Chronic Myeloid Leukaemia: an Overview

Haematology teaching, Wednesday 30th May, 2007

George Ioannidis

Haematology SpR

Overview

- Introduction and History.
- Epidemiology, clinical presentation and natural history
- Molecular and Cellular Biology.
- Imatinib mesylate and 2nd generation Abl TKIs: targeted therapy.
- Treatment, response and treatment algorithm.
- Trials
- Conclusions

WHO Definition CML

- Chronic Myeloproliferative Disease.

- "…that originates in an abnormal pleuripotent bone marrow stem cell and is consistently associated with the Ph chromosome and/or the BCR/ABL fusion gene. Although the initial major finding in CML is neutrophilic leucocytosis, the abnormal fusion gene is found in all myeloid lineages as well as in some lymphoid cells. The disease is bi- or tri-phasic: an initial indolent chronic phase (CML-CP) is followed by one or both of the aggressive transformed stages, accelerated phase (CML-AP) or blast phase (CML-BP)".

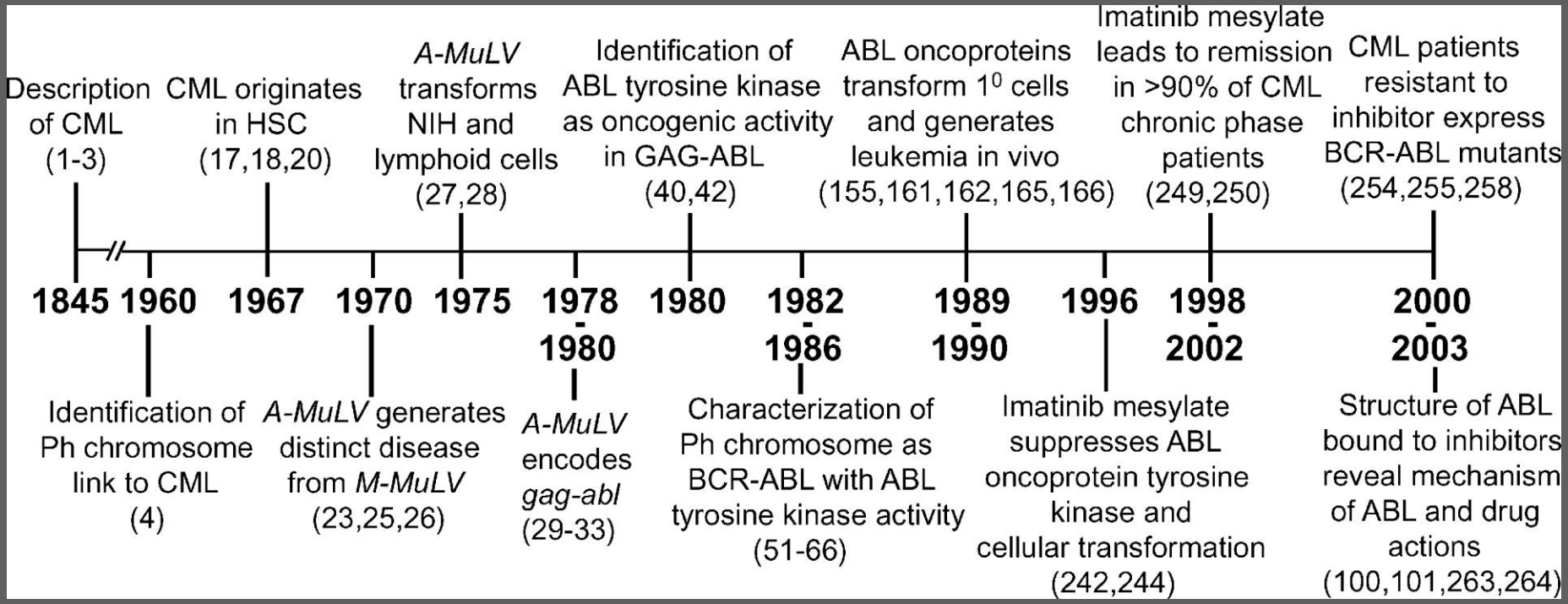
CML – the first leukaemia described

- 1845 – CML was the first leukaemia to be described – Bennett, Cragie, Virchow.

- “A case of hypertrophy of the spleen and liver in which death took place from suppuration of the blood”

John Hughes Bennett

History of CML: generator of paradigms



- First leukaemia described
- Ph chromosome first recurrent cytogenetic abnormality associated with cancer
- BCR-ABL first fusion oncogene described.
- First oncogene to demonstrate prospective *in vivo* transformation.
- First prospective molecularly targeted and monitored malignancy.

Epidemiology of CML

- 1-2 per 100,000 of population per year (2-4 cases per year).
- 15-20% of all leukaemias
- 500-800 new cases per year in UK.
- ~ 7000 cases currently in the UK
- Slight male predominance.
- Age range from infants to >100 (median in 5^{th} and 6^{th} decade).
- Only proven link is with ionising radiation (nuclear weapon survivors of Hiroshima and Nagasaki).

Clinical presentation of CML

- As with other chronic myeloproliferative disorders patients in chronic phase often present as coincidental findings.

- WCC ranging from normal to > 400.
  Thrombocytosis
  Mild anaemia.

- Hypercatabolic symptoms – weight loss, sweats, hyperuriceamia.

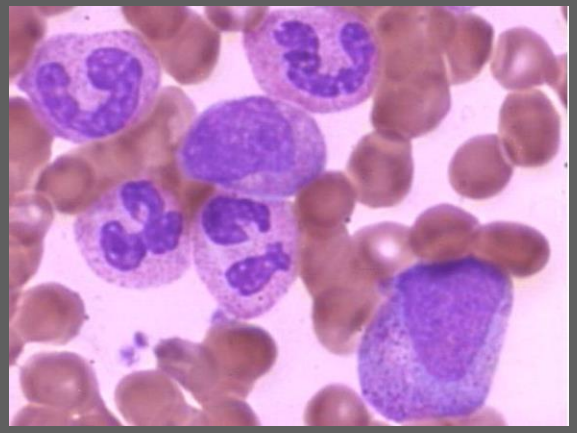
- Pain/discomfort/abnormal bowel function – related to enlargement of spleen (now seen in <50%).

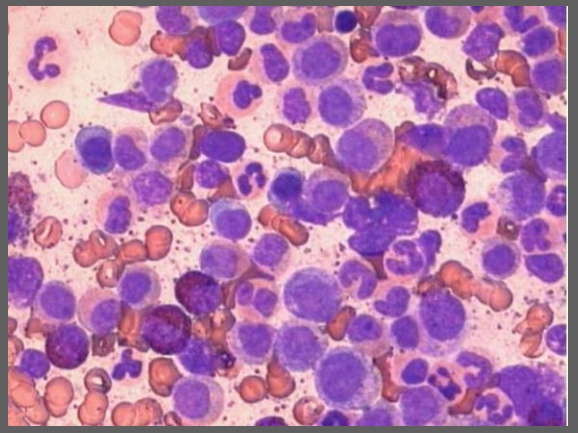
- Progressive phases – constitutional symptoms, bone pain, symptoms of bone marrow failure

Natural History of CML

BCR-ABL Dependent

- **Chronic phase**
  Asymptomatic,
  Δ often coincidental.
  easily treated with medical therapy



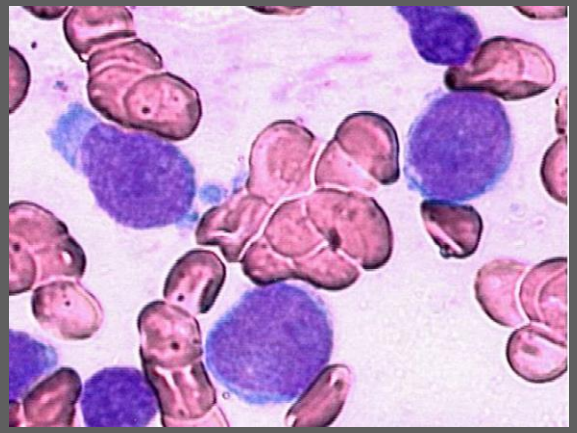


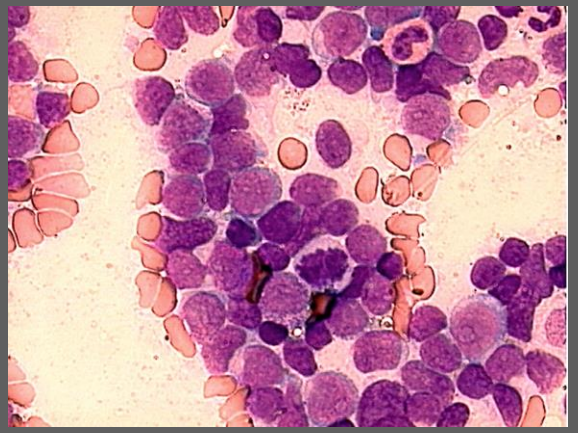
- **Accelerated phase**
  Poorly defined
  Control is increasingly difficult.

PB

BM

- **Blast crisis**
  Acute leukaemia
  Myeloid or Lymphoid lineage.
  New mutations
  Usually fatal.





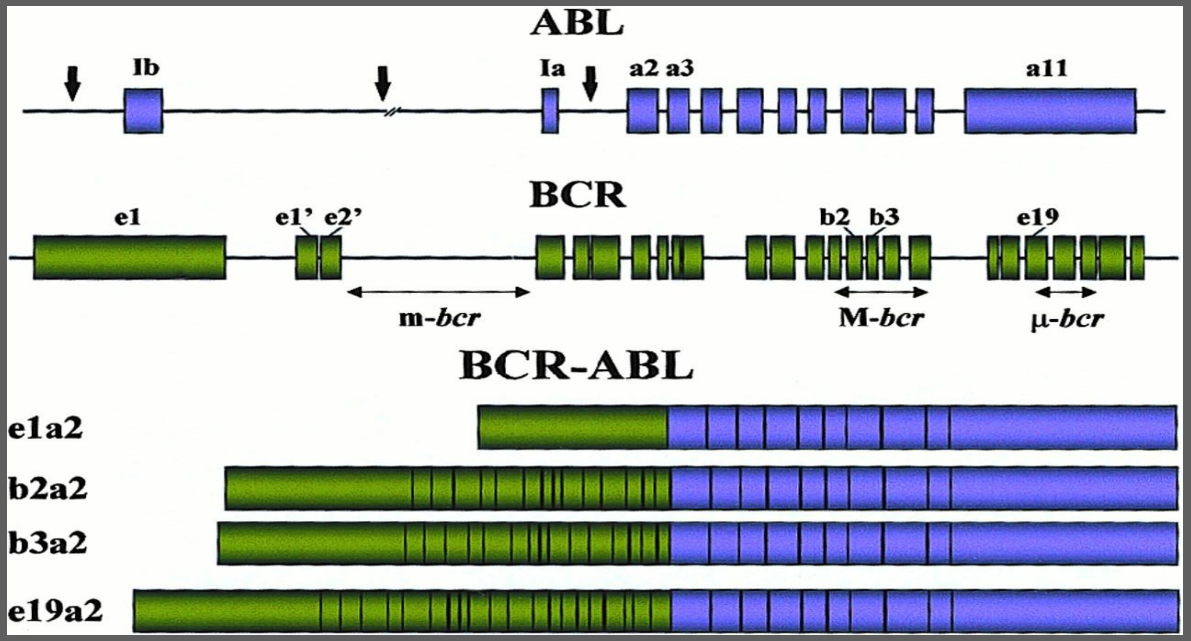
BCR-ABL and FURTHER MUTATION Dependent

Prognostic scoring systems for CML

	SOKAL	HASFORD
Age	0.116 (age-43.4)	0.666 when age ≥ 50
Spleen (cm below costal margin)	0.0345 (spleen-7.51)	0.042 x spleen
Platelet count (x 10^9/L)	0.188[(platelets)^2-0.563]	1.0956 if platelets ≥ 1500
PB blast count (%)	0.0887(myeloblasts-2.1)	0.0584 x blasts
PB basophil count (%)	-	0.204 if basophils > 3
PB eosinophil count (%)	-	0.0413 x eosinophils
Relative risk	Exponential of the total	Total x 1000
Low	<0.8	≤ 780
Intermediate	0.8-1.2	781-1480
High	>1.2	>1480

