

Sydney Adventist Hospital GP Oncology Conference

Current management of leukaemia

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Wednesday 4th May 2011

Overview of talk

- Acute leukaemia
 - Pathogenesis, presentation, diagnosis, prognosis, treatment, outcomes
- Chronic myeloid leukaemia
 - Discovery of pathogenic mechanism
 - Revolution in outcomes with novel therapy
- Chronic lymphocytic leukaemia
 - Epidemiology, presentation, diagnosis, prognosis, evolution in treatment, novel therapies

The Leukaemias

Acute	Myeloblastic (AML)
	Lymphoblastic (ALL)
Chronic	Myeloid (CML)
	Lymphocytic (CLL)

The acute leukaemias

Acute Leukaemias

Acute Lymphoblastic Leukaemia (ALL)

Common in children

Common ALL peak 3-4 years

Second peak > 40 years

Acute Myeloblastic Leukaemia (AML)

All age groups

Most common leukaemia in adults

Increasing incidence with age

Acute Leukaemias

– Clinical Features

1. Marrow failure

Anaemia, neutropenia, thrombocytopenia
Weakness, infection, bleeding

2 Organ Infiltration

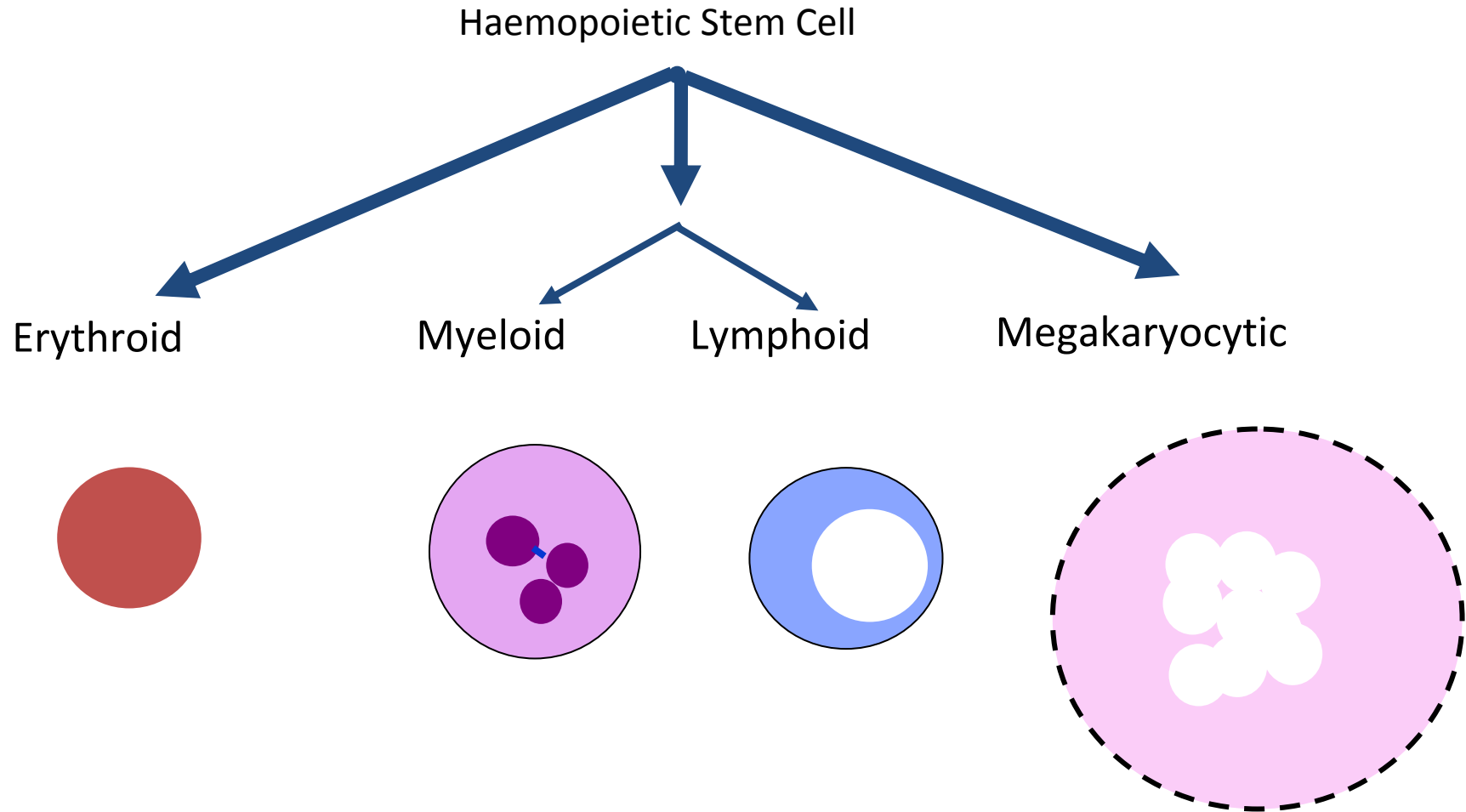
Bone pain, spleen, liver, skin,
Central nervous system (CNS), gum infiltrates

3 Products of leukaemia cells

Disseminated Intravascular Coagulation (DIC)
Hyperuricaemia
Lysozyme -> hypokalaemia

Normal Haematopoiesis

(at its simplest)



Leukaemia - pathogenesis

- Normal haematopoiesis is a tightly regulated process balancing cell division and cell death
- Leukaemia due to multiple accumulated mutations leading to an autonomously proliferating clone

- Mutations in acute leukaemia:
 - **translocations** causing activation of cell pathways
 - BCR-ABL in CML t(9;22)
 - PML-RAR α in APML t(15;17)
 - **deletions** of tumour suppressor genes
 - Rb, p53, ATM
 - **epigenetic** abnormalities
 - Abnormal methylation and histones
 - Alter gene expression
 - Therapeutic targets

Acute Leukaemia

– Laboratory diagnostic tests

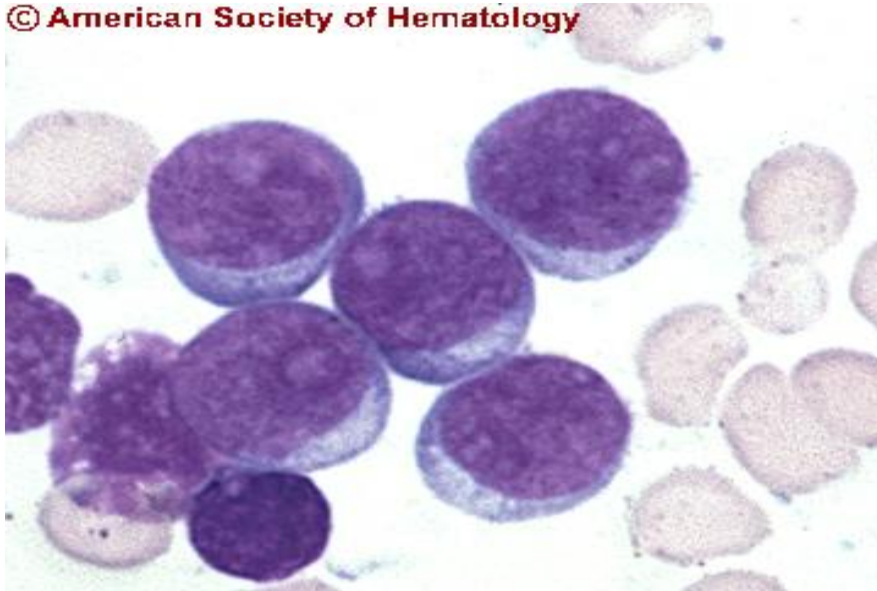
- Blood
- Bone Marrow
- Immunophenotype (flow cytometry)
- Genetics
 - karyotype, FISH and molecular tests
- Coagulation - for DIC especially in AML M3

Diagnosis of acute leukaemia

- Traditionally classification based on morphology (FAB), incorporating lineage and maturation
- Flow cytometry gives information about lineage and maturity
- New WHO classification incorporates cytogenetic and molecular characteristics
 - Prognosis
 - Appropriate therapy
 - Means of monitoring disease

