

PATHOGENESIS OF LEUKEMIAS

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Hematology and Oncology,**

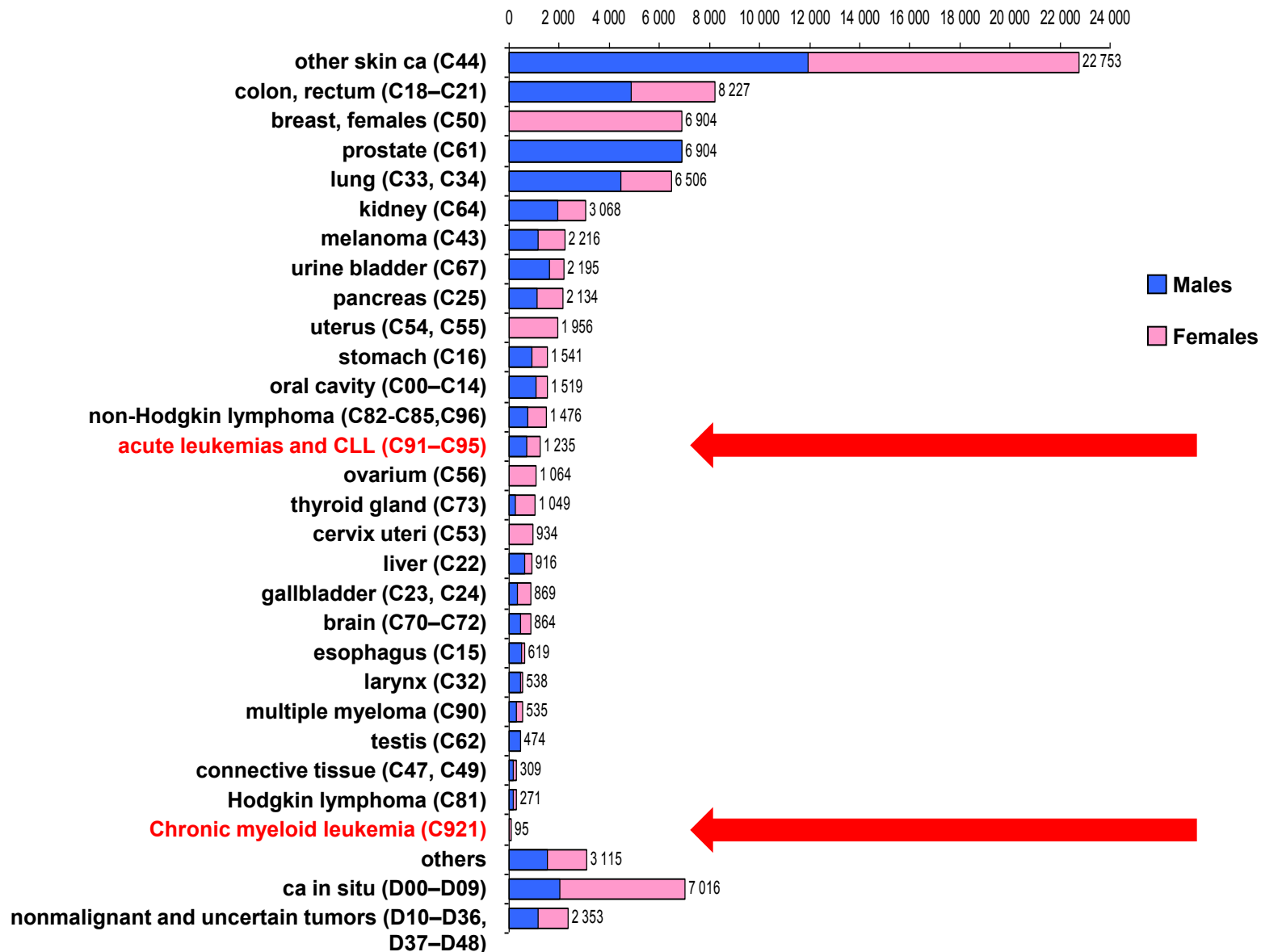
University Hospital Brno
and Masaryk University, School of Medicine

Outline

- Epidemiology
- Clinical signs
- Key subtypes of leukemias
- Model diseases
- Elementary principles of pathogenesis
- Implications of these facts for diagnostics and therapy
 - with time relationships of different discoveries
 - and original data from the literature
- Including case reports

Cancer incidence In Czechia, 2010-2014

Average number of yearly diagnosed cases



Source: National Cancer Registry, ÚZIS ČR

Archiv
für
pathologische Anatomie und Physiologie
und für
klinische Medicin.