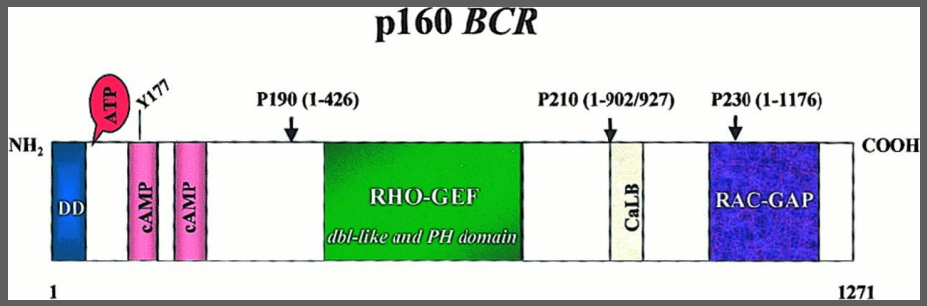
- Although devised for HU/Busulphan and IFN patients scoring systems still apply for IM Rx

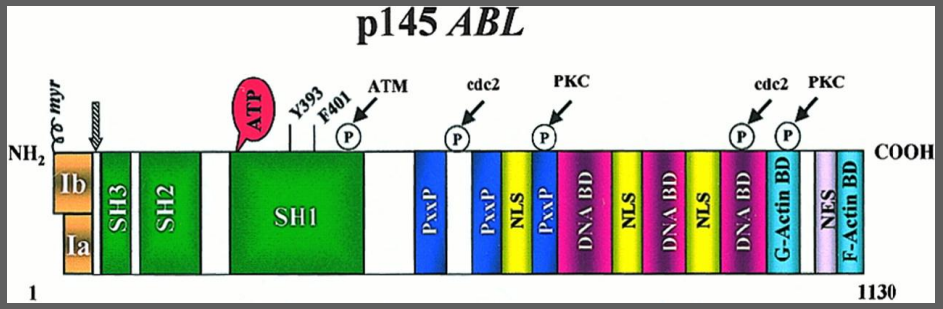
Biology of CML: The Philadelphia translocation and BCR-ABL rearrangement.



e13a2
e14a2

p190	ALL
p210	CML
p230	CNL





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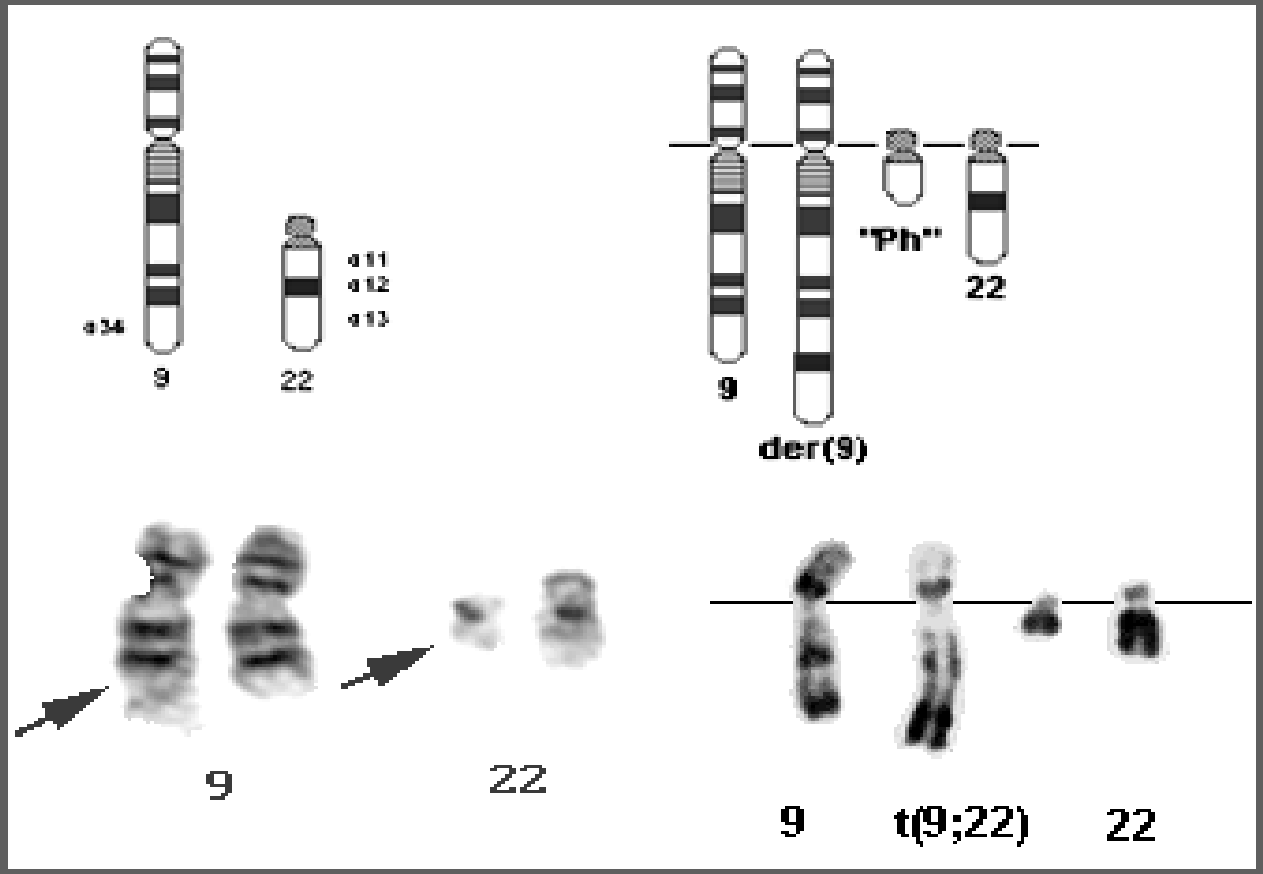
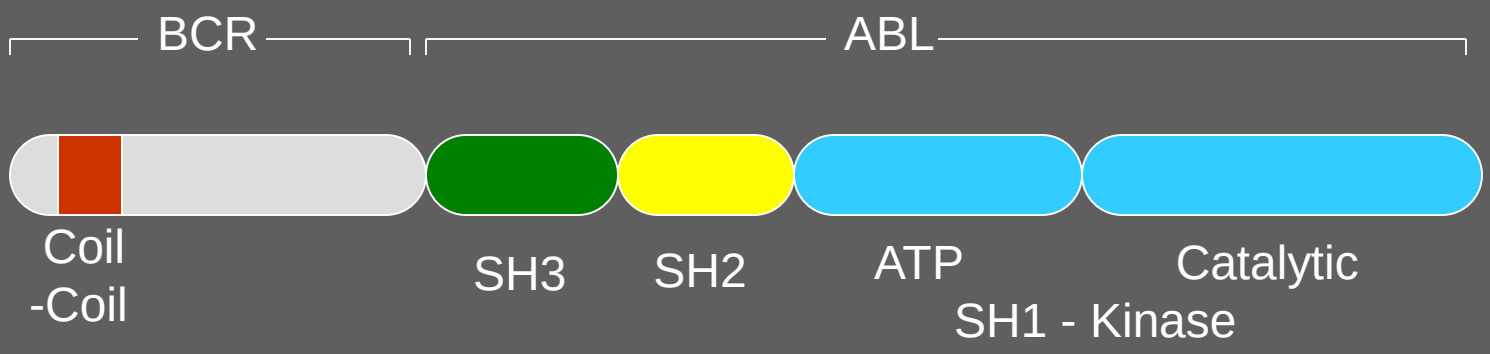
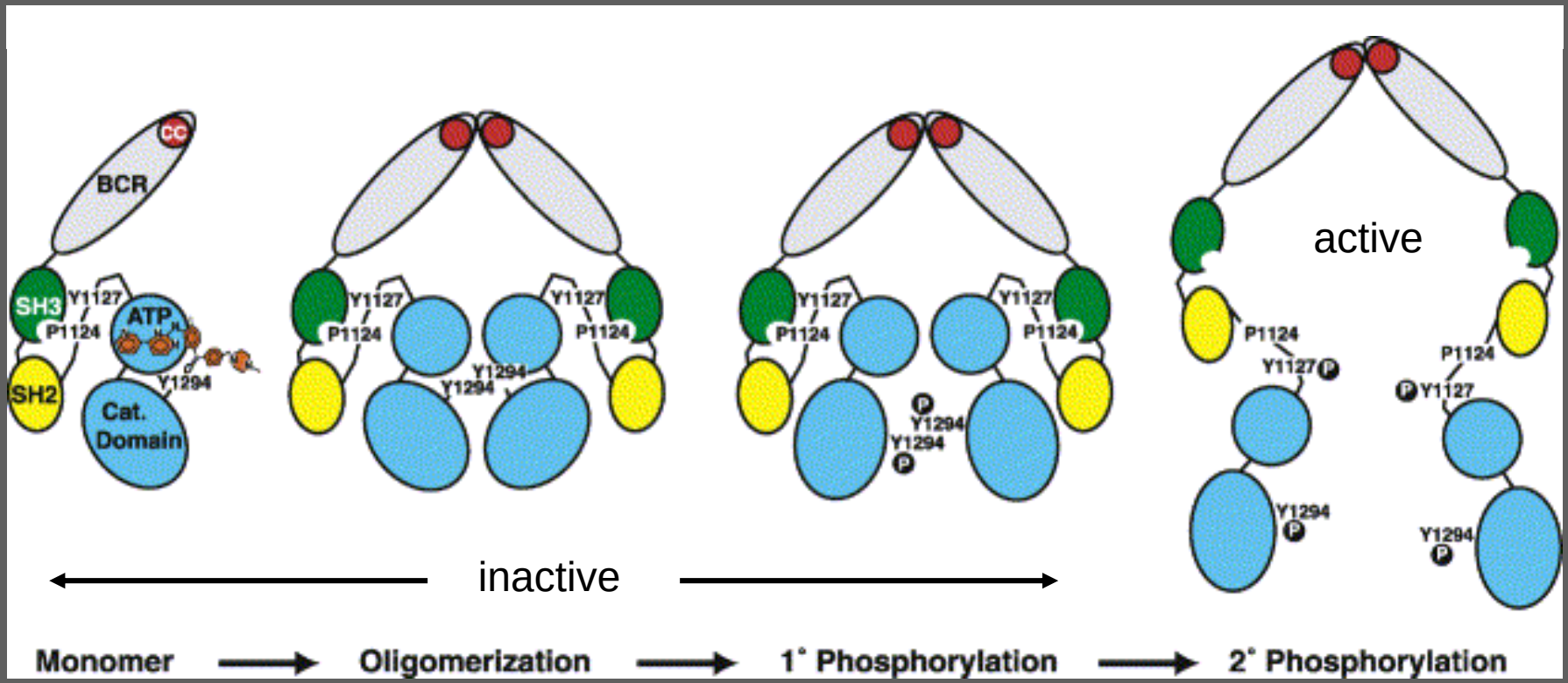


- First recurrent chromosomal abnormality described in cancer – Nowell and Hungerford in 1960 in Philadelphia.