Acute Leukaemia - Morphology

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L1: small, relatively large nuclei, lack visible nucleoli

L2: larger, nucleoli

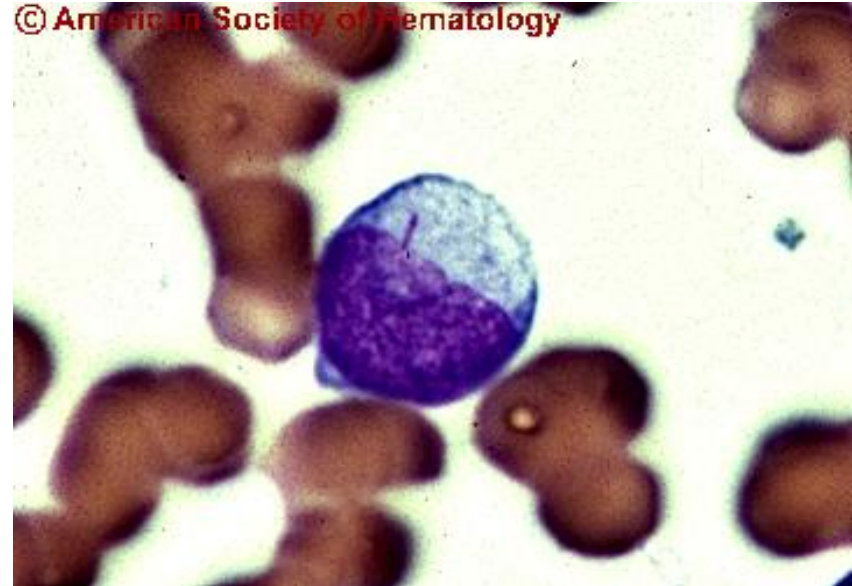
L3: basophilic, heavy vacuolation – Burkitt's

Differentiate L3 from others

T from B for prognosis

ALL

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Auer rods, granules suggest AML

Dysplasia? (Secondary AML, poor prognosis)

Eosinophilia? (AML M4Eo, good prognosis)

Monocytes/monoblasts (M5 – associated with organ infiltration eg gum hypertrophy)

Abnormal promyelocytes ?APML

AML

Acute promyelocytic leukaemia

(APML – M3)

- This is a ***medical emergency***
- Characterised by presence of abnormal promyelocytes
 - Caused by the t(15:17) forming PML-RAR α fusion gene
 - Combination of maturation arrest and uncontrolled proliferation
- Treated with all-trans retinoic acid (ATRA) and arsenic
 - overcomes block in maturation
- Good prognosis with high overall cure rates
 - BUT risk of early death due to complications from DIC

Acute Leukaemia – Phenotype

Acute Lymphoblastic Leukaemia (ALL)

Pre-B cell - 'common' ALL - CD10+

B-cell ALL - Burkitt-like L3 morphology

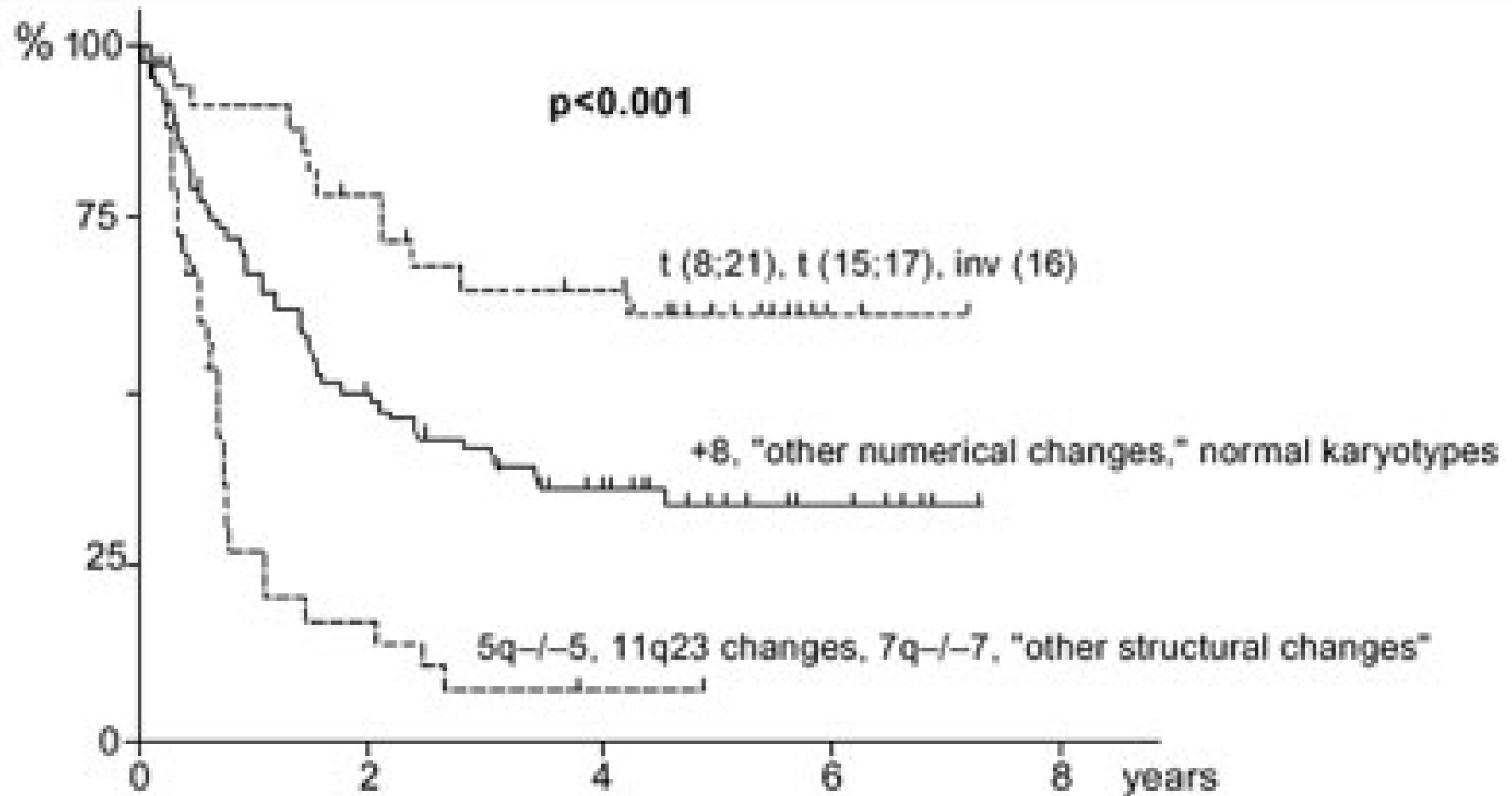
T-cell ALL

Acute Myeloblastic Leukaemia (AML)

Expression of myeloid markers (eg CD13 and CD33)
together with stem cell marker CD34

Risk stratification

- Cytogenetics very important as:
 - ‘good risk’ patients are likely to be cured with chemo alone
 - ‘poor/high’ risk patients often need transplantation
 - However ‘intermediate risk’ patients are more controversial
 - **molecular markers help guide risk**
 - Eg FLT-3, NPM1, CBF
 - monitor ‘residual’ disease by PCR



AML – Other prognostic features

Factor	Favorable	Unfavorable
Age	<45 yrs	<2 or >60 years
Performance status	Good	Poor
WBC	<25	>100
Leukaemia	de novo	MDS / MPD
FAB type	M2, M3, M4	M0, M6, M7
Cytogenetics	t(8;21) t(15;17) inv16	Most others
Molecular	CBF, NPM	FLT3-ITD
Prior chemotherapy	No	Yes
CNS Disease	Absent	Present

