100,000 population per year
- CML affects mainly adults (both males and females) with an average age range at diagnosis of:
- Western countries 50-70 yrs
- Eastern countries 30-60 yrs
  - CML is very rare in children and young people
  - CML is NOT inherited

What causes CML? How is it diagnosed?

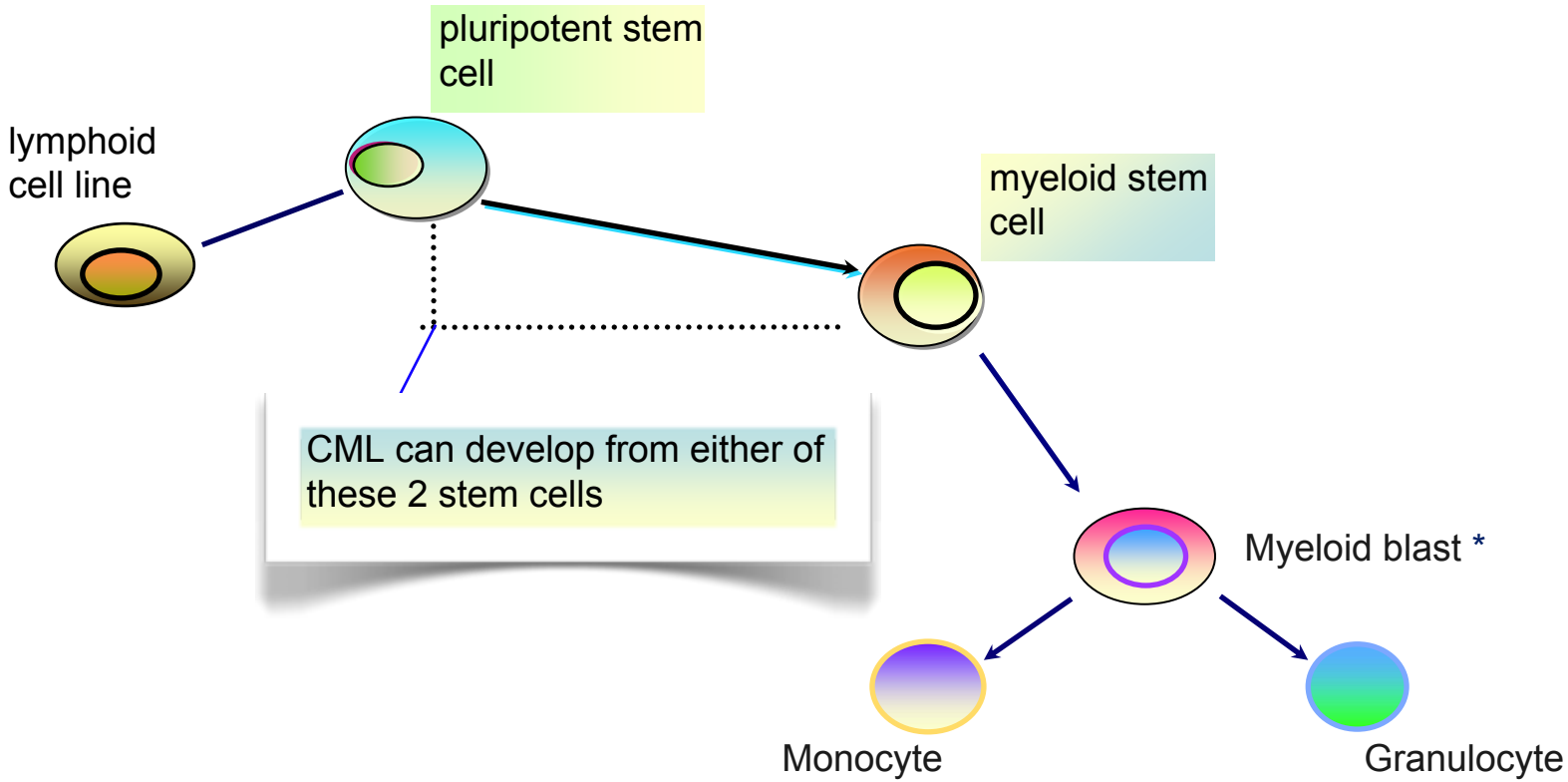
- Exposure to ionising radiation is known to cause CML
- Exposure to chemicals?
- There is no definite consensus on other causes
- Philadelphia Chromosome:
  - 23 pairs of chromosomes
  - In CML, chromosomes 9 and 22 'swap' material parts which results in a new shortened 'variant' of chromosome 22 – the Ph chromosome
  - Bcr/abl is an abnormal gene which leads to excessive production of an enzyme (tyrosine kinase) involved in cell signalling processes
  - Diagnosis comes from the identification of the Ph chromosome in 95% of patients
  - In 2.5% the Ph chromosome is not evident but Bcr/Abl is detectable
  - The remaining 2.5% have 'atypical CML' or CMML (MDS)