Herausgegeben

von

R. Virchow und **B. Reinhardt.**

Erster Band.

Mit 4 Tafeln.

Berlin,
Druck und Verlag von G. Reimer.
1847.

563

heiten während ihres ganzen Verlaufes
größerer Theils desselben permanente, u
derungen in der Blutmischung in Anspru
war geradezu ein Denkfehler, ganze F
heits-Entitäten im naturhistorischen Sinne
ein non-ens zurückzuführen. Wenn die
bute auf Faserstoffmangel beruhten, so hät
stens sagen sollen, ob der Faserstoff, de
Krankheit machte, oder der, welcher übrig
ob etwa jener die Typhen machte und
Diese Art von confusum Denken, dieses Z
schlecht untersuchten Thatsachen und un
mufs einmal aufhören. Räumen wir auch
zusammengebrochenen Systeme weg, und
Platze auch noch nicht lange Strafsen vo
richten können, nun, so haben wir eine
freiere Aussicht. —



II. Weißes Blut (Leukämie).

gibt gewisse Wahrheiten, welche sich in der Wissen
nur sehr langsam und schrittweise Geltung verschaffen.
scheint es meinen Mittheilungen über weißes Blut (d. h.
eine Vermehrung der farblosen Blutkörperchen in dem Maafse,
dafs die rothe Farbe des Blutes dadurch in eine röthlich-
gelblich- oder grünlichweisse verwandelt wird) und dem Zu-
sammenhang desselben mit chronischen Milzanschwellungen zu
ergehen. Bei der ersten Veröffentlichung des von mir be-
obachteten Falls (Froberg's N. Notiz. 1845. No. 780.) hob ich
schon diesen Zusammenhang hervor und zeigte den Unter-
schied dieser Blutveränderung von der sogenannten pyämischen.
Trotzdem übergeht Bischoff (Müller's Archiv 1846. Jahres-
ber. p. 135.) in seinem Referat den ersteren ganz und bemerkt
nur, dafs eine chemische Untersuchung nicht angestellt sei
und dafs der Fall mit anderen, unter dieser Bezeichnung auf-
bewahrten Fällen nur die Aehnlichkeit des äußeren Ansehens

BLOOD

The Journal of Hematology

MARCH, 1960

VOL. XV, NO. 3

Leukemia in Hiroshima Atomic Bomb Survivors

By ROBERT HEYSSEL, A. BERTRAND BRILL, LOWELL A. WOODBURY,
EDWIN T. NISHIMURA, TARUNENDU GHOSE, TAKASHI HOSHINO
AND MITSURU YAMASAKI

Table 5.—Incidence of Leukemia by Type

Type of Leukemia	Japanese Exposed Survivors *			
	< 2,000 m		2,000-10,000 m	
	No.	Incidence	No.	Incidence
Acute Granulocytic	12	80	7	20
Chronic Granulocytic	15	100	1	3
Acute Lymphatic	3	20	0	-
Acute - Type Unspec.	2	13	1	3
Chronic Lymphatic	0	-	1	3