ALL – Other prognostic features

Factor	Good	Bad
WBC	<10	>50
Sex	Female	Male
Phenotype	cALL	B-ALL
Age	2-10 yrs	>15 years
Cytogenetics	Hyperploidy	Ph ¹
Time to remission	<4 weeks	>4 weeks
CNS Disease	Absent	Present

Acute Leukaemia – Therapy

Supportive Therapy

Critical in managing the patient during chemotherapy:

1. Red Cell Transfusion (Anaemia)
2. Antimicrobials for infection (Neutropenia)
 broad spectrum antibiotics, antifungals, antivirals
3. Platelet Transfusion (Thrombocytopenia)
4. Adequate iv access (central lines)
5. Fluids and prophylaxis against tumor lysis syndrome
 (allopurinol, rasburicase)
6. May require inotropic and ventilatory support at times

Acute Leukaemia – Therapy

Remission Induction

High dose chemotherapy to eradicate leukaemia from blood, bone marrow and other sites eg “7/3” regimen in AML (daunorubicin and cytosine)

ALL similar principle however different combinations of drugs (daunorubicin, vincristine, steroids, MTX, asparaginase, cyclophosphamide etc)

Consolidation

Similar drug regimen to induction but slightly shorter course
eg “5/2” regimen in AML (daunorubicin and cytosine)

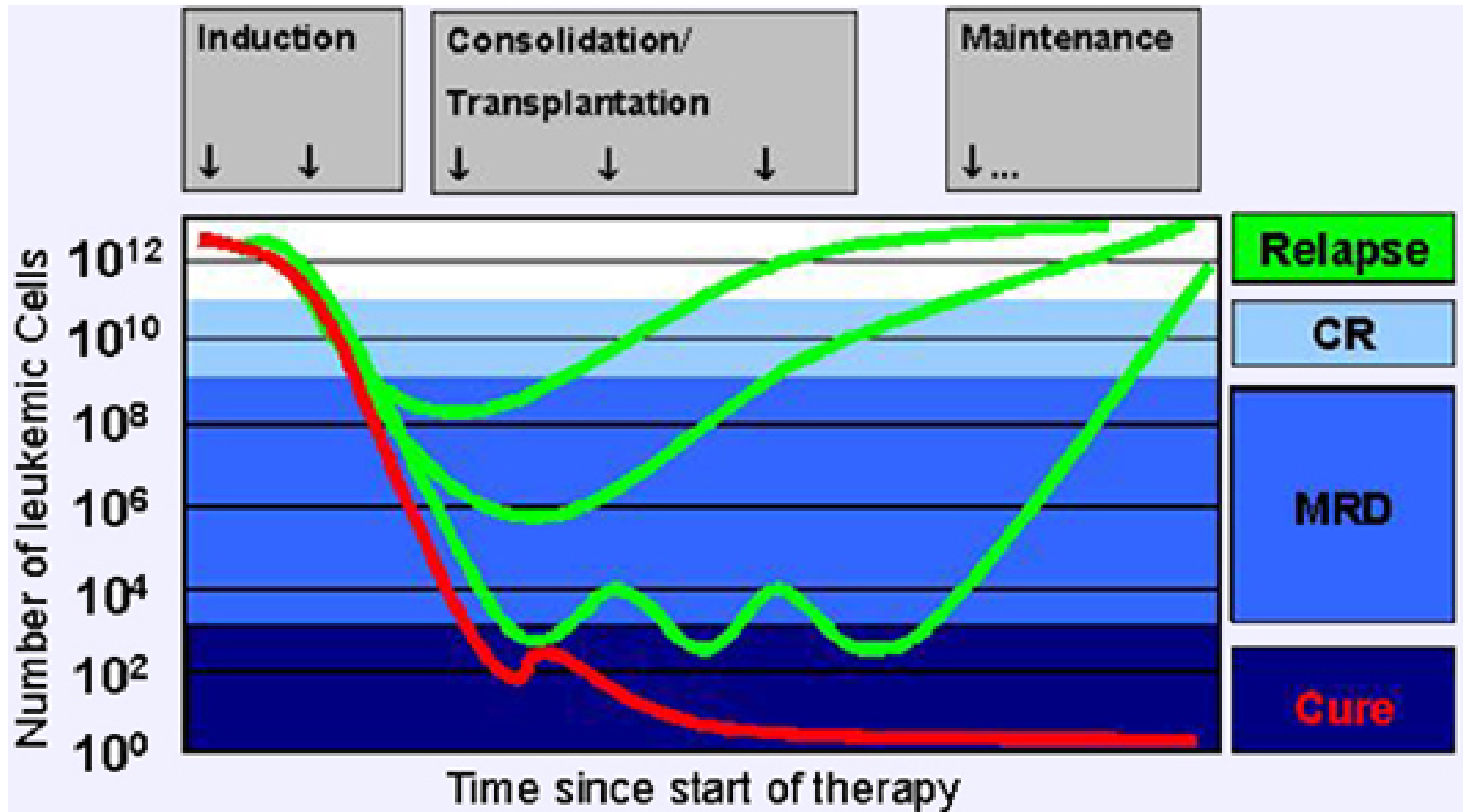
Maintenance

Essential in ALL to prevent relapse: usually 2-3 years MTX + 6-MP
Usually not required for most AML, but with exceptions (eg APML)

CNS Prophylaxis

Craniospinal radiotherapy &/or intrathecal chemotherapy (methotrexate)
Essential in ALL to prevent relapse

Remission



Acute Leukaemia

Typical response rates with chemotherapy

Therapy	Complete Remission	5-year Survival
Childhood ALL 3-4 drug regimens (e.g. Daunorubicin, Vincristine, Prednisone)	85-95%	70-80%
Adult ALL	80%	30% (50% Tx)
Adult AML	60-80%	20-45% (55-60% Tx)

Acute leukaemia - summary

- Investigations: FBC, coags, BM biopsy + flow and cytogenetics
- Treatment: remission induction, consolidation, supportive care, +/- transplantation
- In past decade, increasing use of genetic markers for prognostic and treatment guidance

Chronic myeloid leukaemia

Chronic myeloid leukaemia

Incidence <20% of all leukaemias

Age Any age, mostly 40 – 60

Sex M:F 1.4 : 1

Aetiology Mostly unknown

Increased with radiation exposure

Chronic Myeloid Leukaemia

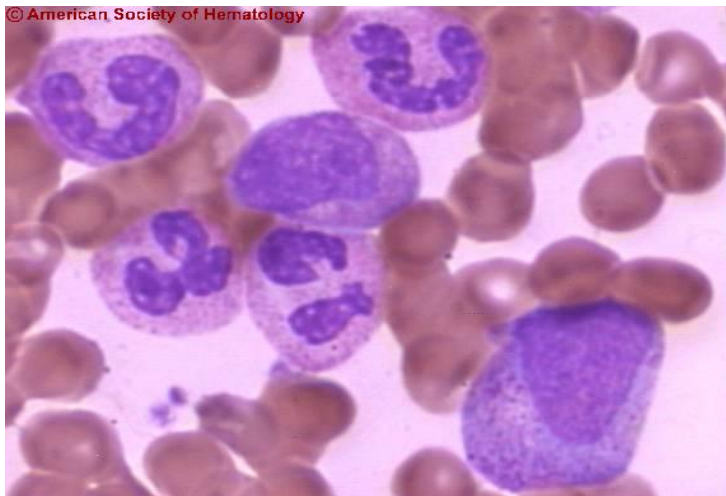
– Clinical Features

- **Splenomegaly & Leucocytosis**
- **Symptoms of Hypermetabolism**
Fever, night sweats, weight loss
Hyperuricaemia
- **Symptoms of Hyperleukocytosis**
Cardiac failure, confusion, coma, visual symptoms
- **Symptoms of Marrow impairment**
Anaemia, neutropenia, thrombocytopenia
Weakness, infection, bleeding