Ph chromosome translocation



1. Abl = normal gene 2. Bcr = break point cluster 3. Translocation of material... resulting in the Philadelphia chromosome, a shortened chromosome 22 with a fusion of genetic material resulting in the oncogene Bcr/Abl

Blood cells develop in the marrow



- Newly formed cells of any type are all called BLASTS *
- Normal blasts mature into different cell types
- Ph+ cells are abnormal and replicate uncontrollably

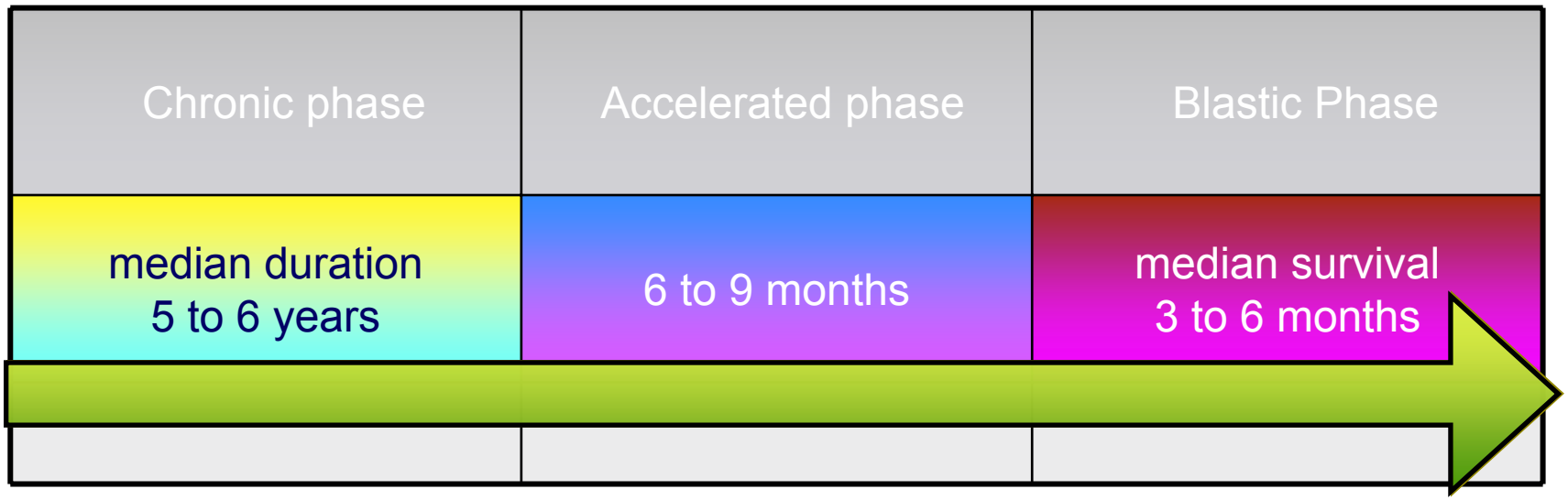
- http://www.youtube.com/watch?v=nP8-9WWp5ZQ