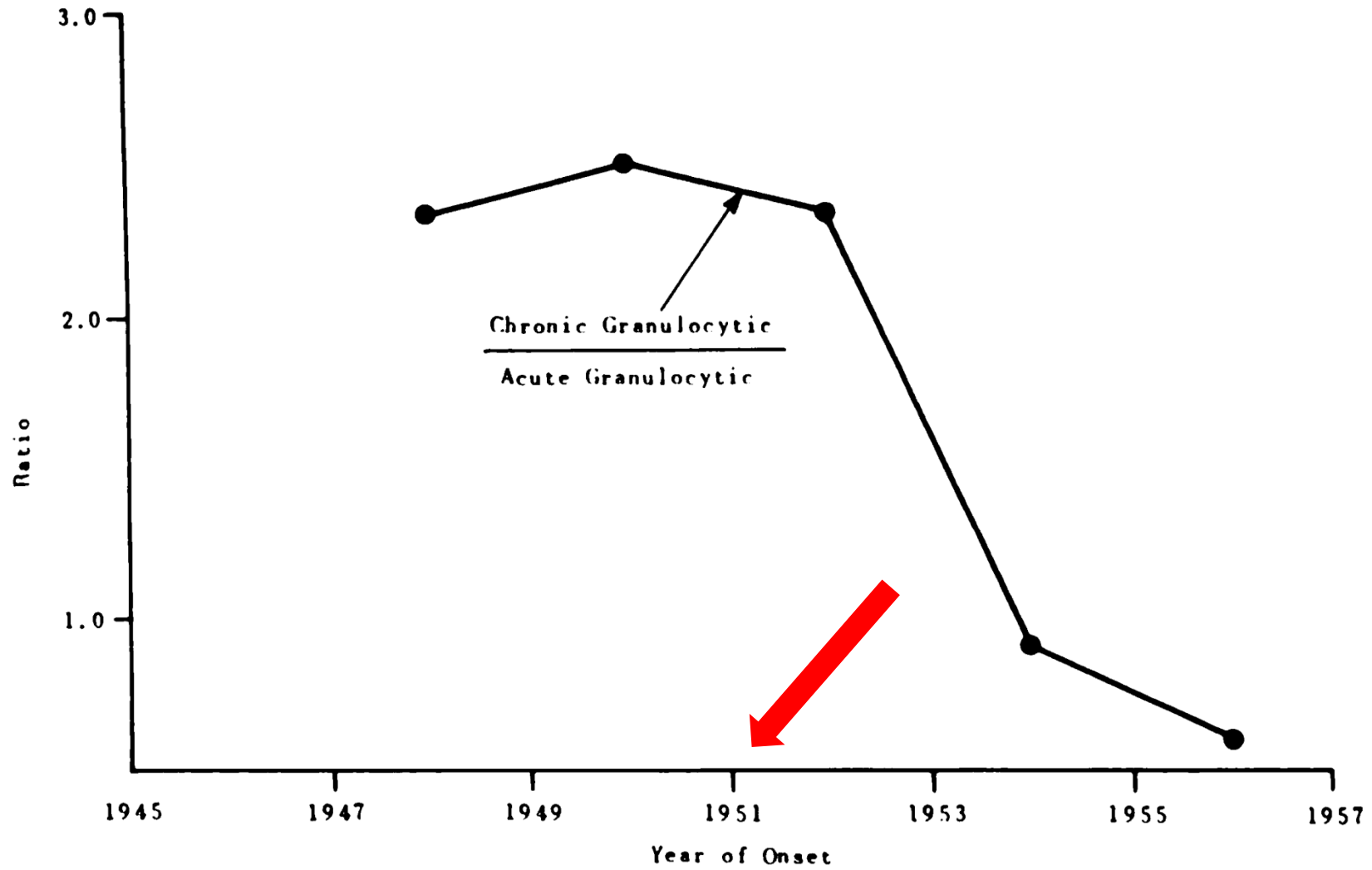


Fig. 6.—Annual changes in type distribution—exposed leukemia patients.

WHO classification, 2022 upgrade

- More than 50 types and subtypes
- Leukemias – disturbances in the regulation of growth and differentiation of WBC, white blood cells
- Key types:
 - **CML**, chronic myeloid leukemia
 - **AML**, acute myeloid leukemia
 - **APL**, acute promyelocytic leukemia
 - **ALL**, acute lymphoblastic leukemia
 - **CLL**, chronic lymphocytic leukemia
 - **HCL**, hairy cell leukemia

Key clinical signs

- **Leukocytes**

- leukocytosis, hyperviscosity
- leukopenia, neutropenia
- diminished cellular immunity, diminished humoral immunity (CLL)
- **infections**

- **Thrombocytes**

- thrombocytopenia
- **bleeding**
- thrombocytosis (CML)