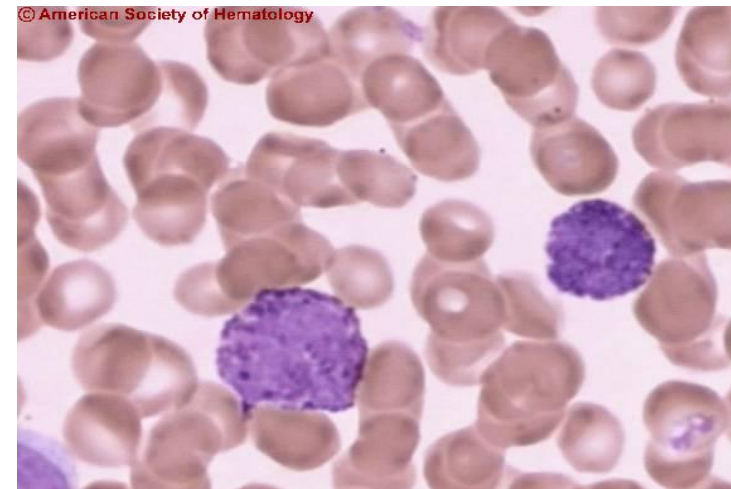
Chronic Myeloid Leukaemia

- Peripheral Blood Morphology

- *Chronic Phase*



- Increased granulocytes
- Left shift
- Myelocyte peak



- Basophilia

Natural history of CML

Chronic phase

Often easily controlled
Typical duration 3-4 years

Accelerated Phase

an acute leukaemia evolution
increasing blasts and basophils

“Blast Crisis”

frank leukaemia (AML or ALL)
~**15%** evolution per year
dismal prognosis
almost impossible to
treat even with

effectively
transplantation

Historically

- Hydroxyurea, IFN, cytarabine had some effect
- ONLY curable by stem cell transplantation in chronic phase

However:

- Chronic phase 5 years on average but highly variable
- Therefore risk of death with early transplantation vs risk of death in blast crisis



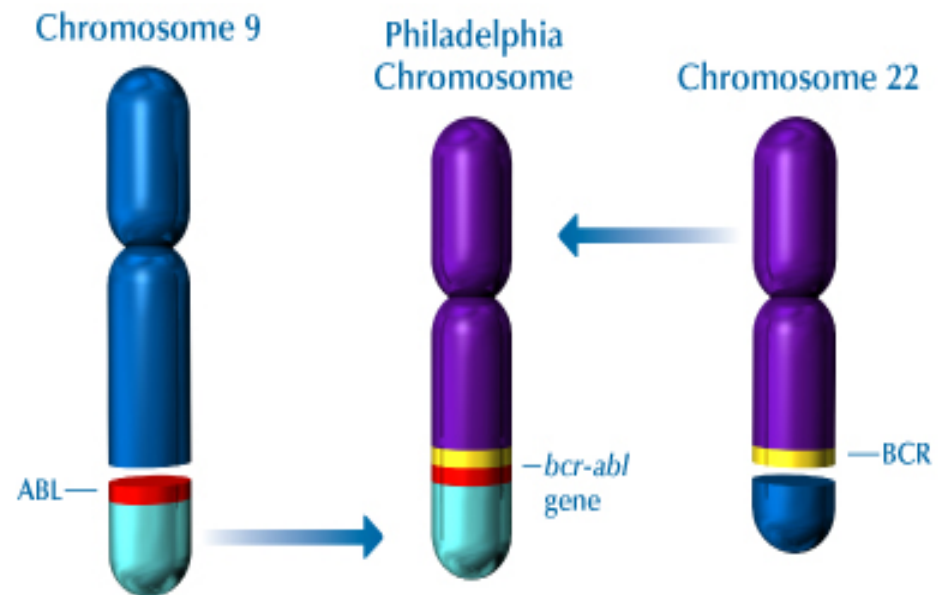
- Peter Nowell and David Hungerford

Philadelphia chromosome

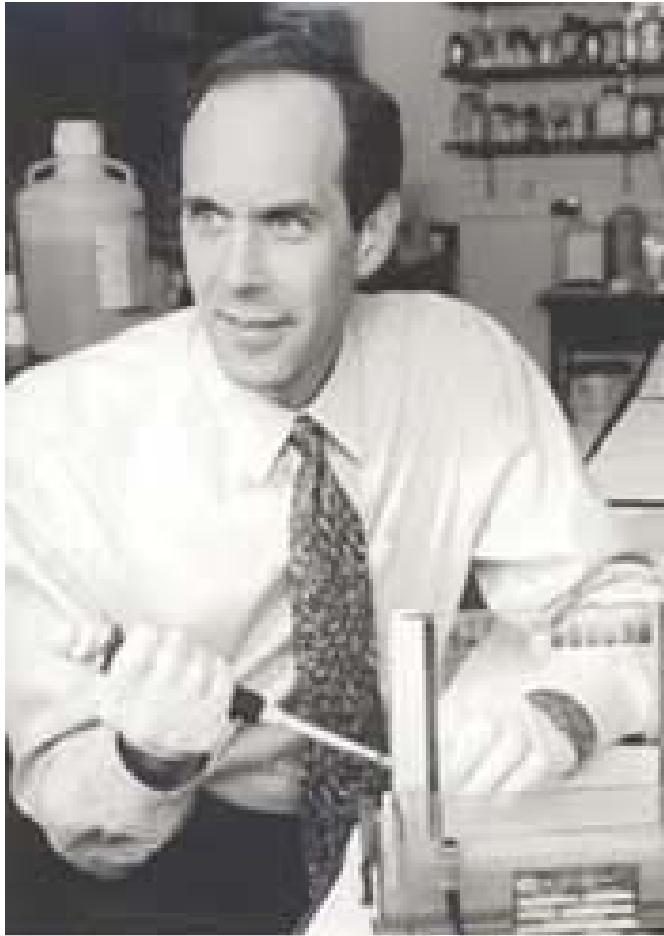
First time an *abnormality in the chromosomes linked with a malignant medical condition*



- Janet Rowley (Chicago 1973)



Tyrosine Kinase Inhibitors (TKIs)



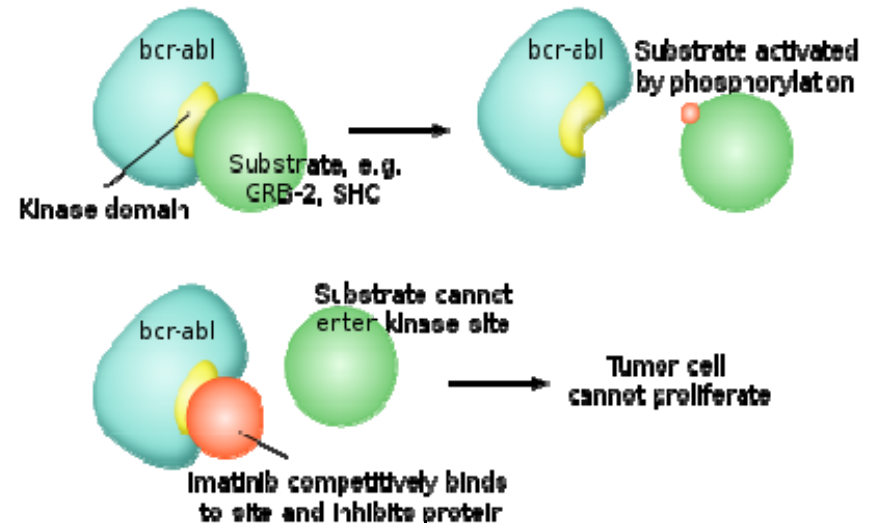
Brian Druker, M.D.