CML therapy – historical overview

Parameter	1980-2000	>2000
Outcome	Fatal	Indolent
Prognosis	Poor	>25 years
1st-line	Allogeneic SCT Interferon-α	Imatinib
2nd-line	not established	2nd-gen.TKI
3rd-line		3rd-gen.TKI novel forms of SCT plus TKI

Clinical prognosis: 3 phases of CML

Timelines in the pre-TKI era



Faderl S, et al. Ann Intern Med. 1999;131:207-219. Pasternak G, et al. J Cancer Res Clin Oncol.

3 phases

Chronic phase	Accelerated phase	Blast phase
• develops slowly • lasts between 3-6 years • no or only vague symptoms • usually high white cell count in blood • <5% immature (blast) cells in the marrow	• lasts between 6-12 mths • more definite symptoms • anaemia – Hgb < 10 • enlarged spleen • increased white cells • increased platelets • 5-30% blasts in marrow • blast cells seen in peripheral blood	• lasts 3-6 months • unpredictable • symptoms increased • enlarged spleen • may not respond to treatment • Ph+ cells have other abnormalities • >30% blast cells in marrow and blood

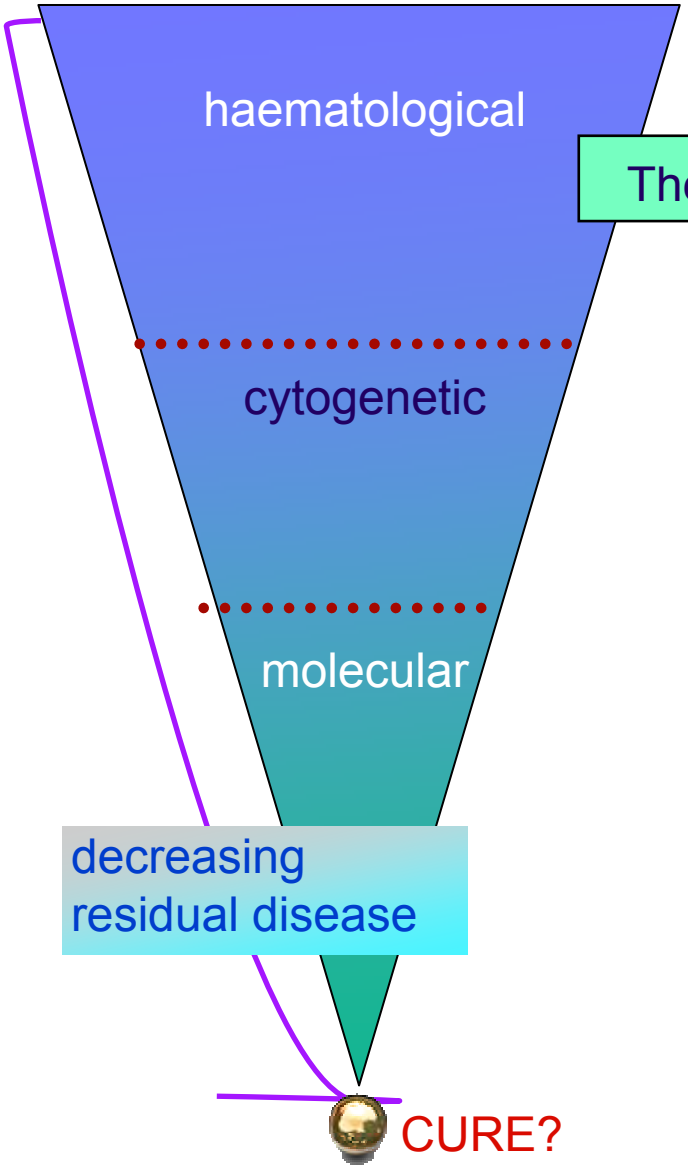
Tyrosine Kinase Proteins – Bcr/Abl

- TKP's signal the cells to divide and reproduce
- The fusion oncogene Bcr-Abl is an abnormal protein which is not regulated as in normal cells … "the switch is always ON"
- The abnormal protein signals the cells to replicate – the production of Ph+ white cells is constant
- Ph+ cells are IMMORTAL!