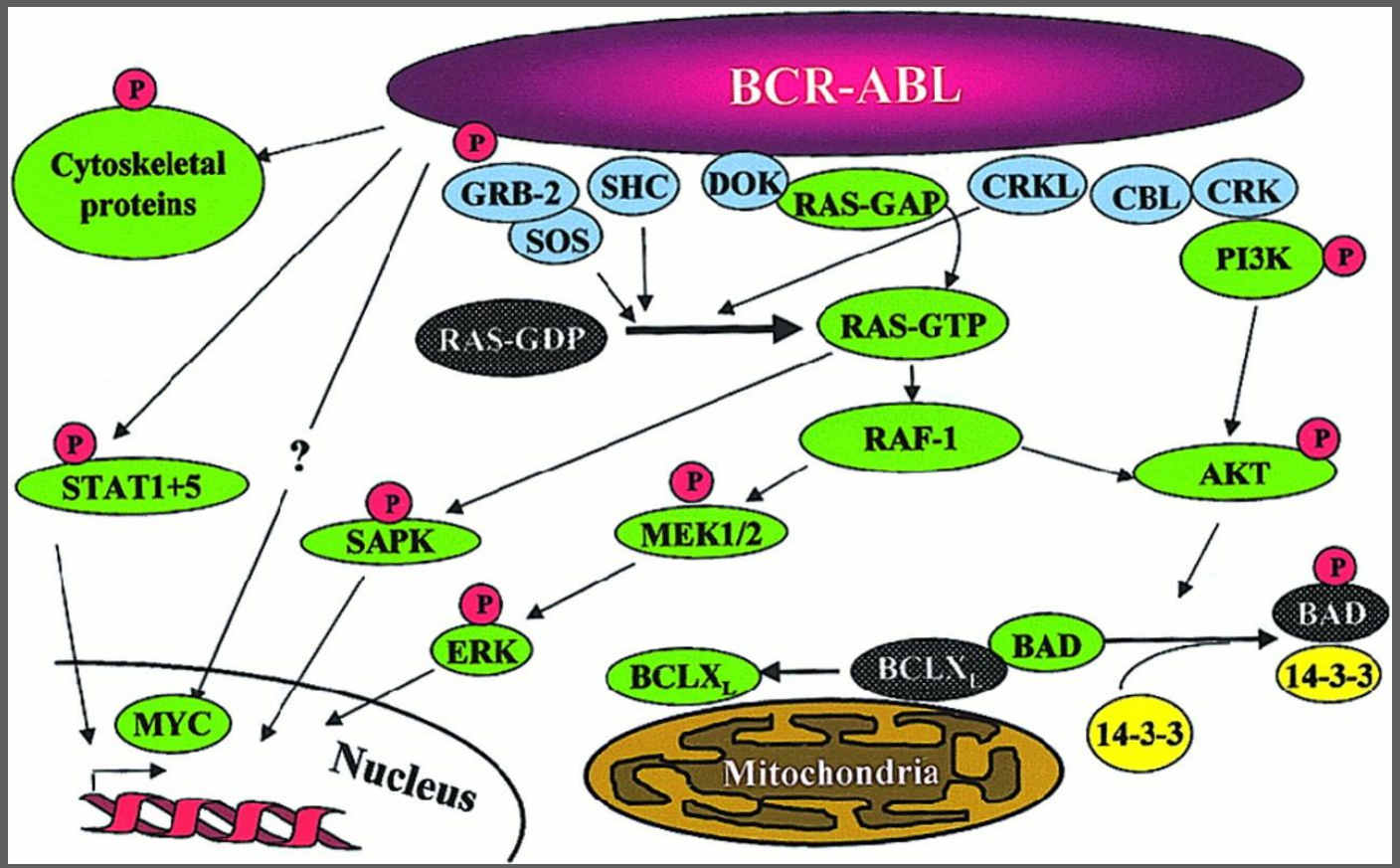
- Translocation between chromosomes 9 and 22 described by Janet Rowley in 1972.

BCR-ABL is an activated tyrosine kinase enzyme



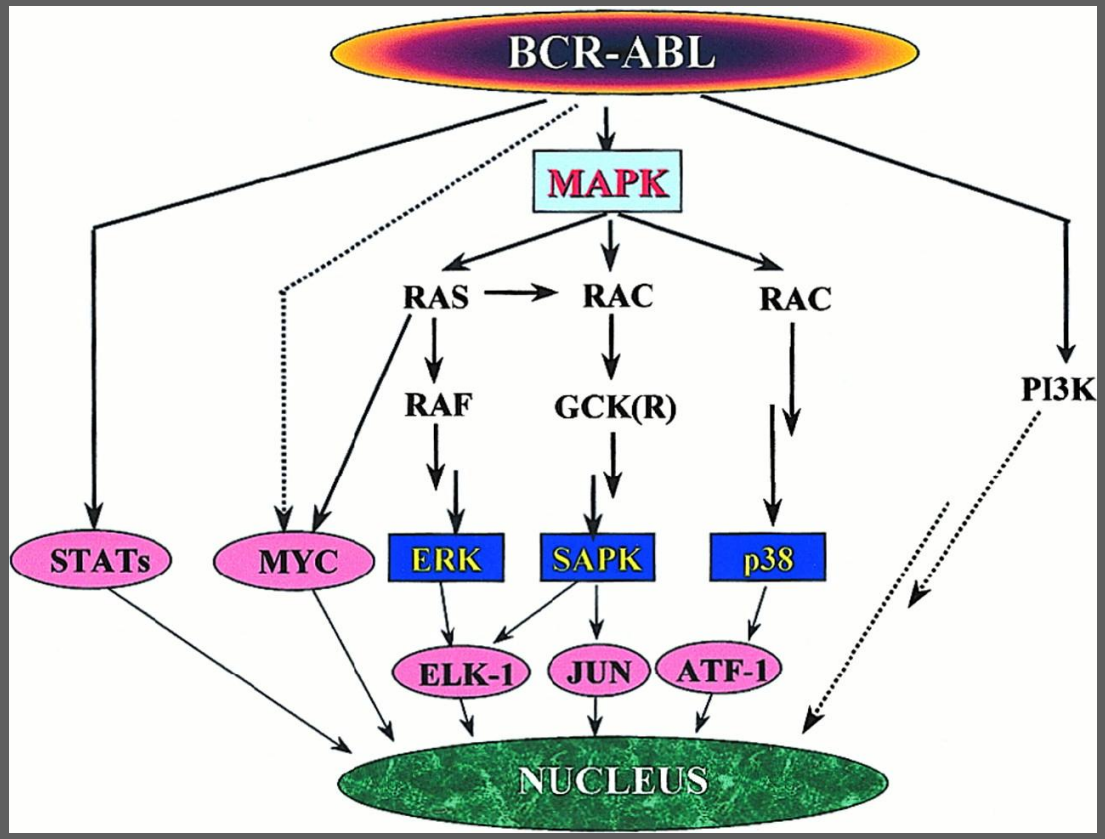


BCR-ABL activates multiple signalling pathways



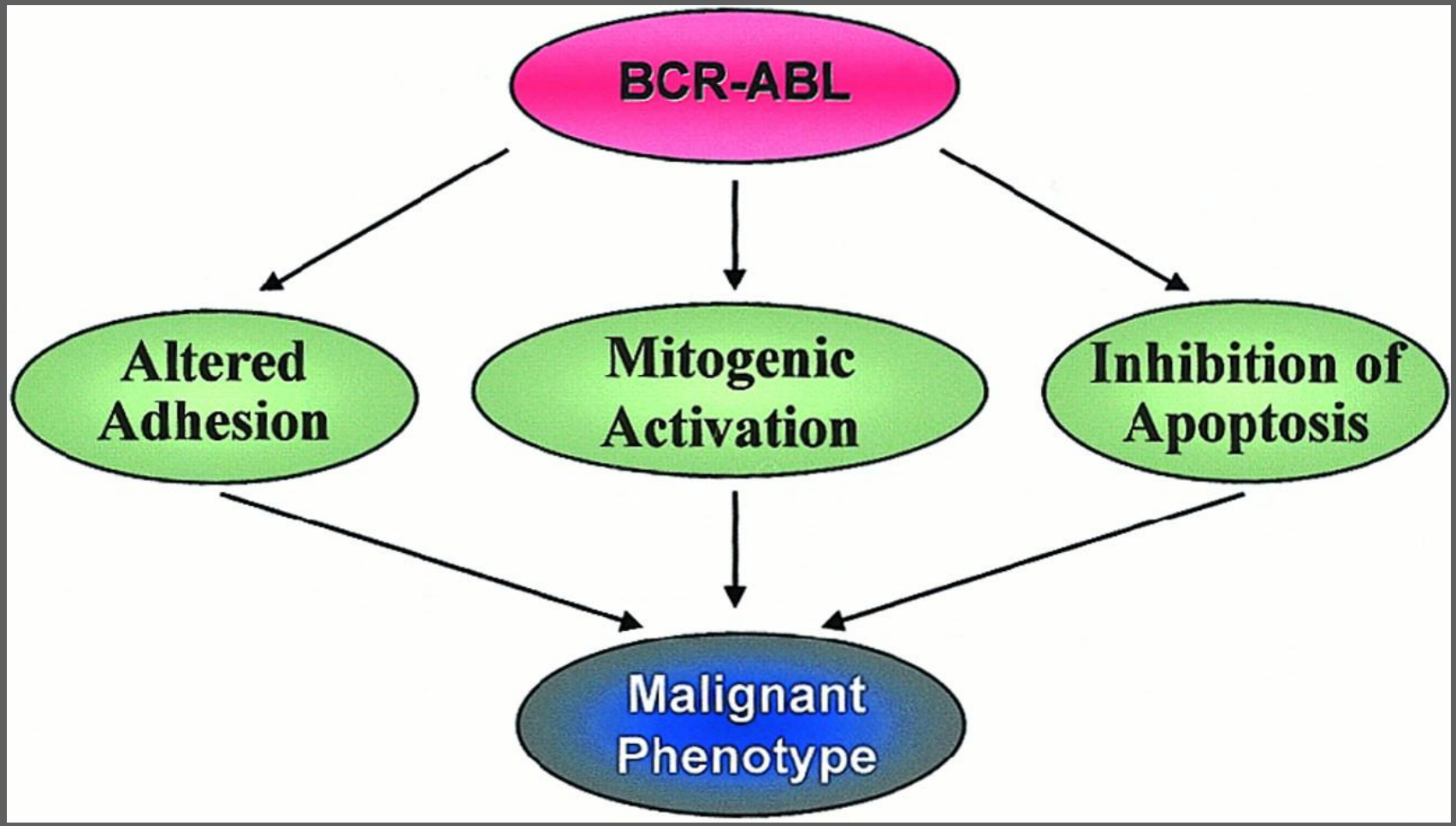
- Multiple signal transduction pathways are activated → STAT, Ras-MAPK, PI3 – K
- End result of many of these pathways is an alteration of gene transcription

BCR-ABL signalling

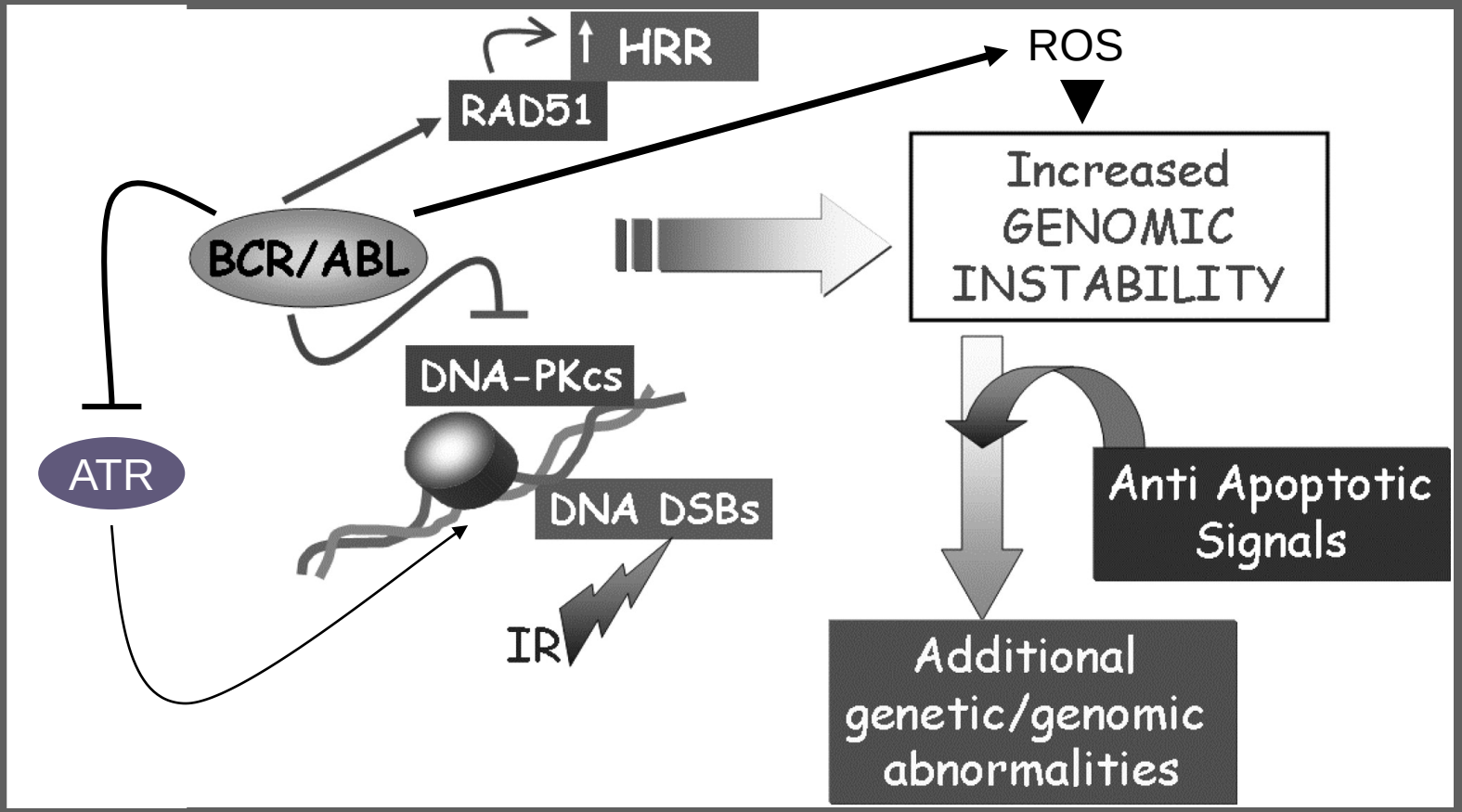


- Multiple signal transduction pathways are activated → STAT, Ras-MAPK, PI3 – K
- End result of many of these pathways is an alteration of gene transcription

BCR-ABL activation affects multiple cellular functions



BCR-ABL leads to increased genomic instability



~ 80% BC patients exhibit karyotypic evolution.