- **Erythrocytes**

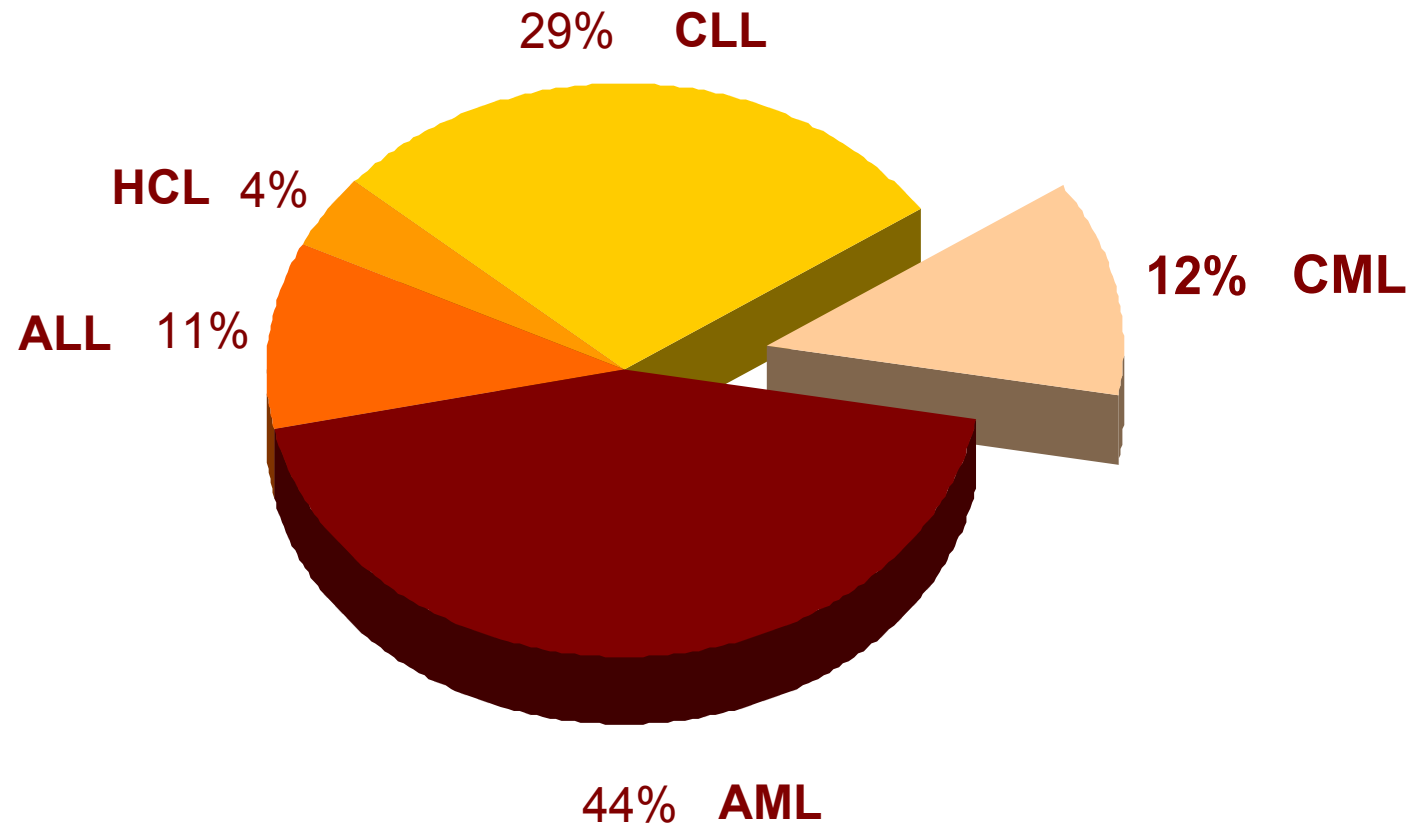
- **anemia**

- **Organ infiltration**

- **bone marrow**, spleen, liver, lymph nodes, brain, testis, skin, ...
- myelosarcoma