CML treatment goals

Objectives	Stabilise blood counts: Haematological response Cytogenetic response Molecular response Cure!
Haematological Response – HR	Normalise WBC and other blood counts Eliminate immature myeloid cells (blasts) Eradicate signs and symptoms of disease
Cytogenetic Response – CR	Partial CR – reduction of 1% to 35% Ph+ cells Major CR – MCyR > 35% reduction of Ph+ cells Complete CR (CCyR) – elimination of the Ph+ cells
Molecular Response – MR	Standardisation studies are ongoing and definitions of MR currently vary
Major MR – MMR	Major molecular response – ≥3-log reduction in the level of bcr/abl transcripts or Bcr/Abl to Abl ratio ≤0.1%
Complete Molecular Response – CMR	Complete molecular response – no detectable bcr/abl transcripts by RT-PCR = PCRu

Goals of therapy with TK inhibitors



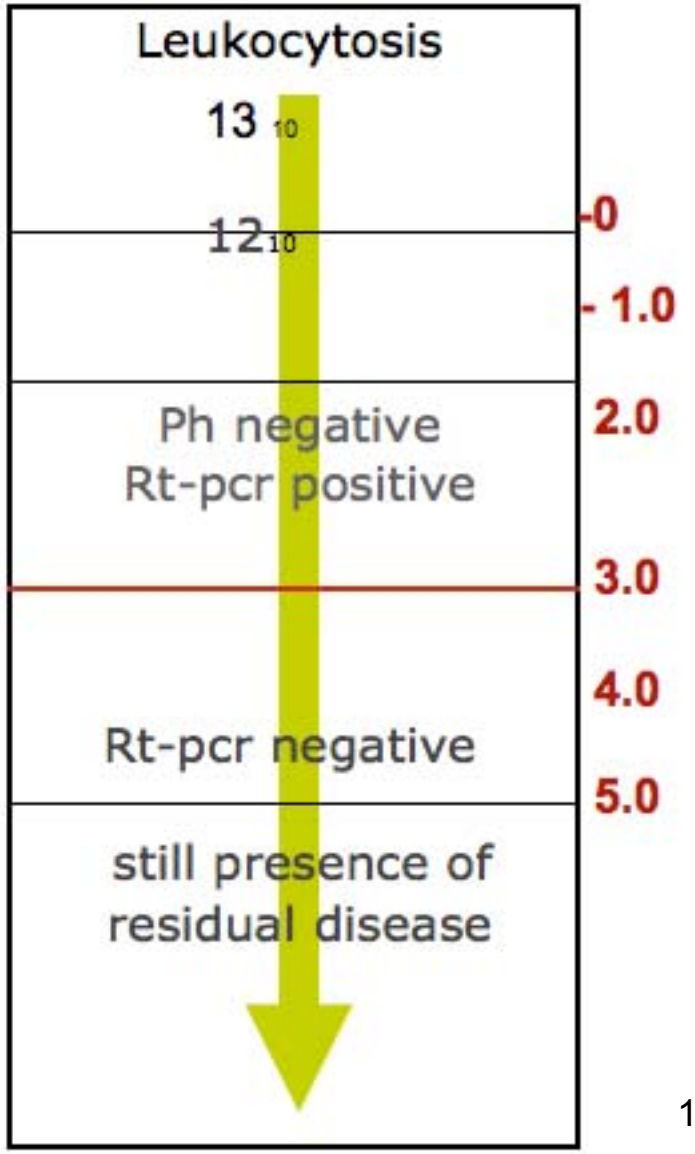
The ideal? An Optimal Response

- CHR within 3 months
- Partial / Major CyR at 6 months
- CCyR at 12 months
- MMR at 18 months
  (later responses are seen)
- CMR: Complete Molecular Response