Progression of CML is associated with the acquisition of specific mutations

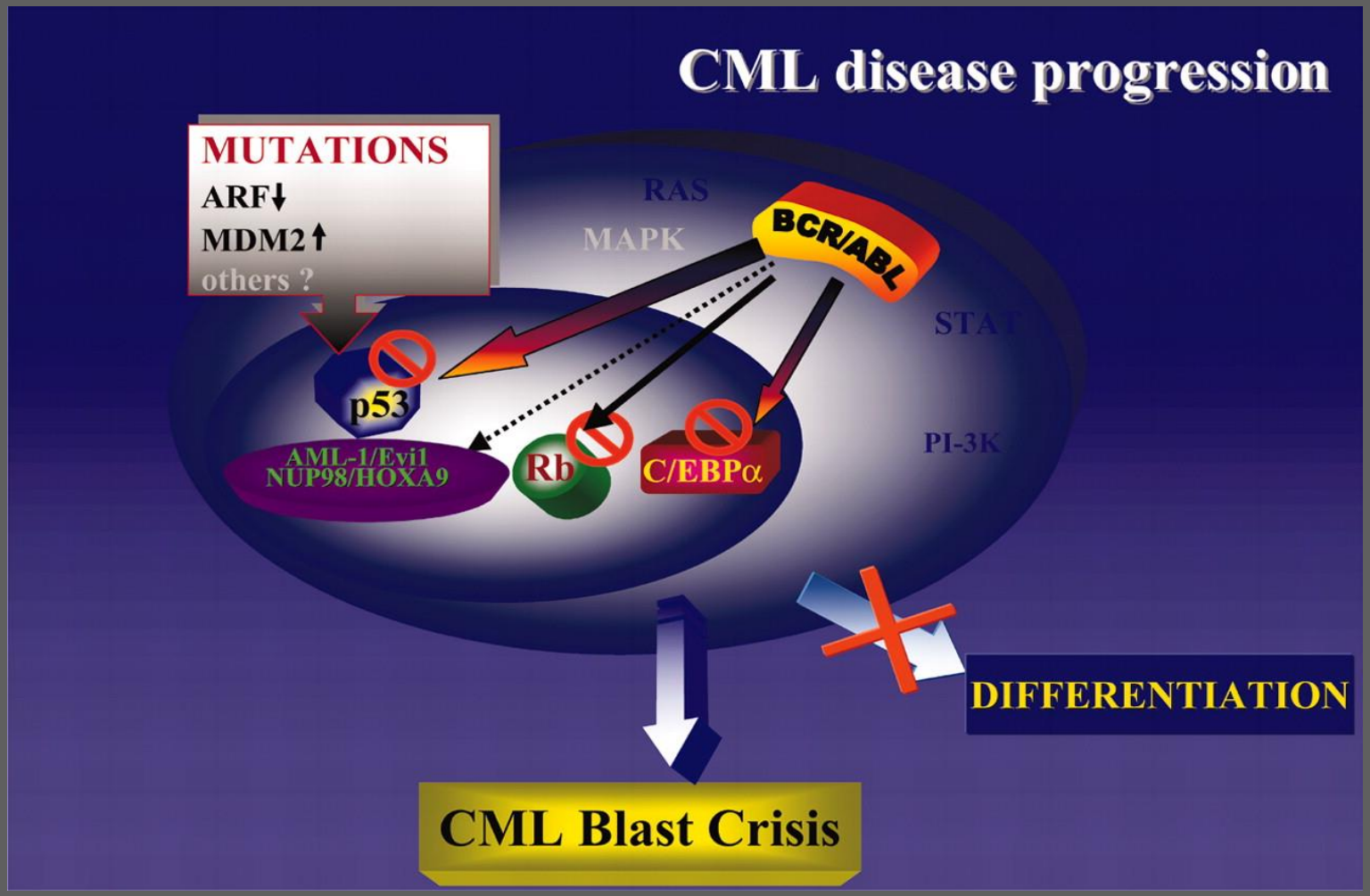
- Cytogenetic abnormalities:

Abnormality	Frequency (%)
Double Ph	38
Trisomy 8	38
Isochrome 17q	20
Trisomy 19	13
t(3;21) [AML1-EVI1]	2
t(7;11) [NUP98-HOXA9]	<1

- Molecular abnormalities:

Abnormality	Frequency (%)
p53 mutations	25-30 (My >Ly BC)
p16/ARF mutations	50 (Ly BC)
Rb mutation/deletion	18
RAS mutations	Rare

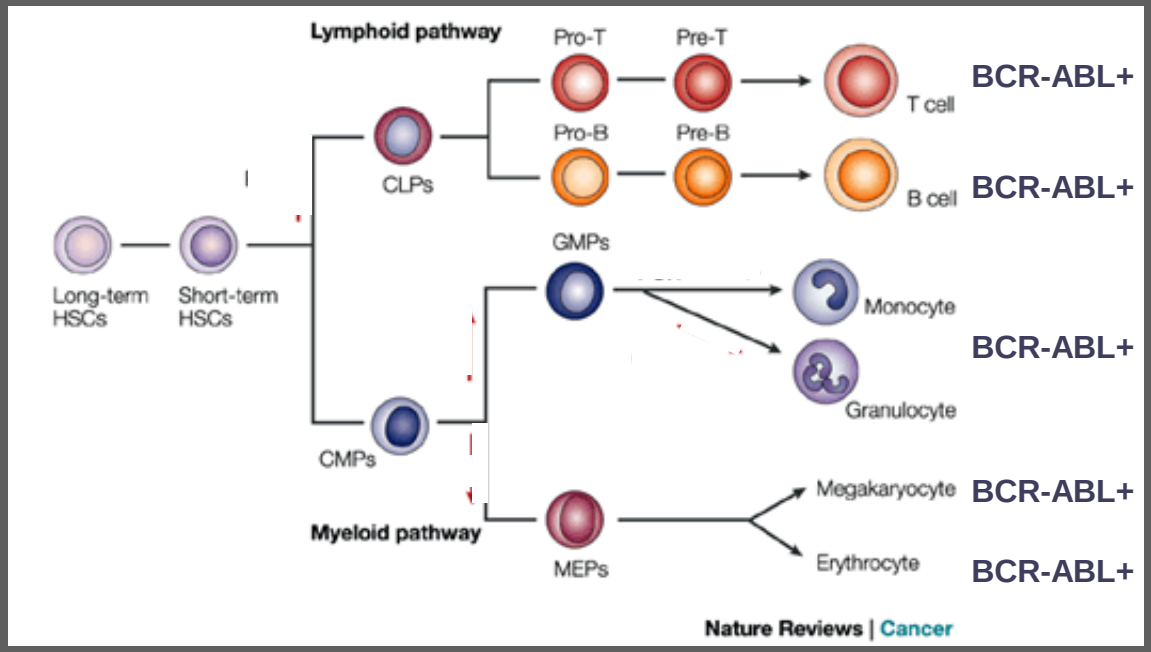
Unifying model for CML disease progression.



- Mutations occur in nuclear proteins and have a net effect on transcription.
- Mutation or loss of TSG predominates over mutation activation of oncogenes
- p53 is genetically or functionally inactivated in a large fraction of the known cases of CML BC

CML is a stem cell disorder

- X inactivation patterns suggest a clonal stem cell origin for the disease.

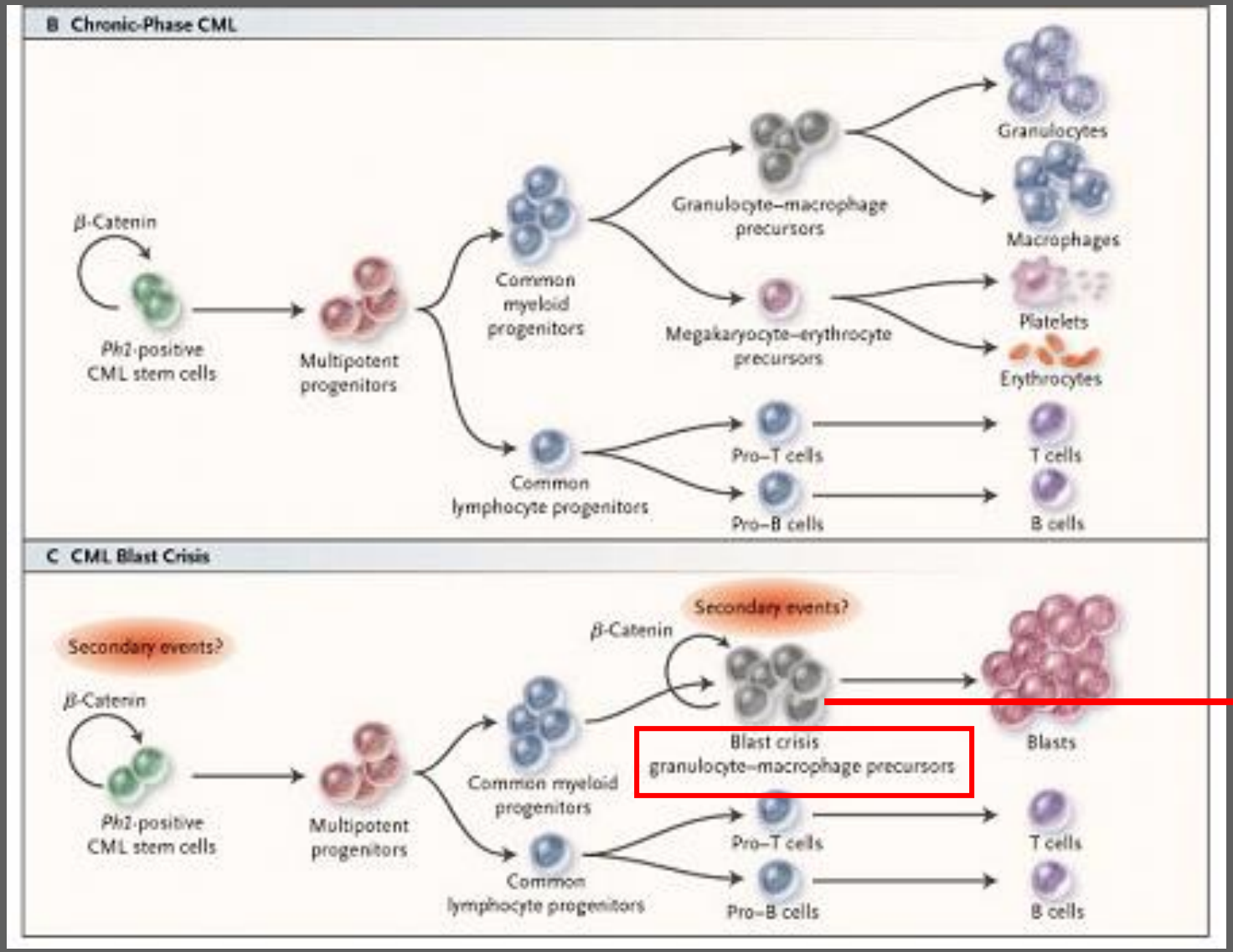


- The presence of the Ph chromosome/ BCR-ABL fusion can be detected in myeloid, erythroid, megakaryocytic and lymphoid lineages.