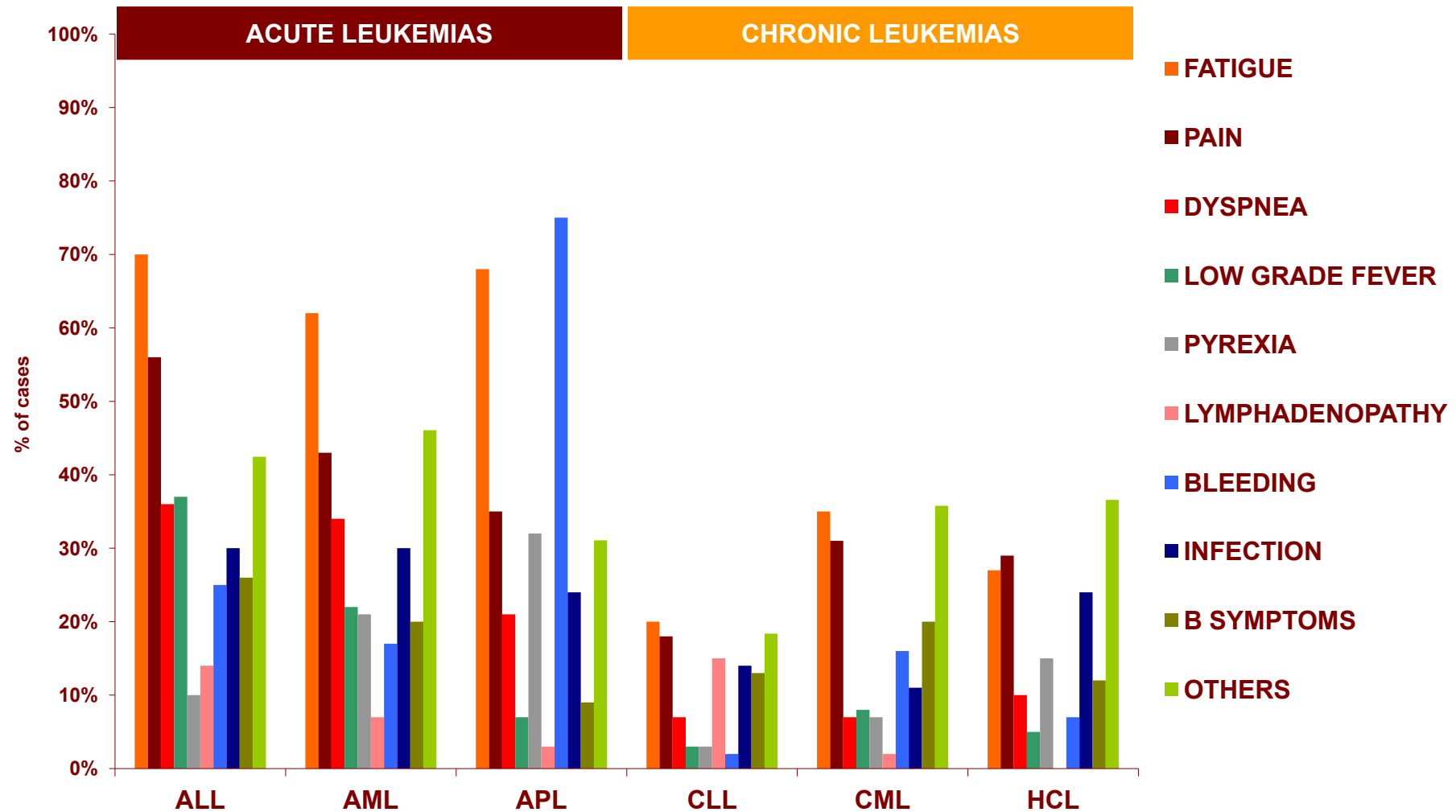
1000 leukemia cases

Number of analyzed cases (2004-2009) – 1007 patients



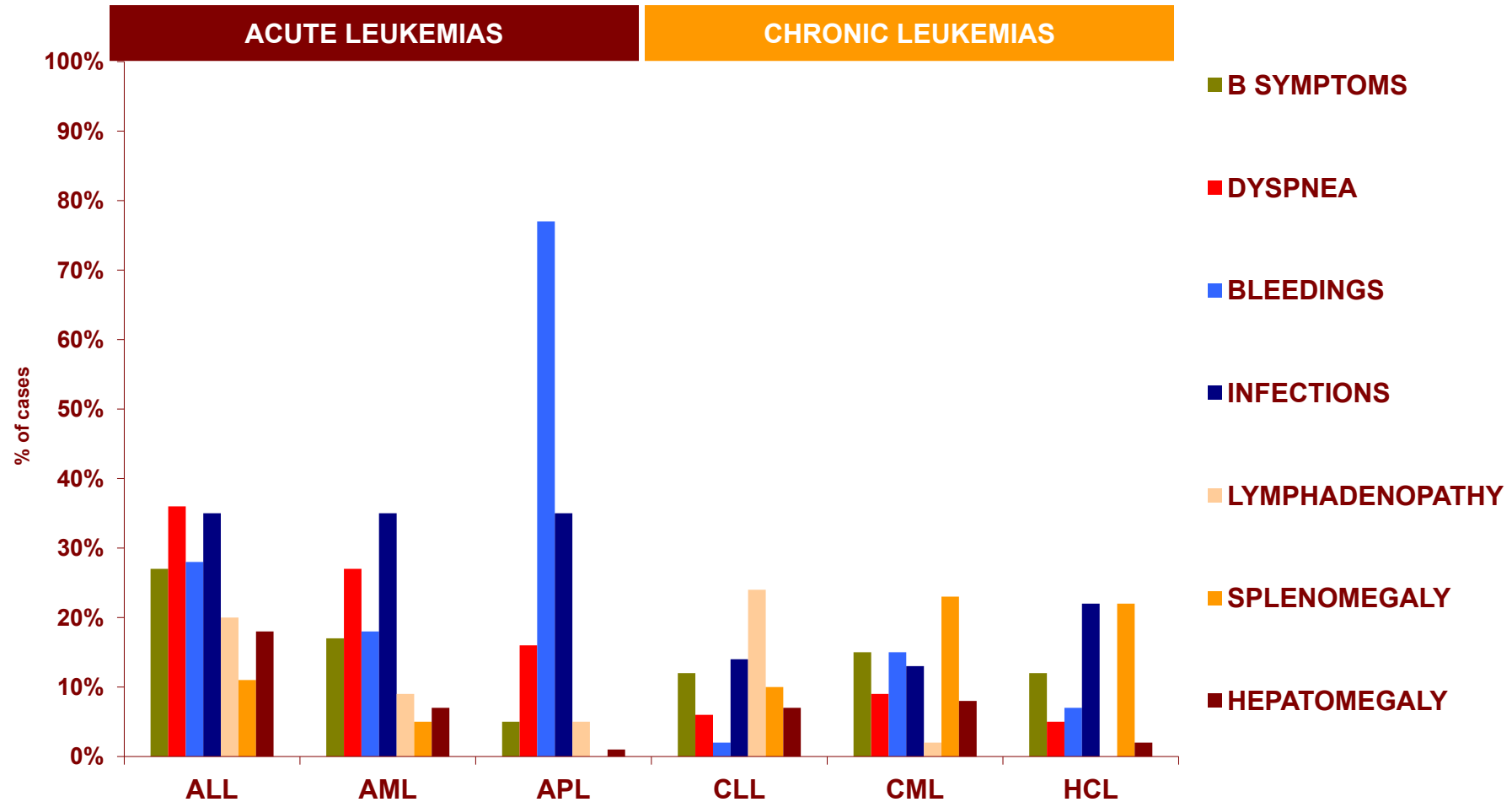
Clinical symptoms

Subjective complaints of patients according to the history at diagnosis



Objective findings

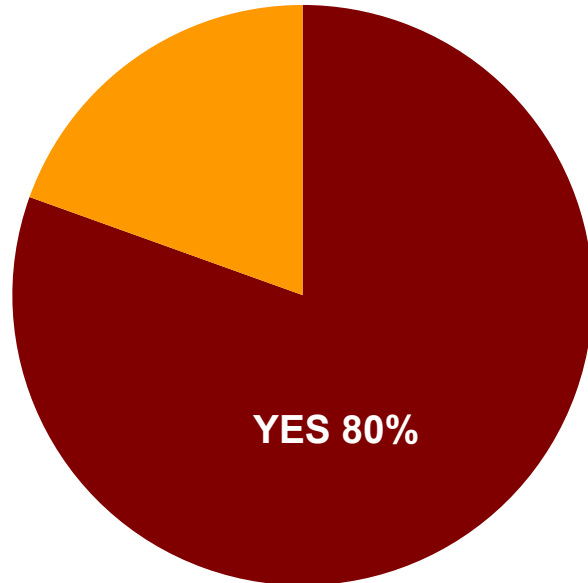
Objective findings by the first visited physician