Photo: Laura Sikes

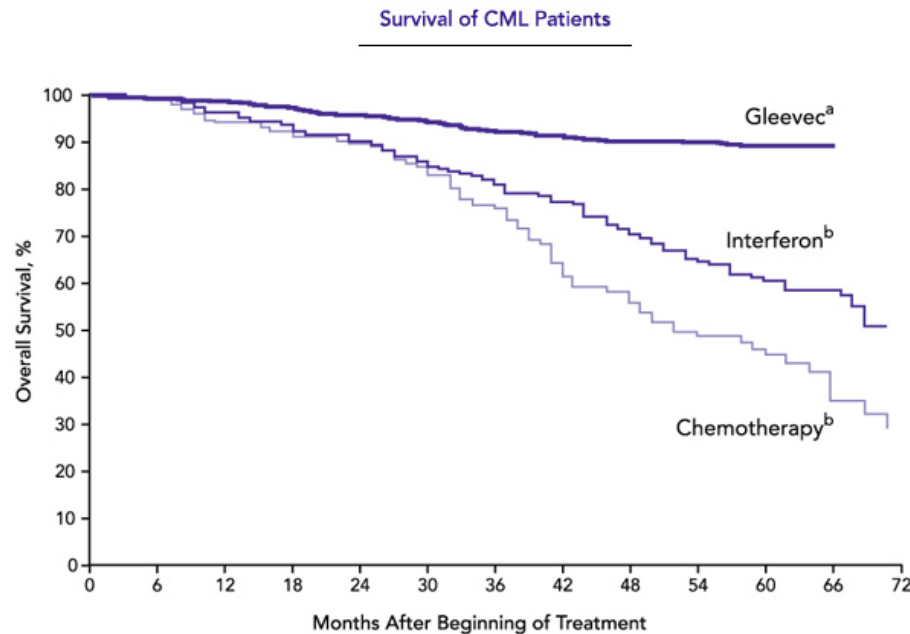
- In the late 1990s, STI-571 (imatinib, Gleevec/Glivec) was developed by Novartis
- Trials led by Dr Brian Druker showed STI-571 inhibits proliferation of BCR-ABL expressing CML cells
- greatly limit the growth of the CML clone and decreased the risk of the feared “blast crisis”

Mechanism of action of imatinib

- Bcr-abl is pro-leukemic by phosphorylating substrates that are then active and lead to increased cellular activity
- Imatinib blocks the kinase domain and prevents substrates from binding

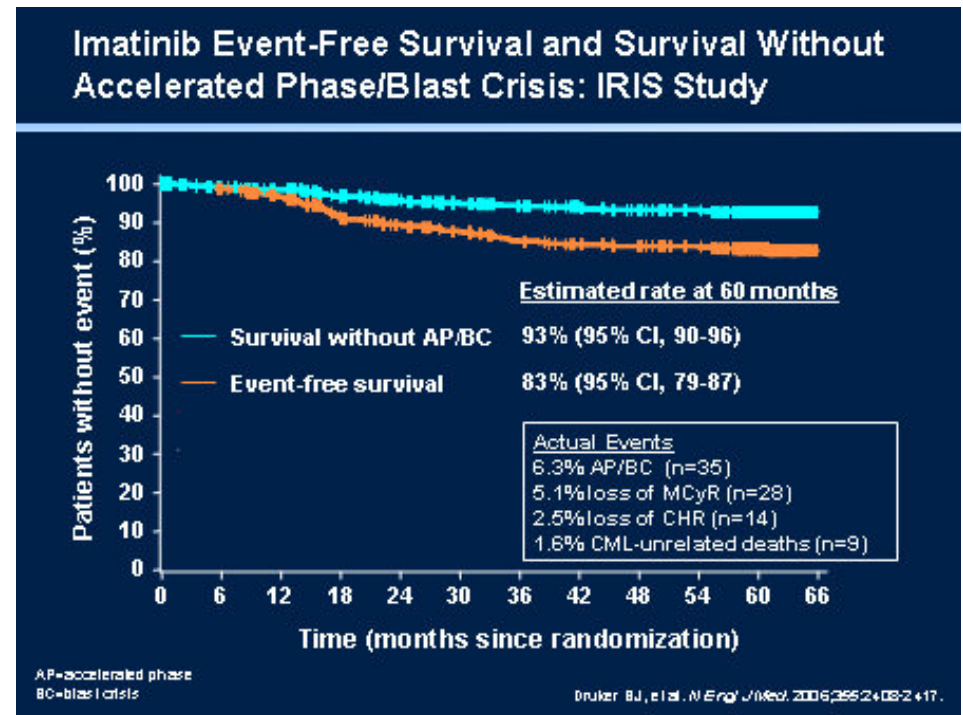


Dramatically improved survival with imatinib



^a From Druker BJ, Guilhot F, O'Brien SG et al. *N Engl J Med.* (2006) 355:2408-2417.

^b From The Italian Cooperative Study Group On Chronic Myeloid Leukemia. *N Engl J Med.* (1994) 330:820-825.



Chronic Myeloid Leukaemia - summary

- First cancer proven due to a specific genetic abnormality
- Good example of molecularly targeted therapy (TKIs)
- Majority of imatinib-resistant patients will respond to other TKIs (except T315I mutation)
- Simple oral treatment with few side effects, however likely to be lifelong treatment
- Imatinib has dramatically improved survival and quality of life for patients with CML

Chronic Lymphocytic Leukaemia

Diagnosis of B-cell Chronic Lymphocytic Leukaemia

Lymphocytosis

Clinical Features

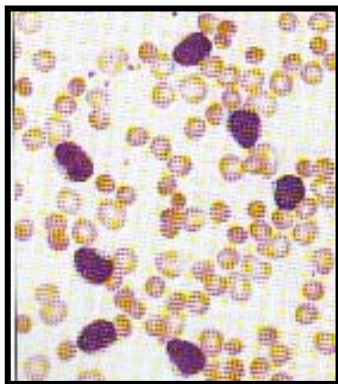
- Lymphadenopathy
- Hepatosplenomegaly

Complications

- Infection
- Autoimmunity
- Transformation

Laboratory Features

Morphology



Phenotype

- CD19, CD20, HLA-DR
- CD5
- CD23
- Weak monoclonal sIg
- CD22 +/-, FMC-7 +/-

Bone Marrow

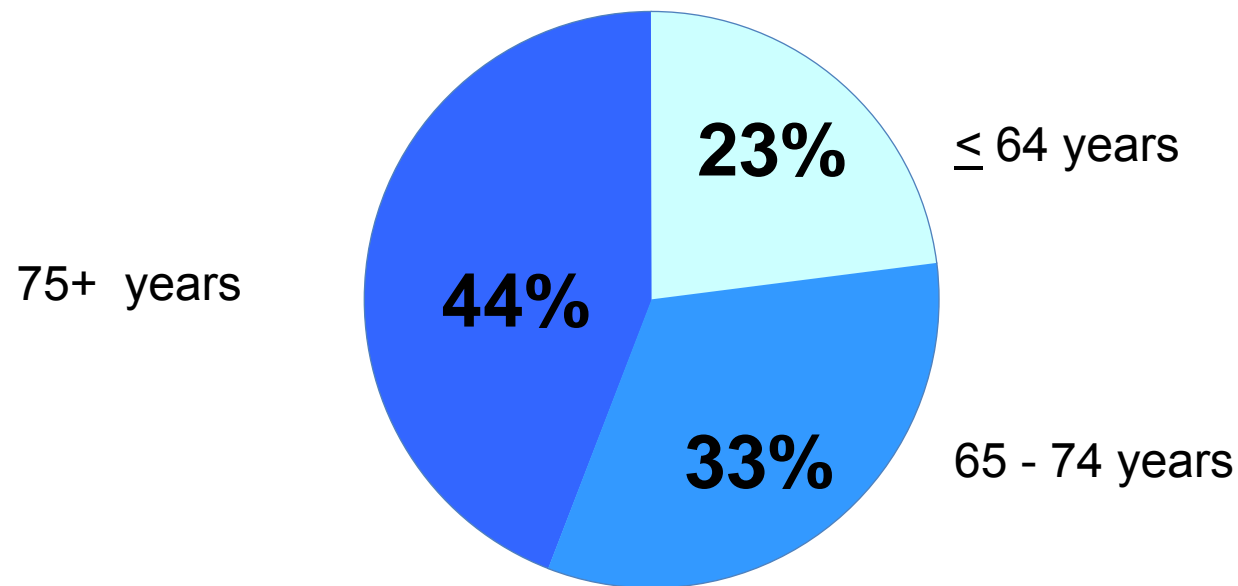
Prognostic value of
pattern of infiltration
on trephine