- Blast crisis may be of myeloid or lymphoid lineages.

- The phenotypic compartment enriched for human haematopoietic stem cells (CD34+/38-/CD90+/lin -) contains the Ph chromosome and expresses BCR-ABL at high levels.

GMP as candidate leukaemia stem cells in Blast Crisis CML



Self-renewal *in vitro*. GMP more efficient in transfer of CML BC than HSC population

Jamieson – NEJM 2004

Treatment options for CML

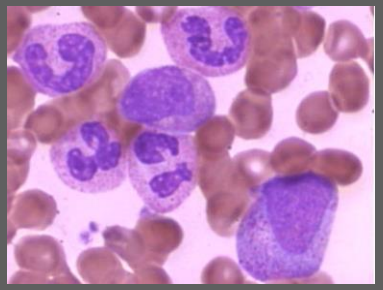
- Selective Abl kinase inhibitors
  - Imatinib Mesylate (IM)
  - AMN107 (Nilotinib)
  - BMS 354825 (Dasatinib).

- Stem Cell Transplantation.
- Interferon-alpha.
- Cytarabine.
- Homoharringtonine.
- Experimental.

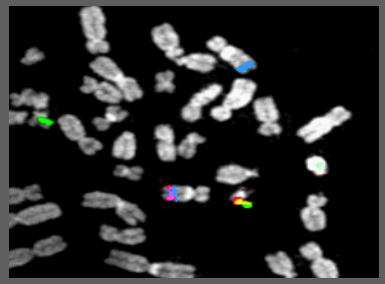
Monitoring response to therapy in CML

- Response measured at 3 Levels of sensitivity:

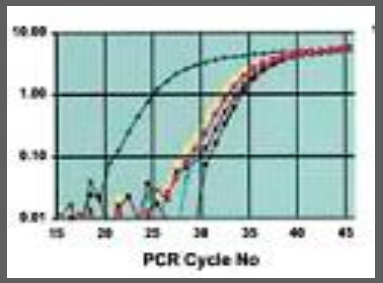
Haematological Response – a Complete Haem Response (CHR) normalisation of the full blood count with no primitive forms seen.



Cytogenetic response – measured by G-banding or FISH:
Complete Cytogenetic Response (CCR) – 0% Ph +
Major Cytogenetic Response (MCR) - <35% Ph +



Molecular response – measured by quantitative RT-PCR
Major Molecular Response (MMoR) - > 3 Log reduction in BCR-ABL/ABL ratio.



- ALL 3 IMPACT UPON SURVIVAL

CML treatment: Bone marrow transplantation

- Pre-Imatinib – most common indication for BMT worldwide.
- 50% overall survival for patients in CP and 20% for those not in first CP (CIMBTR data).
- May still be an indication for allo SCT up front in individual cases, but due to the TRM most patients receive a trial of imatinib.
- Allo SCT also has a major role to play in Imatinib failure (see later).
- In CML can accurately assess TRM and survival likelihood

CML treatment: Bone marrow transplantation

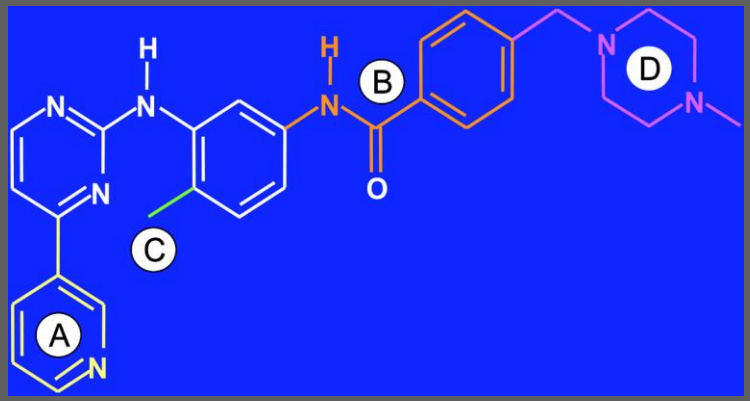
Prognostic factor	Risk score
Age	0 if <20 1 if 20-40 2 if >40
Interval from diagnosis to SCT	0 if ≤ 1 year 1 if > 1 year
Disease phase	0 if CP 1 if AP 2 if BC
Donor-recipient sex match	1 if female donor and male recipient 0 if any other match
Donor type	0 if HLA-identical sibling 1 if any other

EBMT or Gratwohl score

Total risk score	5-year overall survival		
	EBMT series	CIBMTR all patients	CIBMTR ECP patients
0-1	72%	69%	70%
2	62%	63%	67%
3	48%	44%	50%
4	40%	26%	29%
5-7	22%	11%	25%

Imatinib mesylate (IM, STI571, Glivec)

- SELECTIVE Abl kinase inhibitor, also inhibits c-kit, PDRFR-β, PDRFR-α.



- 2-phenylaminopyridine derivative

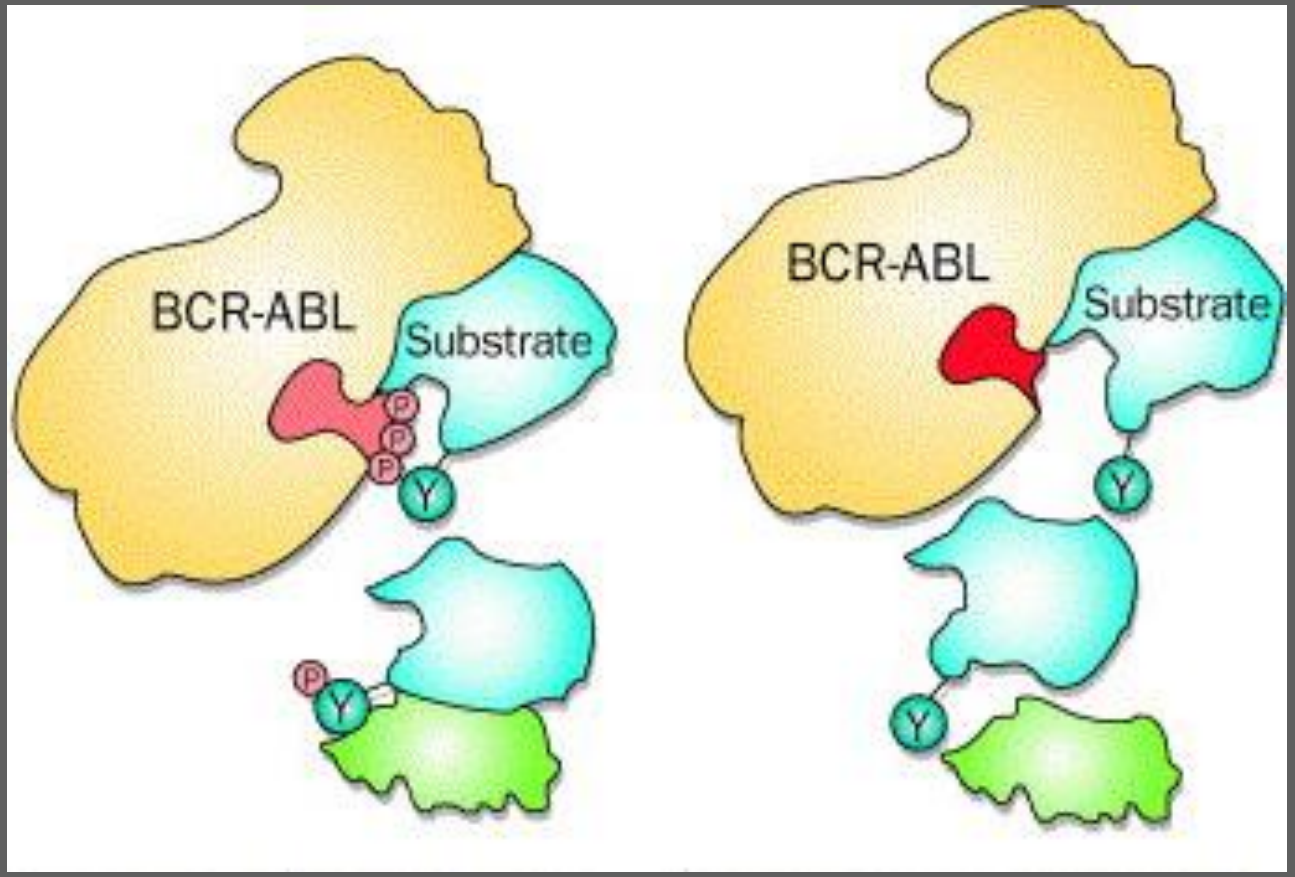
- Developed by Ciba-Geigy in 1990's, initially as a PKC inhibitor (Jorg Zimmermann and Elisabeth Buchdunger).

- Championed as a selective Abl kinase inhibitor by Brian Druker, showed that ↓ growth, tumor formation in CML cell lines and CFU in CML primary cells (1996, Nat Med).

- Entered clinical trials in 1997/1998.

- First reports at ASH 1999.

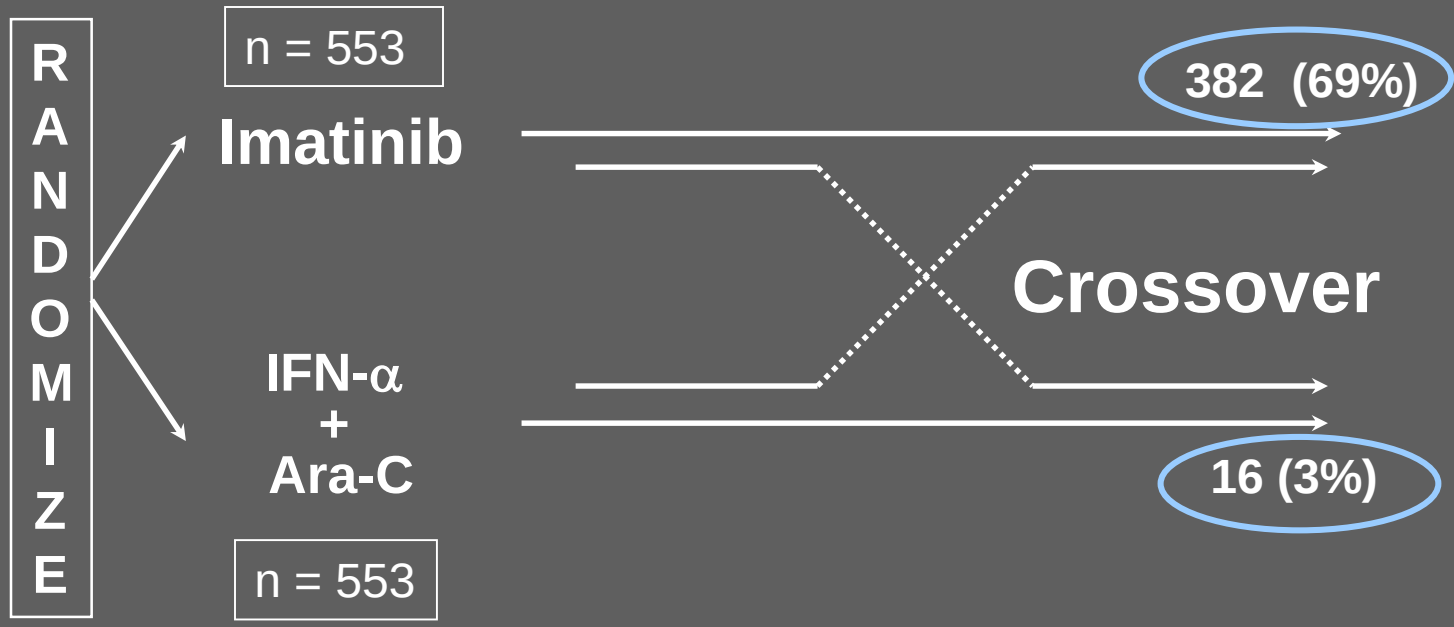
Imatinib Mesylate: mechanism of action



- ATP mimetic – competitively binds to BCR-ABL (inactive conformation) in the ATP pocket and prevents substrate tyrosine phosphorylation.