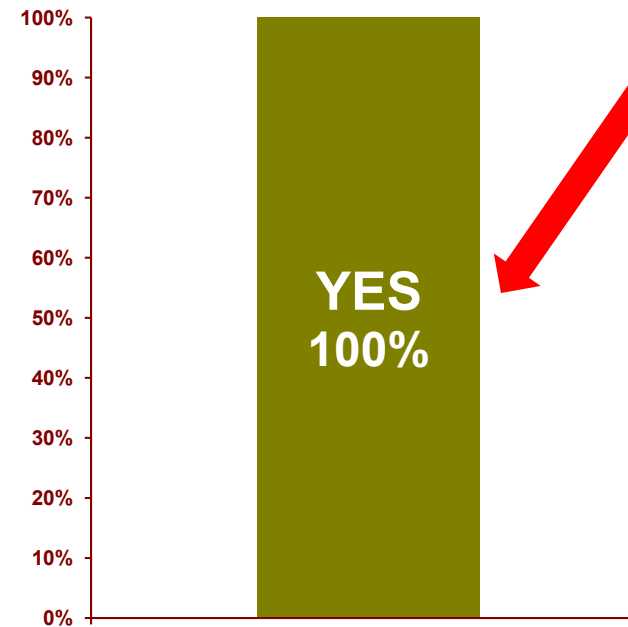
Blood count

Lab exam by the first visited physician

PERFORMED?



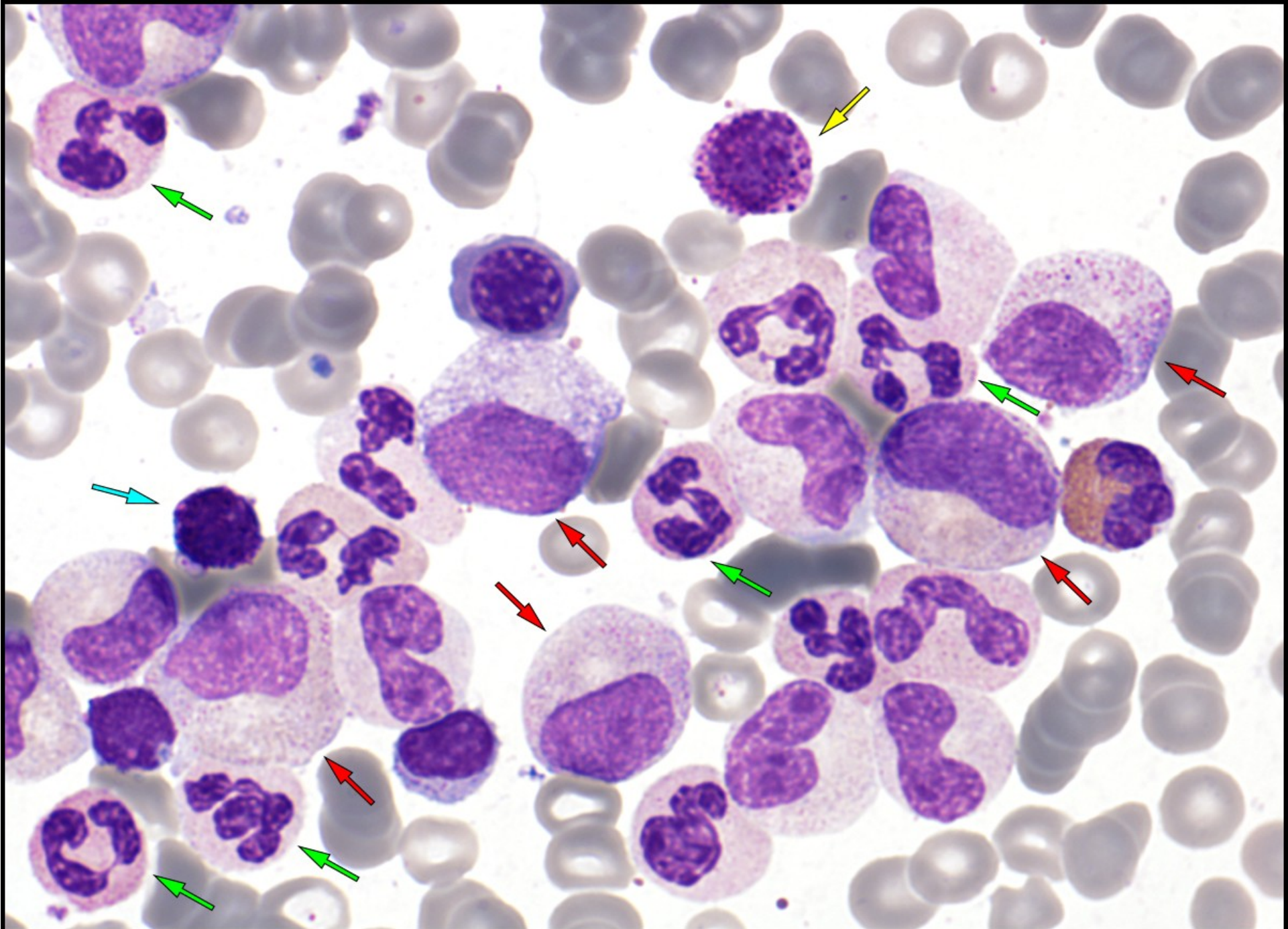
ABNORMALITY?