Genetics

13q-, 12+, 11q-, 17p-

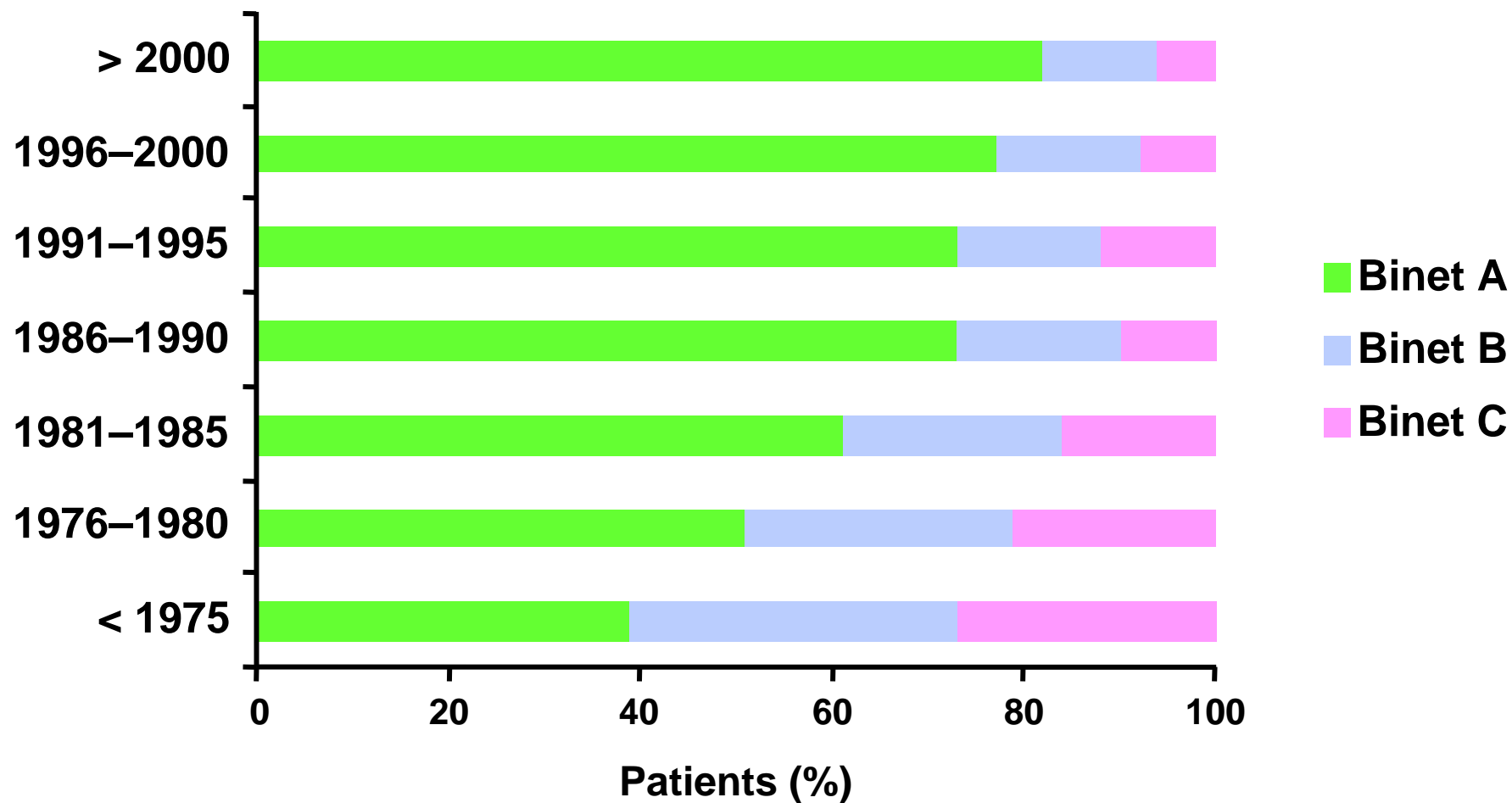
Epidemiology of chronic lymphocytic leukemia

SEER Report 1998



More than half of all patients with CLL are aged >70 years
Typical median age on clinical trials = 50 – 60 years

≥ 80% of patients are now diagnosed with low-risk disease (Barcelona series)



n = 1200

Hospital Clinic Provincial (HCP) Barcelona.

CLL - Staging Systems

Rai

<u>Stage</u>	<u>Findings</u>	<u>Survival</u> (months)
0	Lymphocytosis only	>120
I	Lymphocytosis plus lymphadenopathy	95
II	Lymphocytosis plus splenomegaly &/or hepatomegaly	72
III	Lymphocytosis plus anaemia (Hb < 11.0g/dl)	30
IV	Lymphocytosis plus thrombocytopenia (Platelets < 100)	30

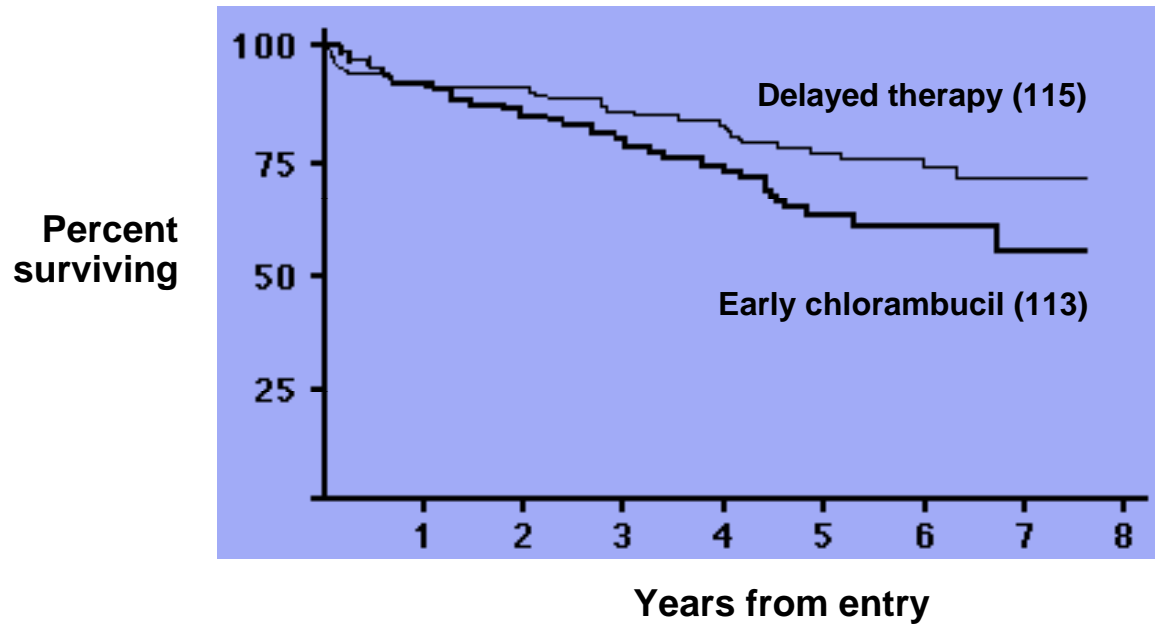
Binet

<u>Stage</u>	<u>Findings</u>	<u>Survival</u> (months)
A	Hb \geq 10, Plts \geq 100, < 3 involved areas	>120
B	Hb \geq 10, Plts \geq 100, \geq 3 involved areas	84
C	Hb < 10, or Plts < 100	24

Involved areas include cervical, axillary or inguinal nodes, spleen or liver.
Hb : haemoglobin, Plts : platelets