IM therapy in newly diagnosed patients – IRIS study.

- Randomised trial of IM vs IFN and Cytarabine.
- IM tolerated much better, with ↑ QOL.

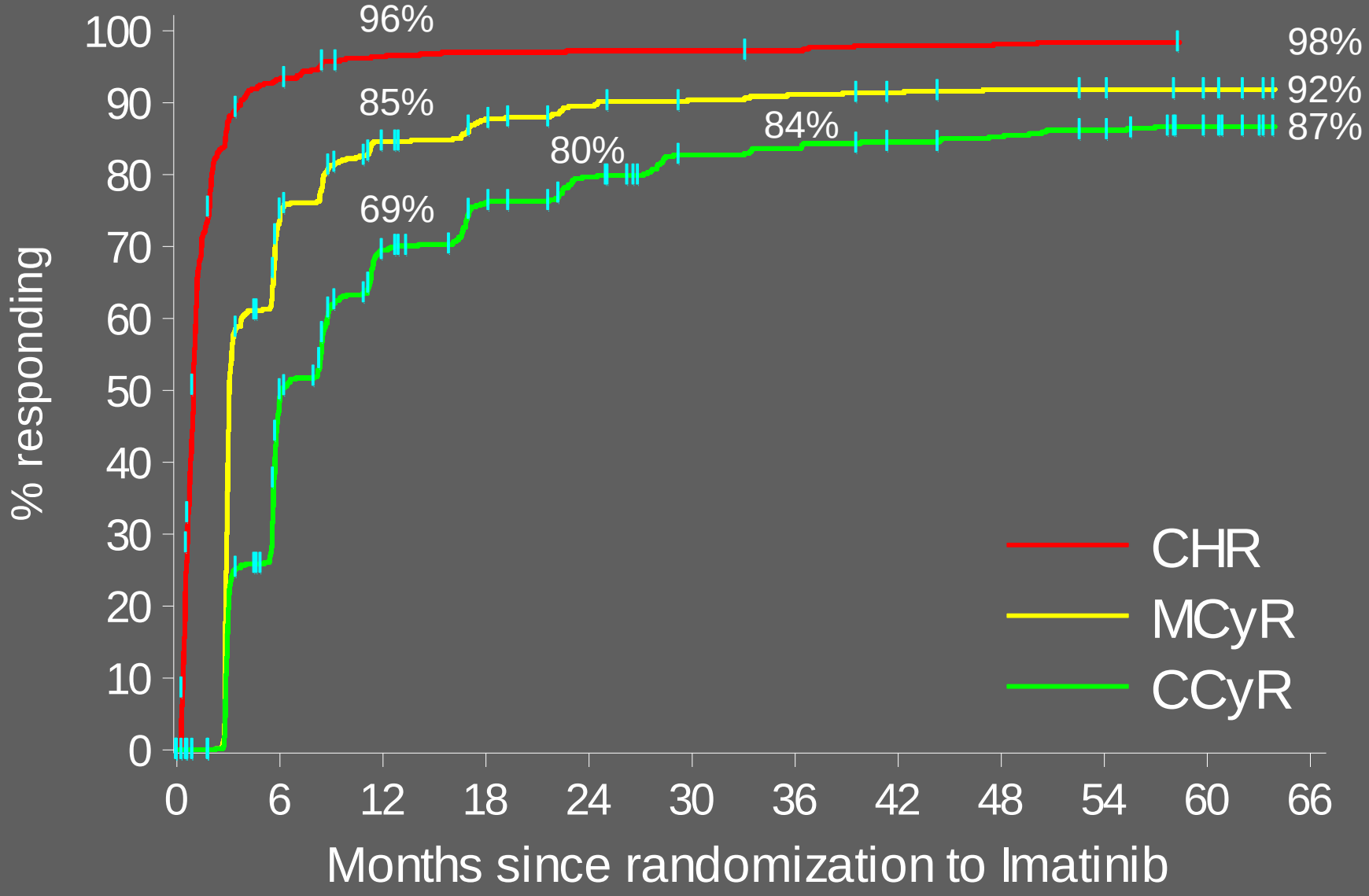


IM therapy in newly diagnosed patients – IRIS study.

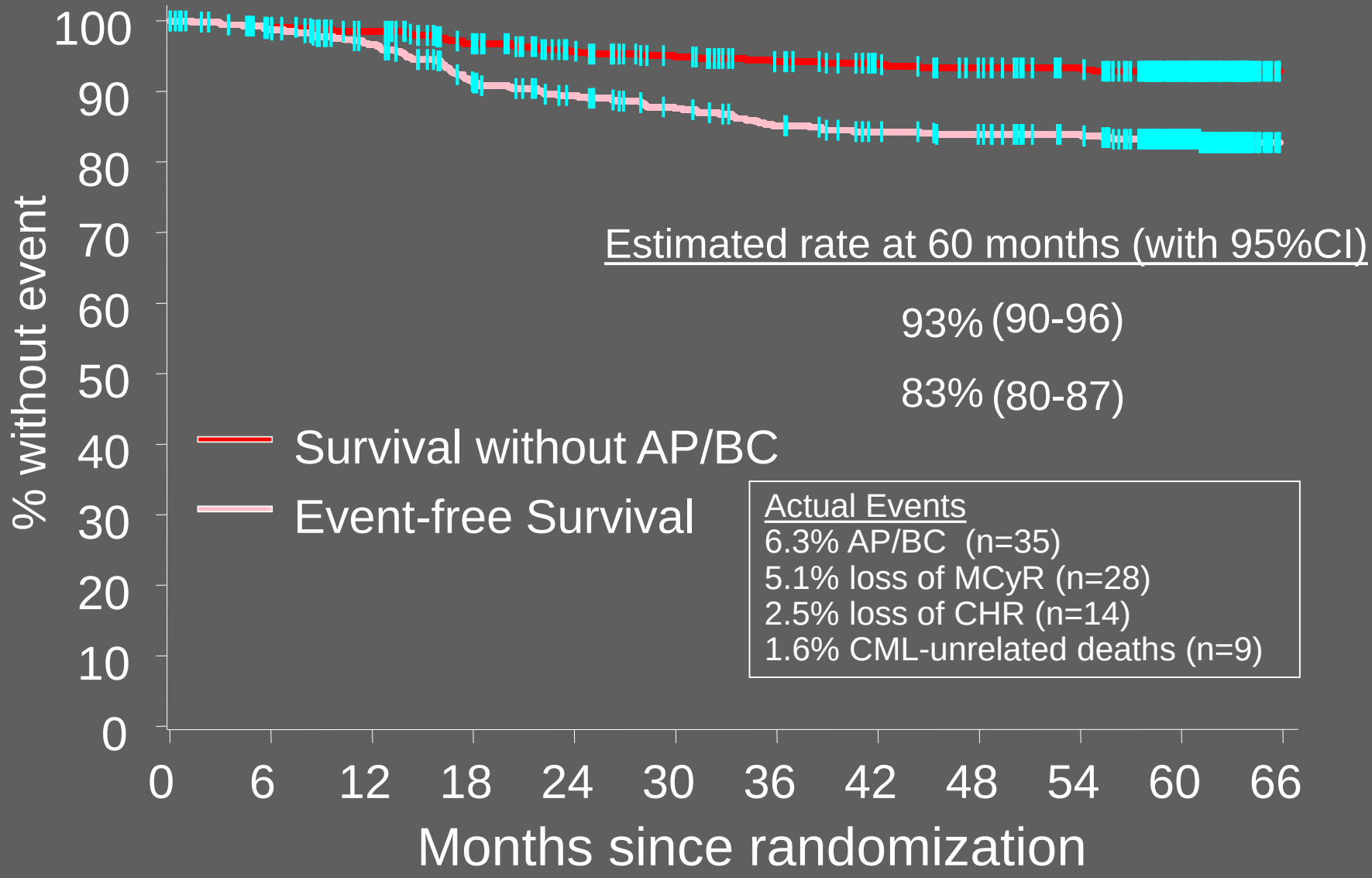
Treatment arm	CHR %	MCR %	CCR%	Prog Free survival at 14 months	Prog Free survival at 42 months
IM	95.3	85.2 (91 42mo)	73.8 (84 42mo)	92.1	84
IFN + Ara-C	55.5	22.1	8.5	73.5	
p value	0.001	0.001	0.001	0.001	

- Survival Benefits confirmed against IFN Rx historical controls (96 vs 81% at 3 years, $p < 0.01$, Kantarjian et al, Blood, 2006)
- Lack of response is mainly due to acquired resistance.

Cumulative Best Response at 12 and 60 months on First-line IM



Event-free Survival and Survival Without AP/BC on first line IM



IM has efficacy in advanced phases of CML

Phase disease	Overall Haem response/CHR (%)	Sustained Haem response % (>4 wks)	MCR (%)	CCR (%)	Median Survival mo
My BC (n=229)	52/15	31	16	7	6.8
Ly BC / Ph ALL (n=229)	59/22	27	-	-	4.9
Accelerated Phase n=181	82/53	69	24	17	Not reached
CP post IFN failure	95/95	95	60	41	Not reached

Imatinib markedly improves QOL

- Previous gold-standard IFN/Ara-C – both agents sub-cut and associated with significant side-effects.

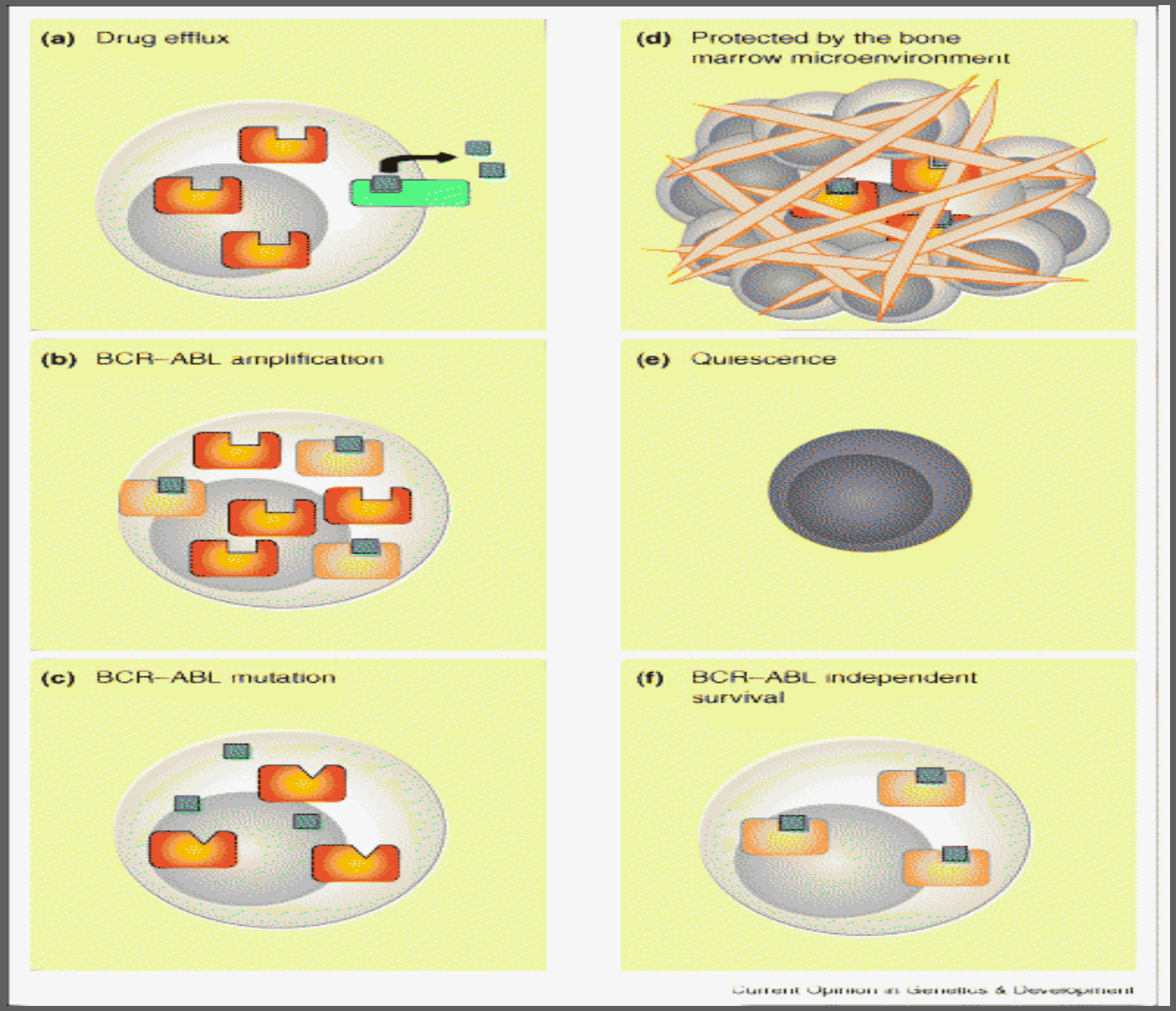
- Imatinib oral, very well tolerated.