measurement of response to treatment

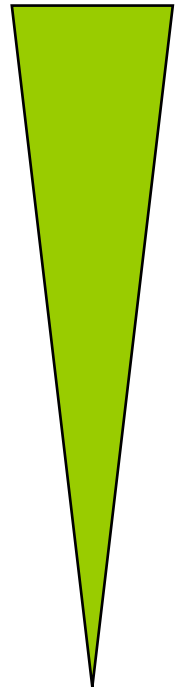
Numbers of Ph+ cells
and level of bcr/Abl transcripts
are the indicators of
response to therapy
with decreasing
levels of leukaemia

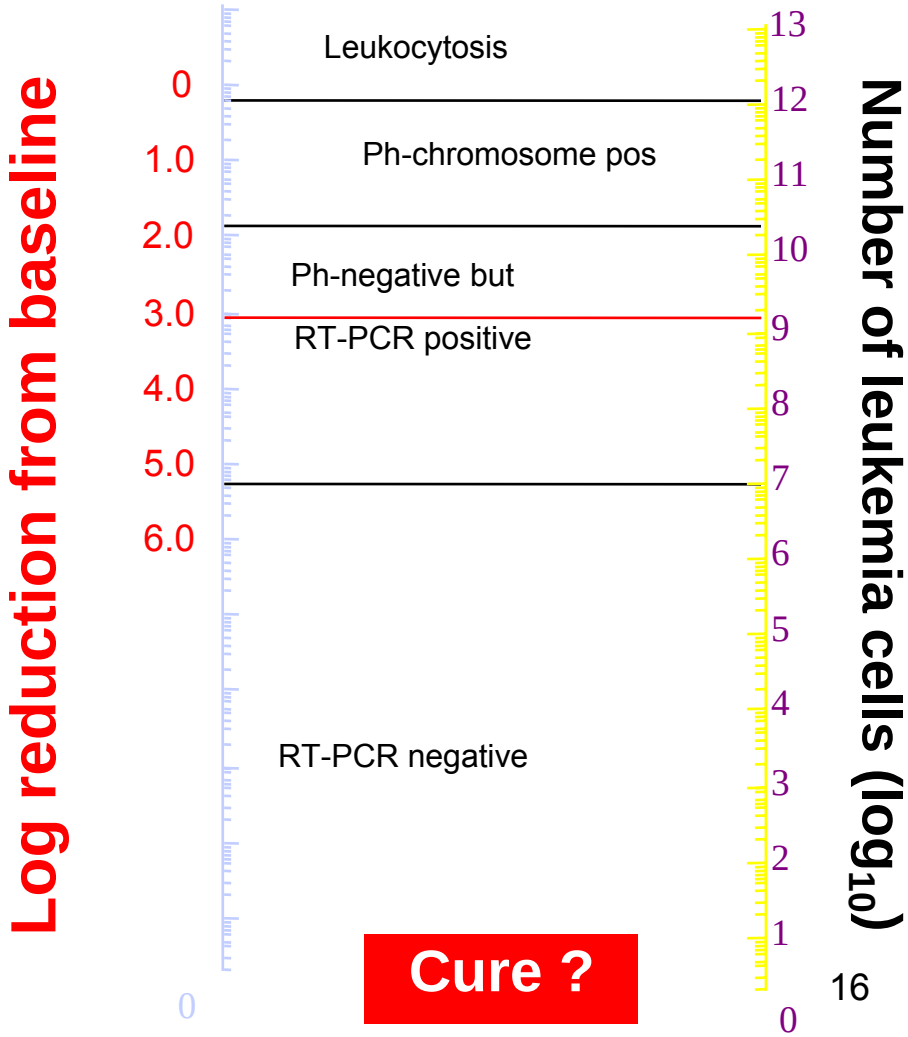
Current goal of TKI therapy-
100% Survival
and good quality of life