Effect of Therapy in Stage A CLL

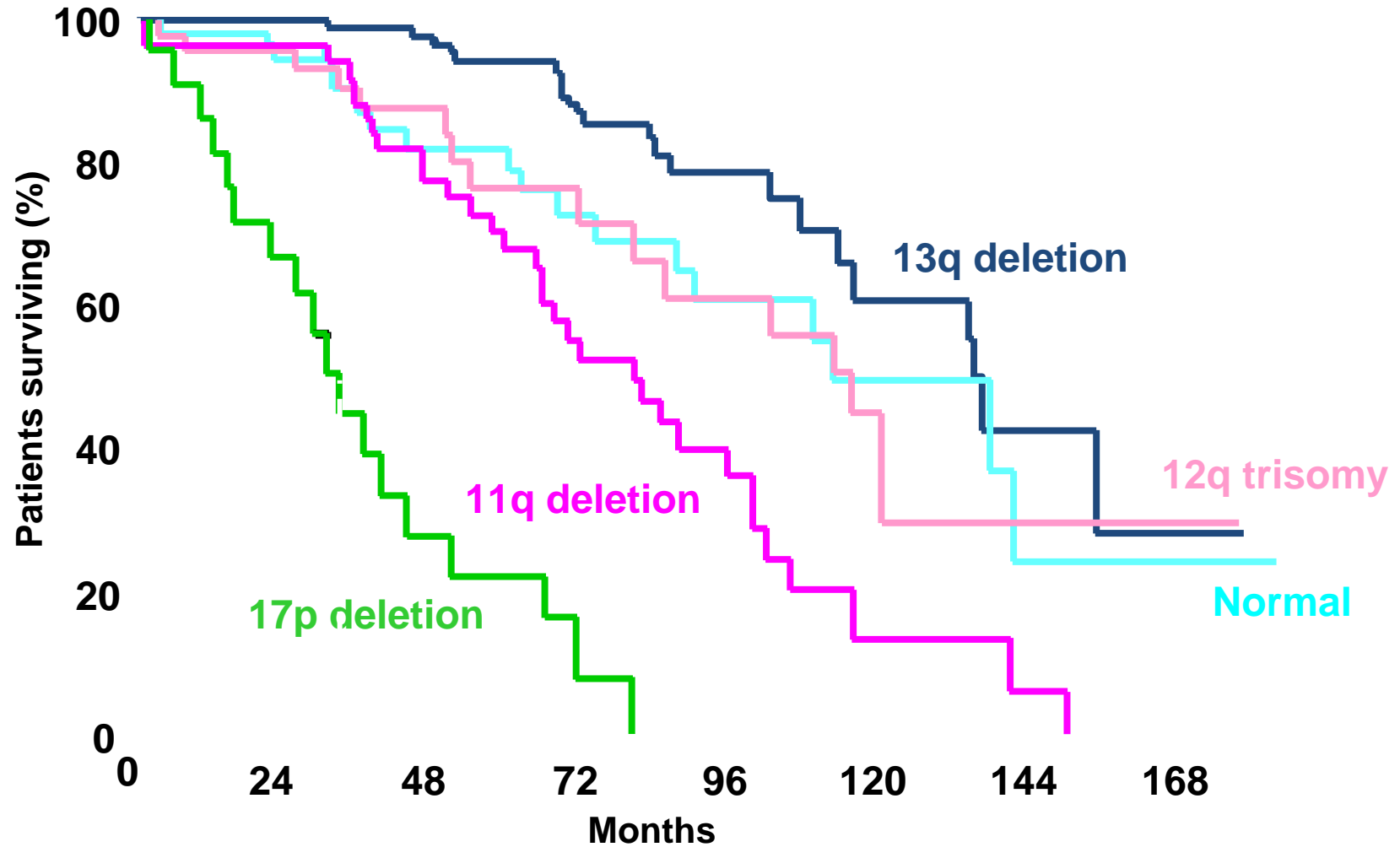
**MRC CLL 2 Trial
(Deaths from all causes)**



Prognostic Factors

Factor	Favourable	Adverse
Lymphocyte Doubling time	> 12 months	< 12 months
Bone marrow histology (trephine)	Nodular Interstitial Mixed nodular & interstitial	Diffuse
Karyotype	13q-, Normal	17p-, 11q-, Complex
IgV gene	Mutated	Unmutated
Sex	Female	Male
% prolymphocytes	< 10 %	10 - 55 %
Other		Advanced age Hypogammaglob. Poor response to Rx

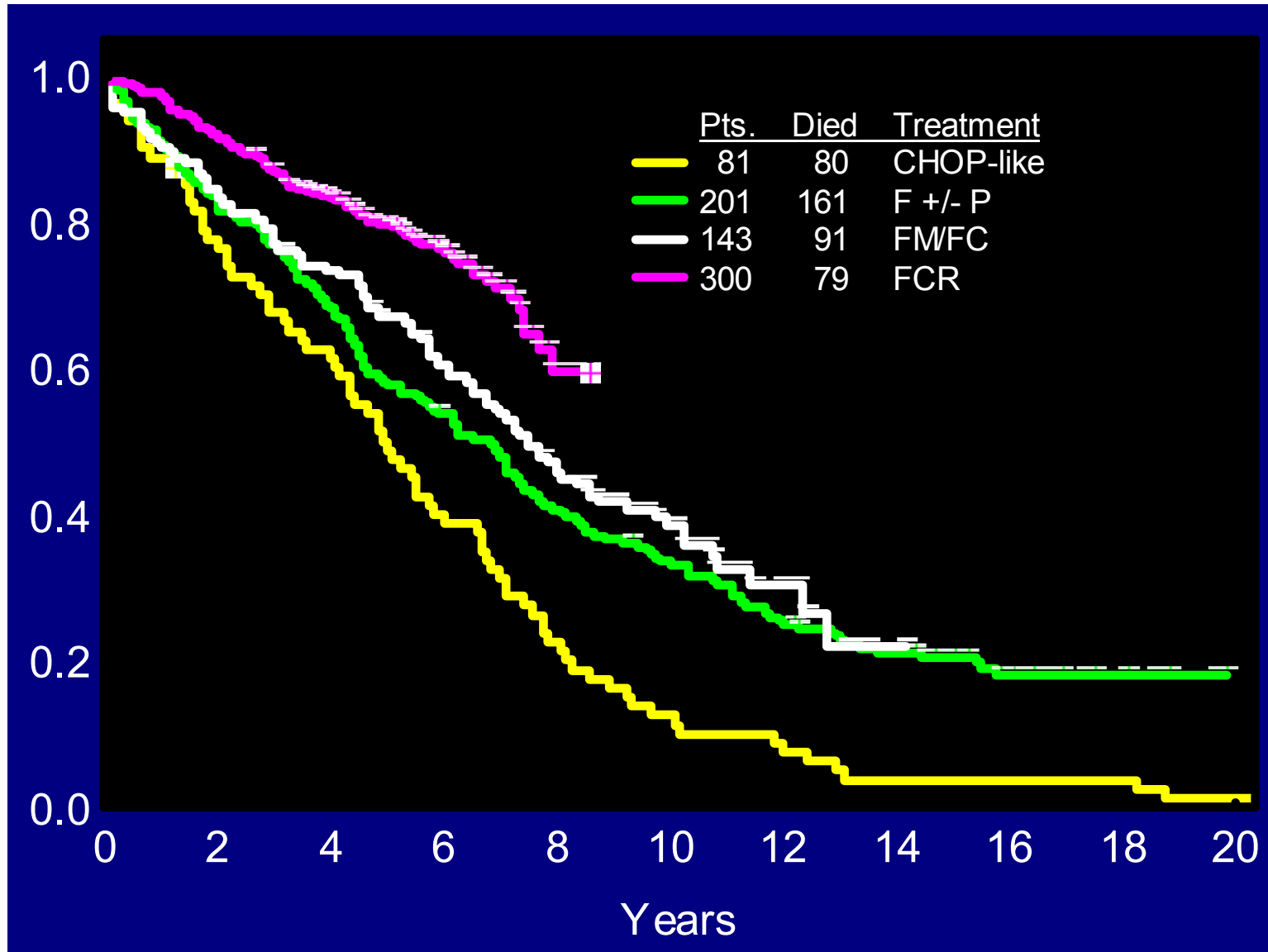
Probability of survival



The therapeutic revolution in CLL: progress to immunochemotherapy

<u>Era</u>	<u>Therapy</u>	<u>PFS</u>
1950s -	Chlorambucil (still in use)	~20 months
1990s -	Fludarabine (F)	~23 months
2000s -	F+C (Cyclophosphamide) UK CLL4 (FC > F > Cbl)	~43 months
Late 2000s :	FC + Rituximab (FCR) i) Pioneered by MJ Keating, MD Anderson ii) CLL8 Randomised Study	>51 months