Cloud in the silver lining: problems with Imatinib

- Development of resistance

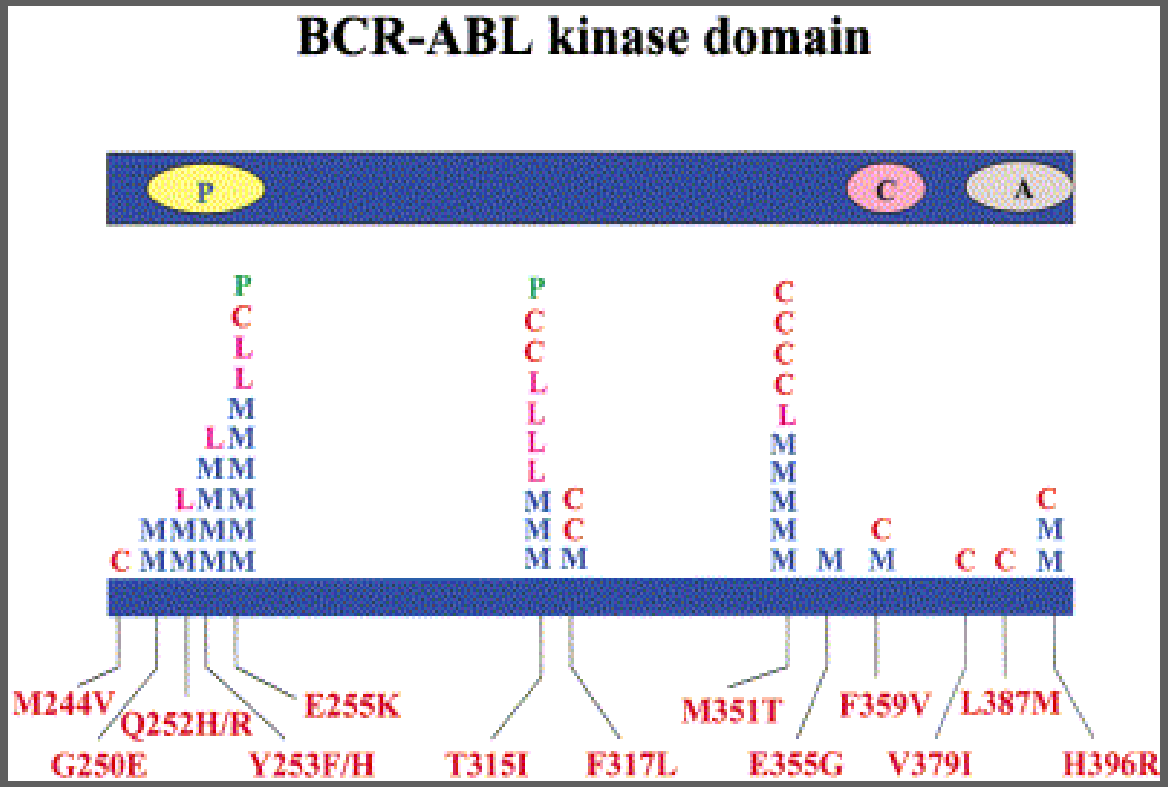
- Imatinib fails to cure CML

Cellular and Molecular mechanisms of CML resistance.



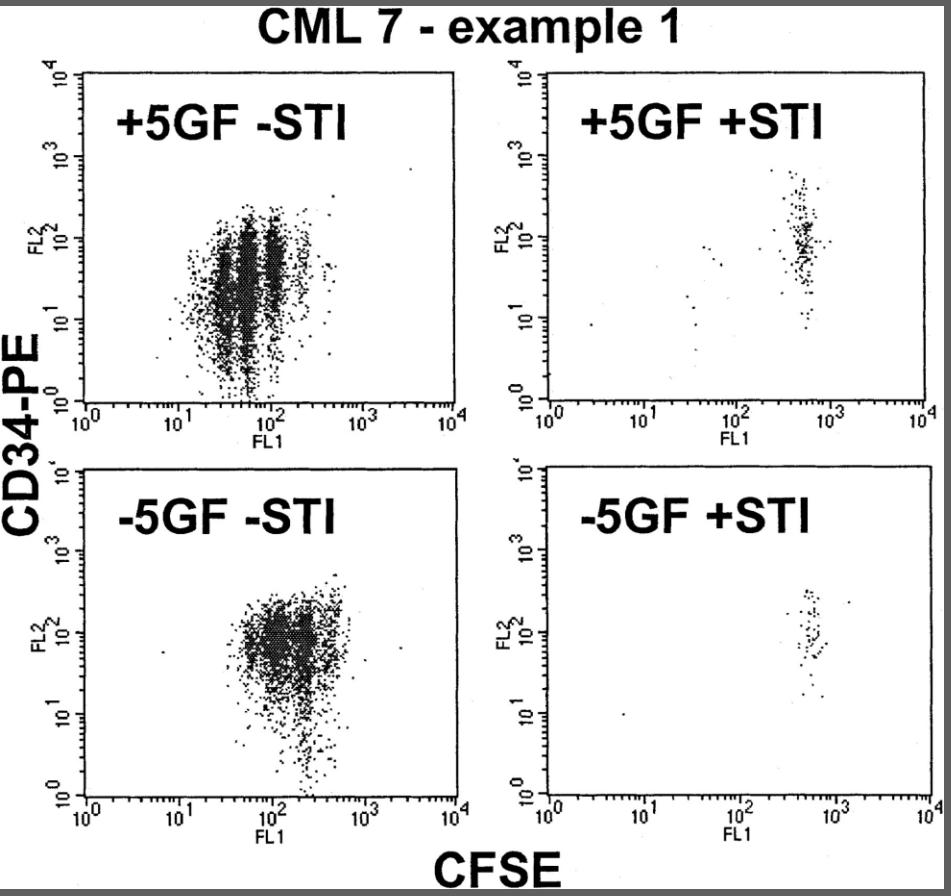
Resistance to IM

- Primary resistance –poorly understood.
- Acquired resistance – Amplification/ overexpression of BCR-ABL (8-30%)
- Mutations of the ABL kinase domain (50-90%).



- P loop (poor prognosis)
- C catalytic domain
- Activation loop – prevent adoption of the inactive form.
- T315I – H bond with IM
- M351T – contacts Abl SH2 region stabilising inactive form

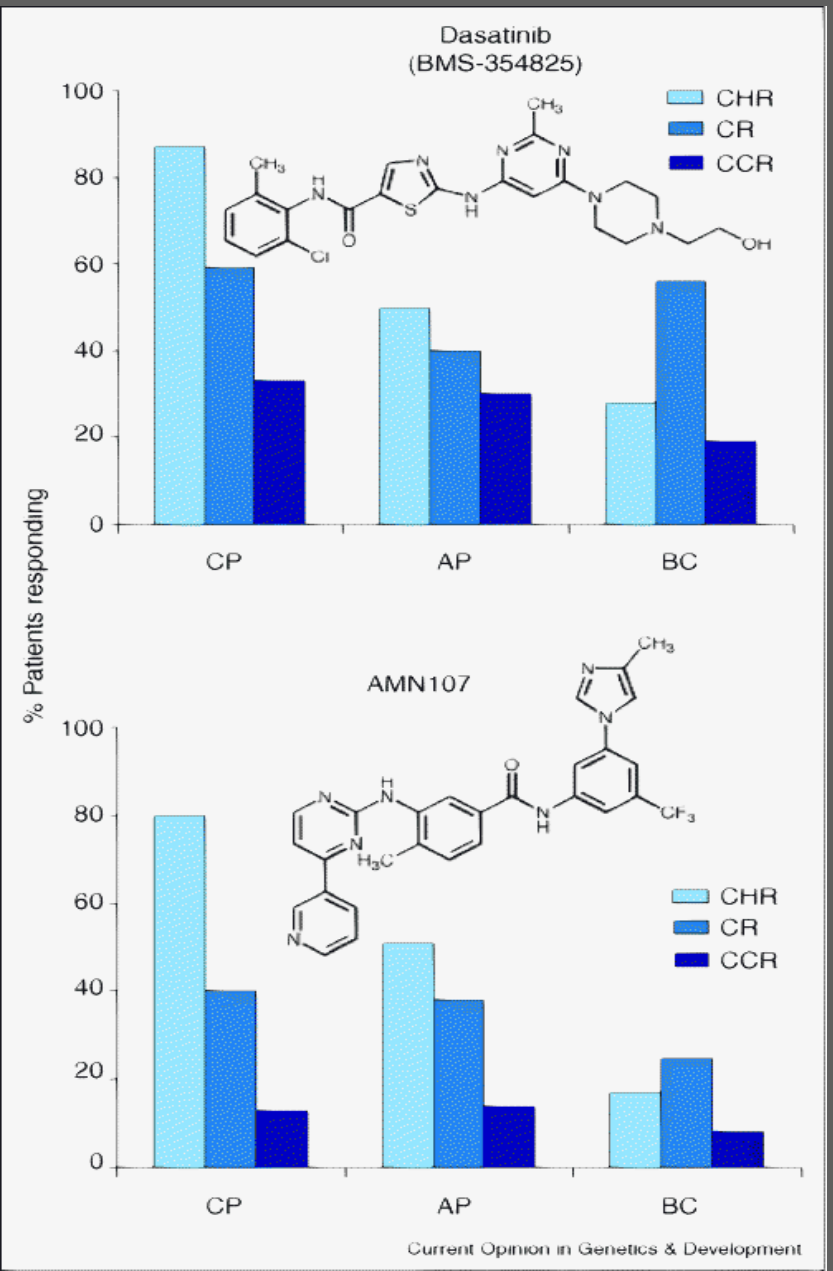
Quiescent CML stem cells are resistant to IM



- Primary CML CD34+ cells
- Cultured in the presence and absence of growth factors and IM.
- Dividing cells exquisitely sensitive to IM.
- However, quiescent cells not sensitive to IM
- BCR-ABL+ CD34+ cells are present in patients in CCR.
- CD34+ cells carry resistance mutations

- Suggests that CURE of CML with tyrosine kinase inhibitors is UNLIKELY.

New therapies for CML: Novel Abl kinase inhibitors.