Ph chromosome and BCR-ABL transcript numbers as measures of 'residual' leukemia during treatment

Decreasing residual leukemia





Tests and monitoring

- Blood tests counts – measure the number of cells in peripheral blood including WBC, RBC, HGB and platelets
- BMA / BMB – bone marrow aspirate / biopsy
- Cytogenetics from BMA – measures PH+ cells and can detect other clonal evolution (trisomy 8; monosomy 7 etc.)
- FISH (Fluorescence In Situ Hybridization) – analyses around 200 inter-phase cells taken from peripheral blood to detect bcr/abl
- RT-QPCR (Real-Time Quantitative Polymerase Chain Reaction) – a very sensitive molecular test which measures low levels of disease by calculation the ratio of bcr/abl oncogene to the normal abl (housekeeping) gene. More sensitive than FISH (can detect 1 abnormal cell in 1,000,000 normal cells)
- Mutation testing

Meaning of PCR results

- Results indicate that the time taken to achieve MR varies – some patients take a year or more to achieve MMR
- Ph+ CML patients who achieve CCyR and MMR have the best overall prognosis
- A one-time rise in PCR values is no indicator for relapse. The trend of 3 and more tests is more important
- Smaller or erratic fluctuations indicate that the reliability of the RQ-PCR assay should be questioned
- A rise in bcr/abl transcript levels can require analysis for drug resistant mutations
- A rise in bcr/abl transcripts may be due to inadequate drug plasma levels caused by pharmacokinetic factors or lack of adherence to therapy

ELN Treatment Recommendations – Chronic Phase 2009

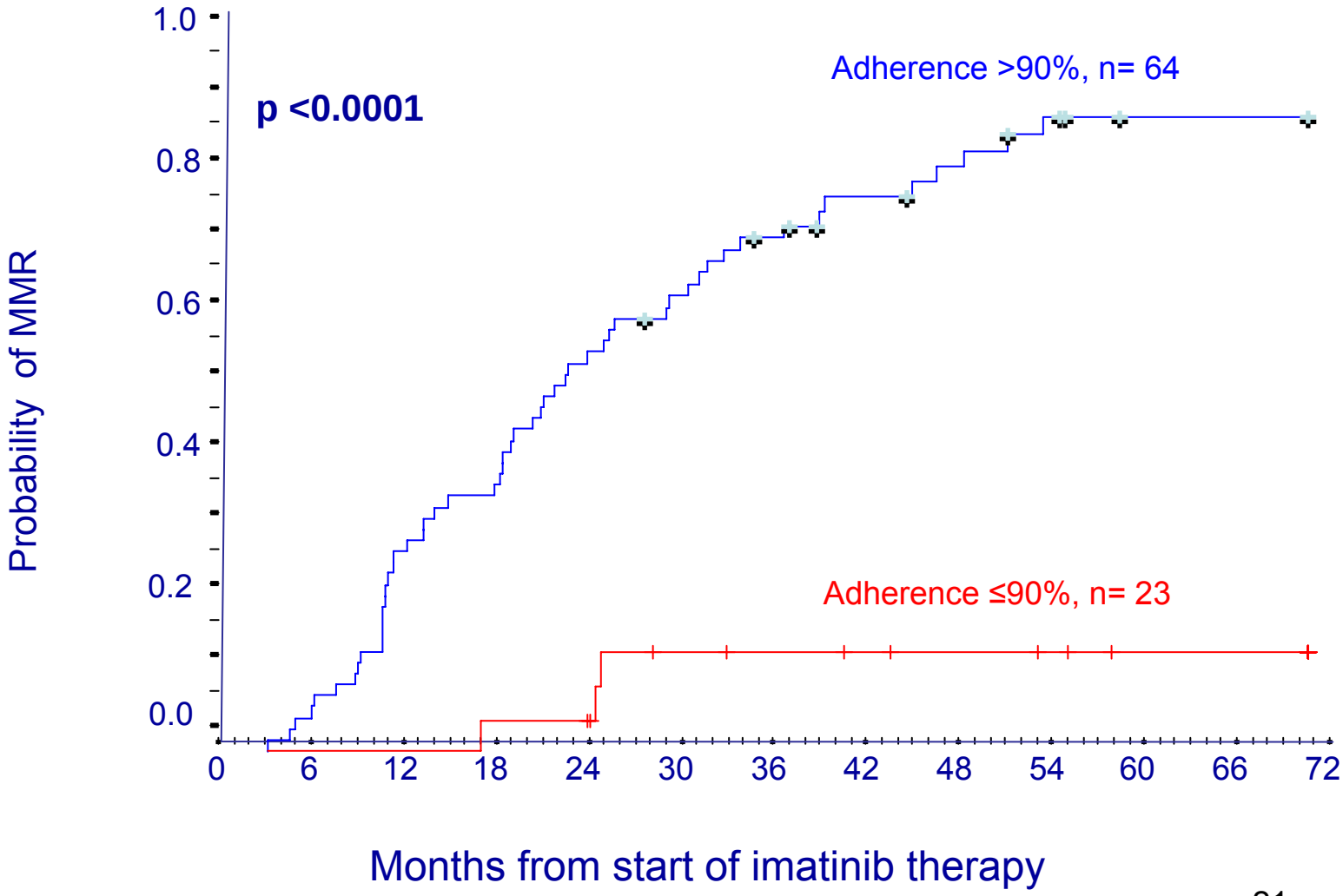
1st-line	Imatinib 400mg
IM intolerance	Dasatinib or nilotinib
Suboptimal response	– Continue IM or increase dose – Dasatinib or nilotinib
IM failure	Dasatinib or nilotinib
2nd-gen. TKI failure	– Allogeneic stem cell transplantation if applicable – 3rd-gen. drugs in clinical trial