MD Anderson: FCR results in improved survival compared to historical controls

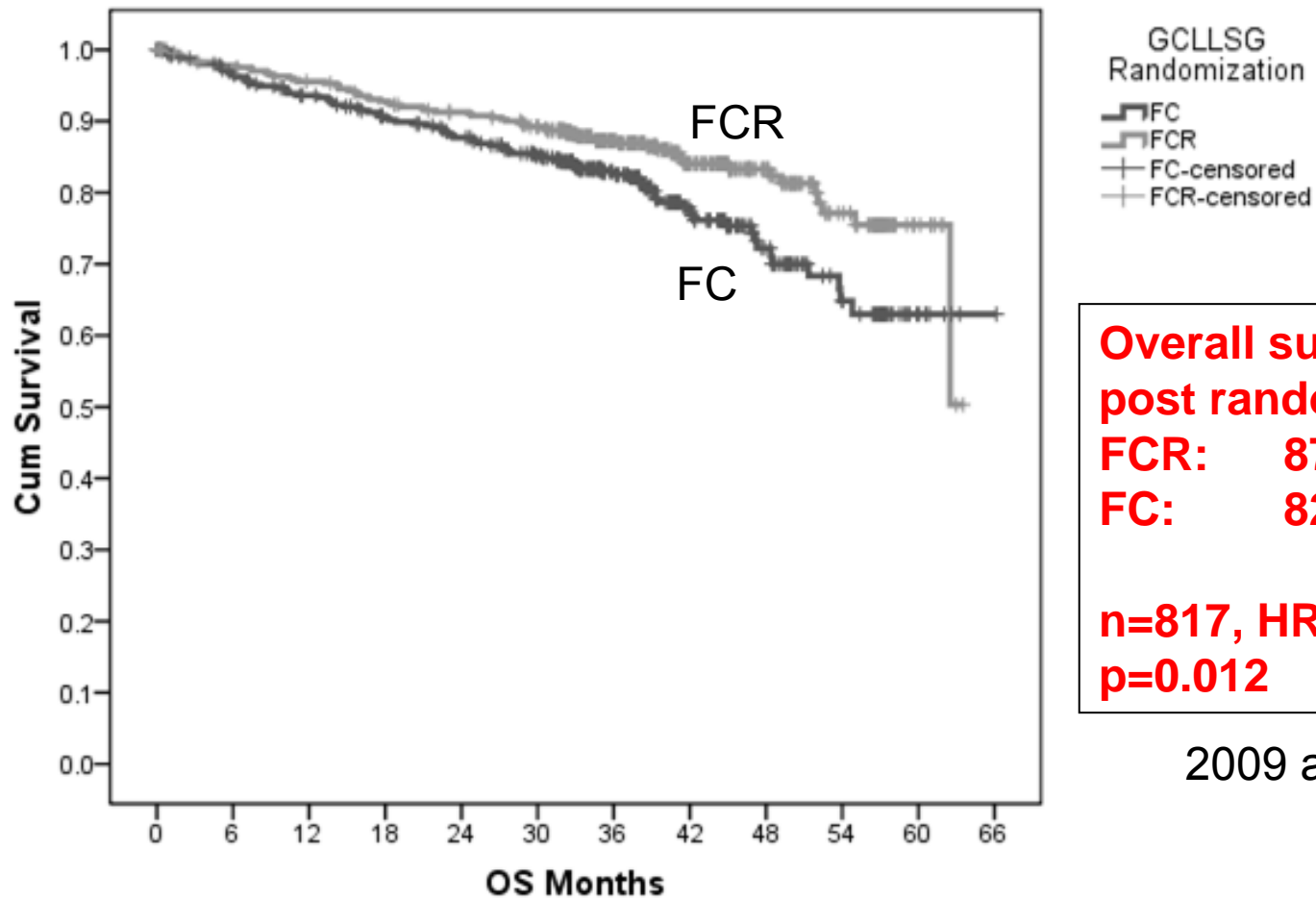


CLL8 trial

Efficacy: Response rates

Best response	FC	FCR
responder: CR/nPR/PR	88,4%	94,9% (CR 44.7%)
non-responder: SD/PD	11,6%	5,1%

CLL8 Overall survival



**Overall survival 3 years
post randomisation:**

FCR: 87.2%

FC: 82.5%

**n=817, HR 0.664,
p=0.012**

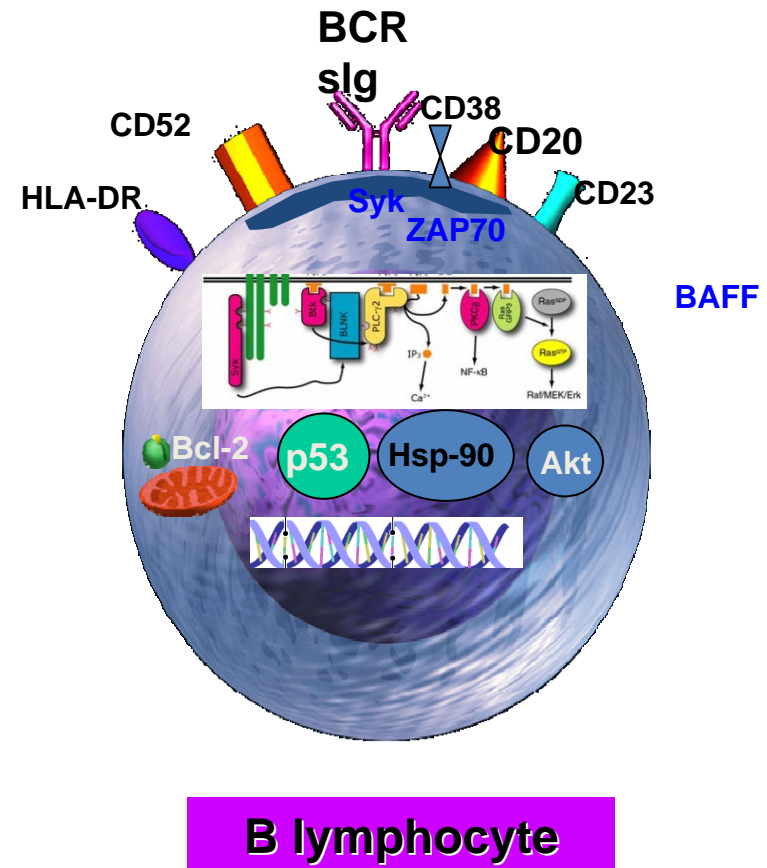
2009 analysis

FCR as first-line treatment in CLL

- FCR is superior to FC with regard to
 - Response rate (CR, OR)
 - Progression-free survival
- FCR is safe:
 - it causes more hematologic toxicity,
 - but not more infections or other severe side effects.
- FCR is the new standard treatment for physically fit CLL patients
 - **median age in CLL8 Study = 61 years**
 - **Median age of CLL patients = 72 years**

Therapeutic Targets

1. Surface Molecules
2. Membrane Lipid Rafts
3. Signaling Pathways
4. Apoptosis induction
5. P53 modification
6. Bcl-2 inhibitors
7. Nucleoside biochemistry
8. 'Microenvironment'



Chronic lymphocytic leukaemia - summary

- Early disease → lymphocytosis → “Watch & Wait”
- Progressive disease
 - adenopathy, organomegaly, marrow failure
 - treatment
 - FCR preferred first-line therapy
- FISH gives prognostic and response information