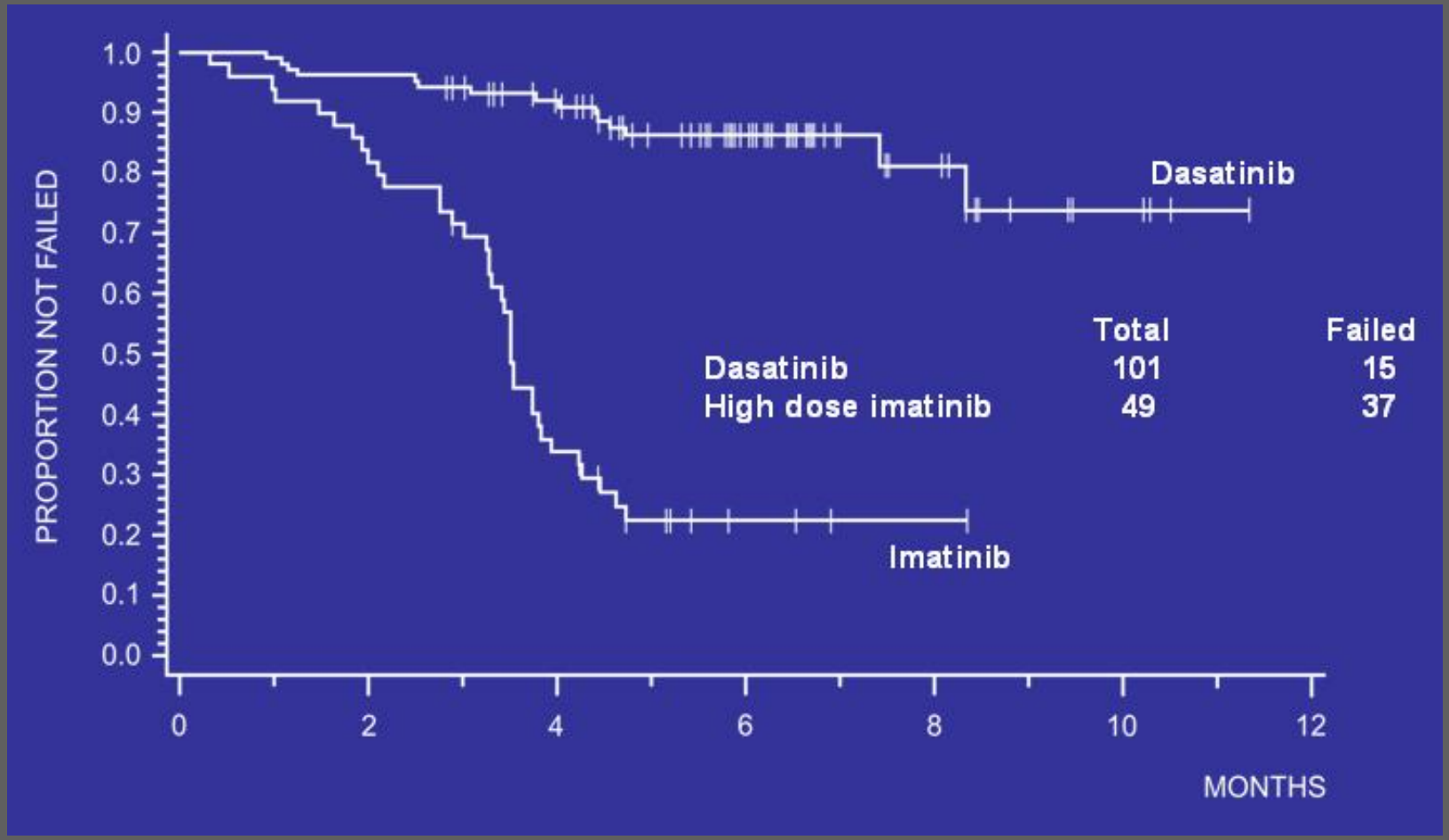


- BMS-354825 – Dasatinib (BMS)
  300 fold potency vs BA
  binds the active and the inactive form
  binds most kinase mutations (NOT T315I)

- AMN107 – Nilotinib (Novartis)
  30 fold potency vs BA
  binds the inactive form.
  binds most kinase mutations (NOT T315I)

- Efficacy against leukaemia stem cells?

START- R study Dasatinib vs Imatinib 800mg



Failure was defined as either progression, lack of response, crossover, off treatment or death

Progression was defined as confirmed accelerated/blast phase, loss of complete haematologic response/major cytogenetic response or increasing white blood cells

At follow-up, 15% of dasatinib and 76% of imatinib patients had progression or crossover due to intolerance

Shah et al Dasatinib START studies, ASCO 2006

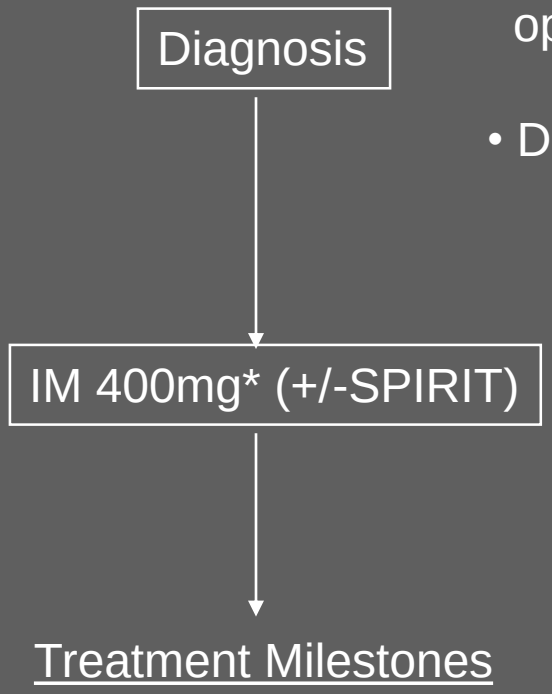
Definitions of treatment failure and suboptimal response in CML

ELN guidelines

	Minimum response	Ideal response
3 months	CHR	Minor cytogenetic response
6 months	Minor cytogenetic response	MCR/CCR
12 months	MCR	MMolR
18 months	CCR	MMolR

Baccharani et al Blood 2006

Initial treatment algorithm for CML patients (I)



- If <60 leucapherese, assess transplant options and tissue type patient and sibs.
- Discuss SPIRIT trial.

(*300mg minimum dose necessary to inhibit BCR-ABL)

- 3/12 – CHR.
- 6/12 – Minimum of a minor Cytogenetic response.
- 12/12 – MCR.
- 18/12 – CCR and MMR (>3 logs reduction) desirable.

Initial treatment algorithm for CML patients (II)

Recommended monitoring

- Once CHR achieved, FBC every 6-12 weeks.
- Marrow minimum every 6/12 until CCR
- qPCR for BCR-ABL/ABL ratio every 4/12.
  (if rise >1 log, repeat immediately and FISH, if >2 logs then perform BM for morphological assessment of disease phase).
- G-banding every year.
- Mutation screening for patients who fail therapy.

Failure to reach milestones (+loss of response)

- ↑ IM dosage to 600-800mg.
- Clinical trial of 2nd generation Abl kinase inhibitor (as available).
- Consider SCT if beyond CP and evidence of marrow response to induction with 2nd generation Abl kinase inhibitor.

Trials available for CML

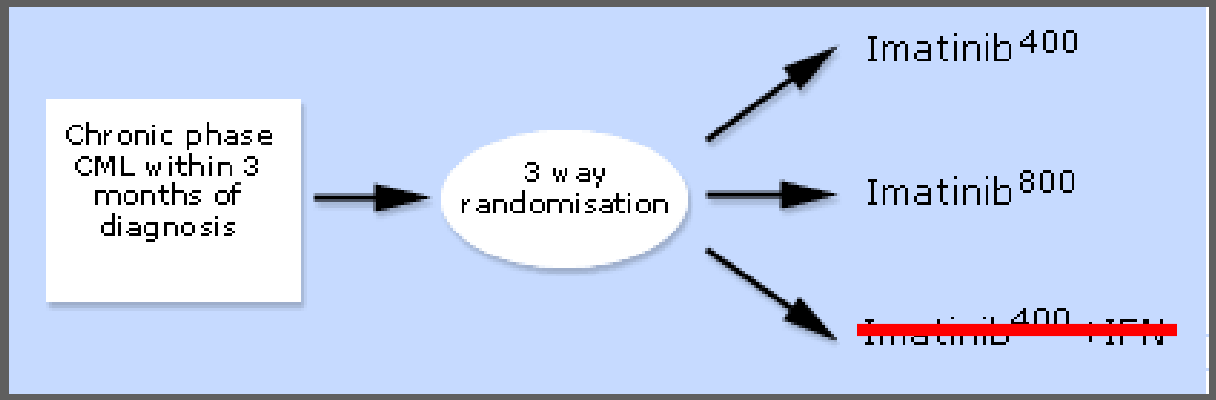
- UK SPIRIT study.

- BMS 043 Dasatinib 100mg vs Imatinib 800mg.
  CP patients who are “suboptimally treated” by ELN guidelines.

- ENACT – expanded access trial for Nilotinib.
  Imatinib resistant or intolerant patients in all phases of CML.

SPIRIT STI571 Prospective International Randomised Trial

- Chronic phase CML.
- Comparison of 2 doses of IM and combination of IM/Peg-IFN.



DASATINIB

- Endpoints – Overall 5 year survival (1ry).
  Molecular response at 1 year.
  Time to progresion in each arm.
  Time to Rx failure in each arm.
  Rate of CHR and Cyto response at 1 year.

- Problems with offering IM combination and with toxicity

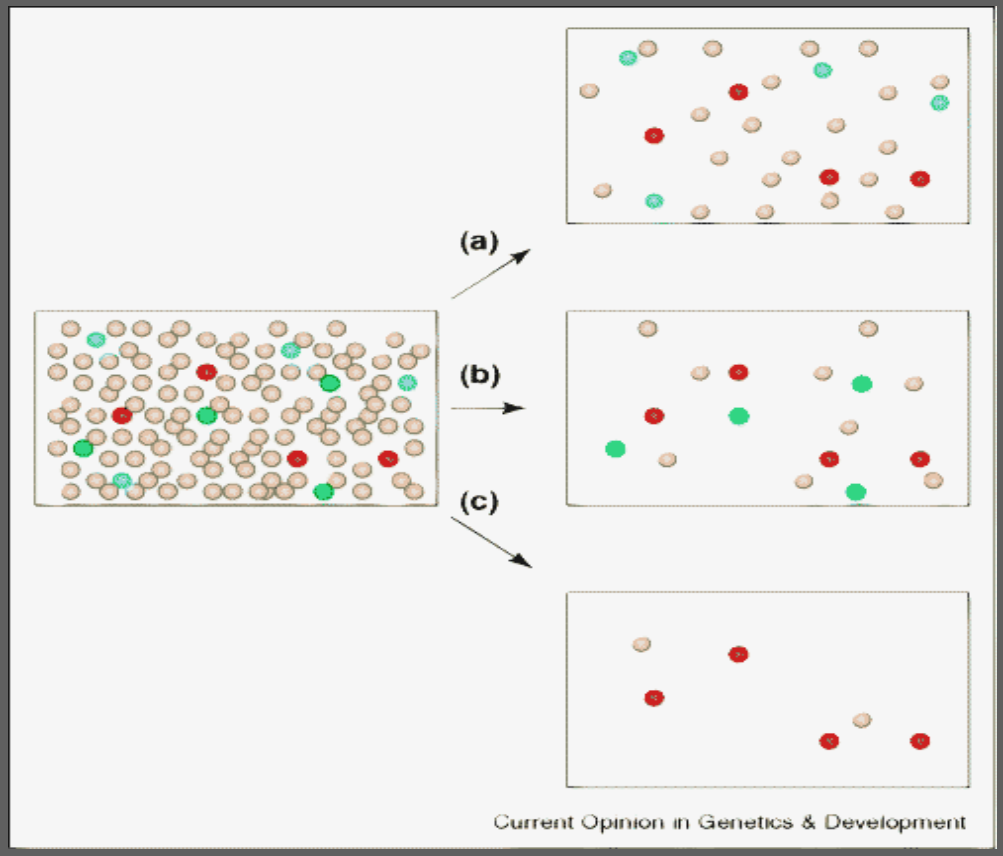
CML: conclusions and challenges ahead

- Pathogenesis of CP CML is very well understood: dependence upon BCR-ABL kinase activity.
- Imatinib Mesylate is a highly efficacious, selective inhibitor of BCR-ABL.
- Resistance to IM develops.
- IM does not target leukaemia stem cells in CML and is therefore unlikely to cure the disease.

- ➢ Effectively target the leukaemia stem cell compartment.
- ➢ Devise strategies to decrease the incidence of resistance.
- ➢ Develop better strategies for treating advanced phase CML.
- ➢ Develop strategies for decreasing the toxicity of allo SCT without compromising its efficacy

Rationale for combination therapy

- Resistance is the single greatest reason for treatment failure currently.
- cf HIV therapy prior to multipleinhibitors.
- Recent prospective screen for resistant mutations to Dasatinib, 3 mutations accounted for > 90% of the mutations- T315I, T315A* and F317F*



Treated with drug X

Treated with drug Y

Treated with drugs X + Y