Optimal response & adherence

- Adagio Study Conclusions
  - Adherence to therapy is associated with optimal response
  - Non-adherence is very common, more than patients / clinicians / caregivers realise
  - Non-adherence must be ruled out as a cause of suboptimal response or relapse before switching therapy

- Imatinib plasma trough level testing can be considered in the following clinical situations:
  - Adherence concerns
  - Suspicion of a drug-drug interaction
  - A less-than-expected response
  - Side effects that are unusually severe for the dose taken

Six-year probability of MMR according to the measured adherence rate



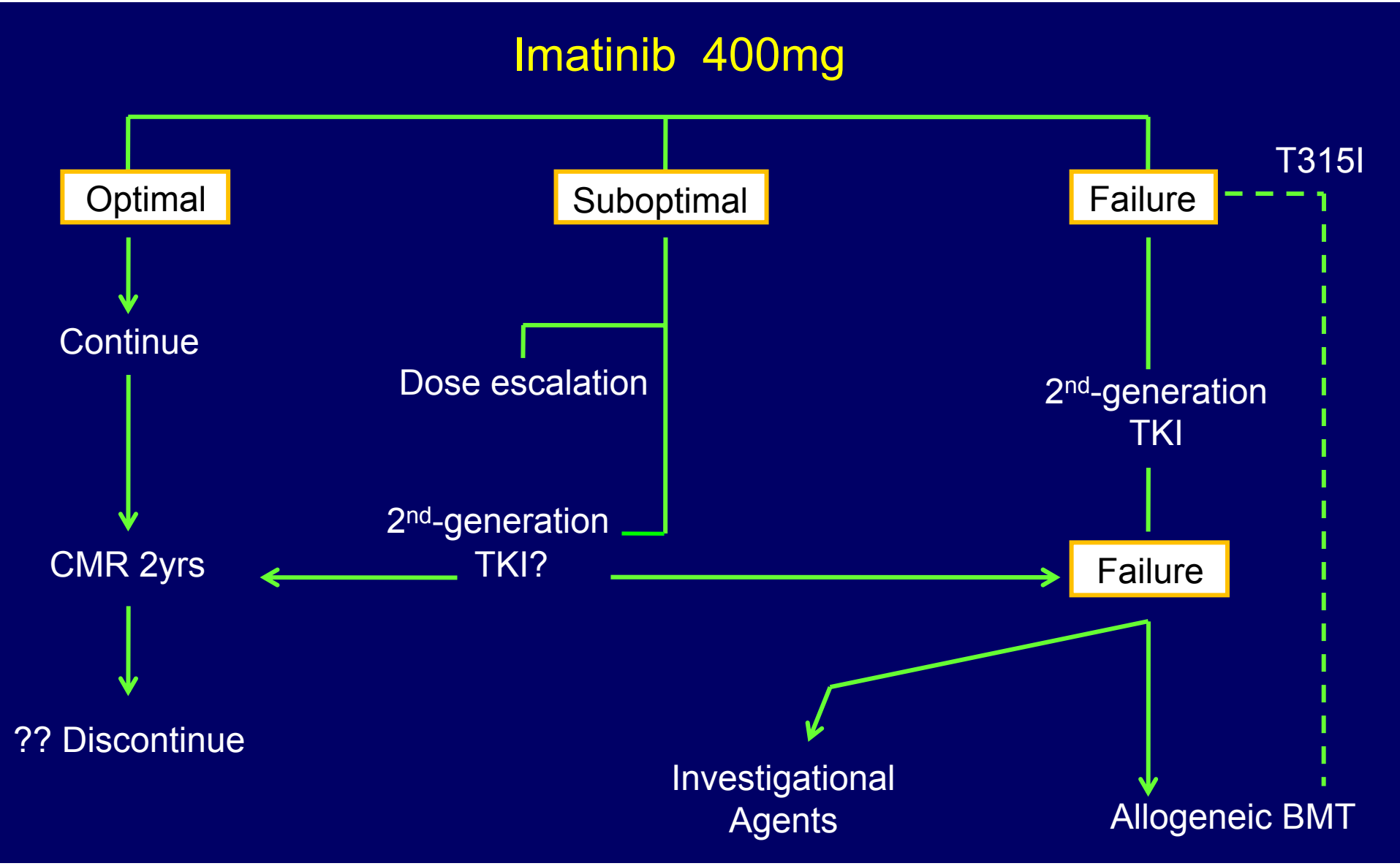
IRIS study – 8 year data imatinib

- Event-free survival 81%
- Overall survival 85%
- Transformation-free survival 92%
- If MMR at 12 months survival 100%

- Major molecular response (MMR) has been defined as > 3 log (1,000-fold) reduction below a standardised baseline derived from a median ratio of Bcr-Abl to Bcr obtained from 30 untreated patients with chronic-phase CML who participated in the IRIS study
- Annual rate of transformation: 1.5%; 2.8%; 1.8%; 0.9%; 0.5%; 0%; 0%; 0.4%

M Deininger et al, ASH 2009

New diagnosis CML: 2010 (May)



Allogeneic stem cell transplant

As 1st-line	AP or BP at diagnosis – pre-treatment with TKI
Disease progression	Failure of 2nd- / 3rd-gen. TKI
Primary or acquired resistance	T315i mutation / clonal evolution

Information and support

The CML Advocates Network

www.cmladvocates.net

The CML Support Group

www.cmlsupport.org.uk

Israeli CML Support Group

www.cml.org.il

www.cml-foundation.org

www.leukemia-net.org

European Treatment and Outcome Study

www.themaxfoundation.org

- http://www.youtube.com/watch?v=oCRJ4r0RDC4&feature=player_embedded

THANKS FOR YOUR ATTENTION