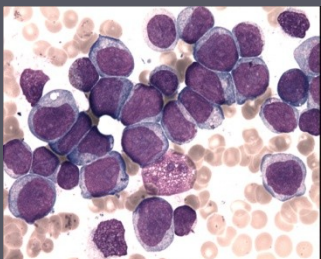
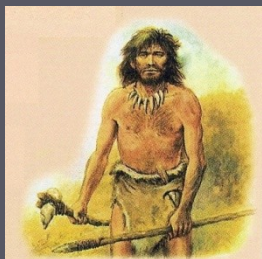
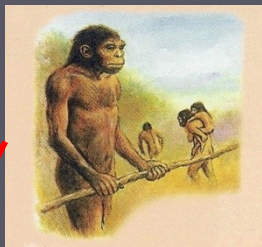
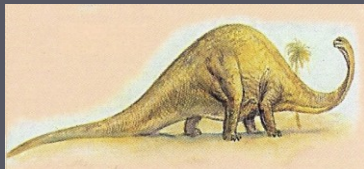
CML

Chronic Myeloid Leukemia

model disease of a **single chromosomal abnormality**



time



„nothing“

a lot of

leukemia
(1850)

chemotherapy
(1950)
Ph¹ (1960)

BMT IFN
BCR/ABL PCR

imatinib, dasatinib,
nilotinib
others



A Minute Chromosome in Human Chronic Granulocytic Leukemia

In seven cases thus far investigated (five males, two females), a minute chromosome has been observed replacing one of the four smallest autosomes in the chromosome complement of cells of chronic granulocytic leukemia cultured from peripheral blood. No abnormality was observed in the cells of four cases of acute granulocytic leukemia in adults or of six cases of acute leukemia in children. There have been several recent reports of chromosome abnormalities in a number of cases of human leukemia [including two of the seven cases reported here: Nowell and Hungerford, *J. Natl. Cancer Inst.* 25, 85 (1960)], but no series has appeared in which there was a consistent change typical of a particular type of leukemia.

Cells of the five new cases were obtained from peripheral blood (and bone marrow in one instance), grown in culture for 24-72 hours, and processed for cytological examination by a recently developed air-drying technique (Moorhead, *et al.*, *Exptl. Cell Research*, in press). The patients varied from asymptomatic untreated cases to extensively treated

cases of several years duration in terminal myeloblastic crisis. All seven individuals showed a similar minute chromosome, and none showed any other frequent or regular chromosome change. In most of the cases, cells with normal chromosomes were also observed. Thus, the minute is not a part of the normal chromosome constitution of such individuals.

The findings suggest a causal relationship between the chromosome abnormality observed and chronic granulocytic leukemia.

PETER C. NOWELL

*School of Medicine,
University of Pennsylvania*

DAVID A. HUNGERFORD

Institute for Cancer Research

1960

*A minute chromosome in
human granulocytic leukemia.
Science 132, 1960, 1497.*

P.C. Nowell, D.A. Hungerford,
University of Pennsylvania in
Philadelphia

...the findings **suggest a causal relationship** between the chromosome abnormality observed and chronic granulocytic leukemia...



1973: translocation of chromosomal material

Rowley JD: A new consistent chromosomal abnormality in chronic myelogenous leukemia identified by quinacrine fluorescence and Giemsa staining. Nature, 243, 290-293, 1973

...suggesting that there may be a hitherto **undetected translocation** between the long arm of **22** and the long arm of **9**, producing the 9q+ chromosome...



BCR (22q11)

ABL1 (9q34)

ABL1 (9q34)

Ph chromosome (der(22q) with BCR-ABL1 fusion)

BCR (22q11)

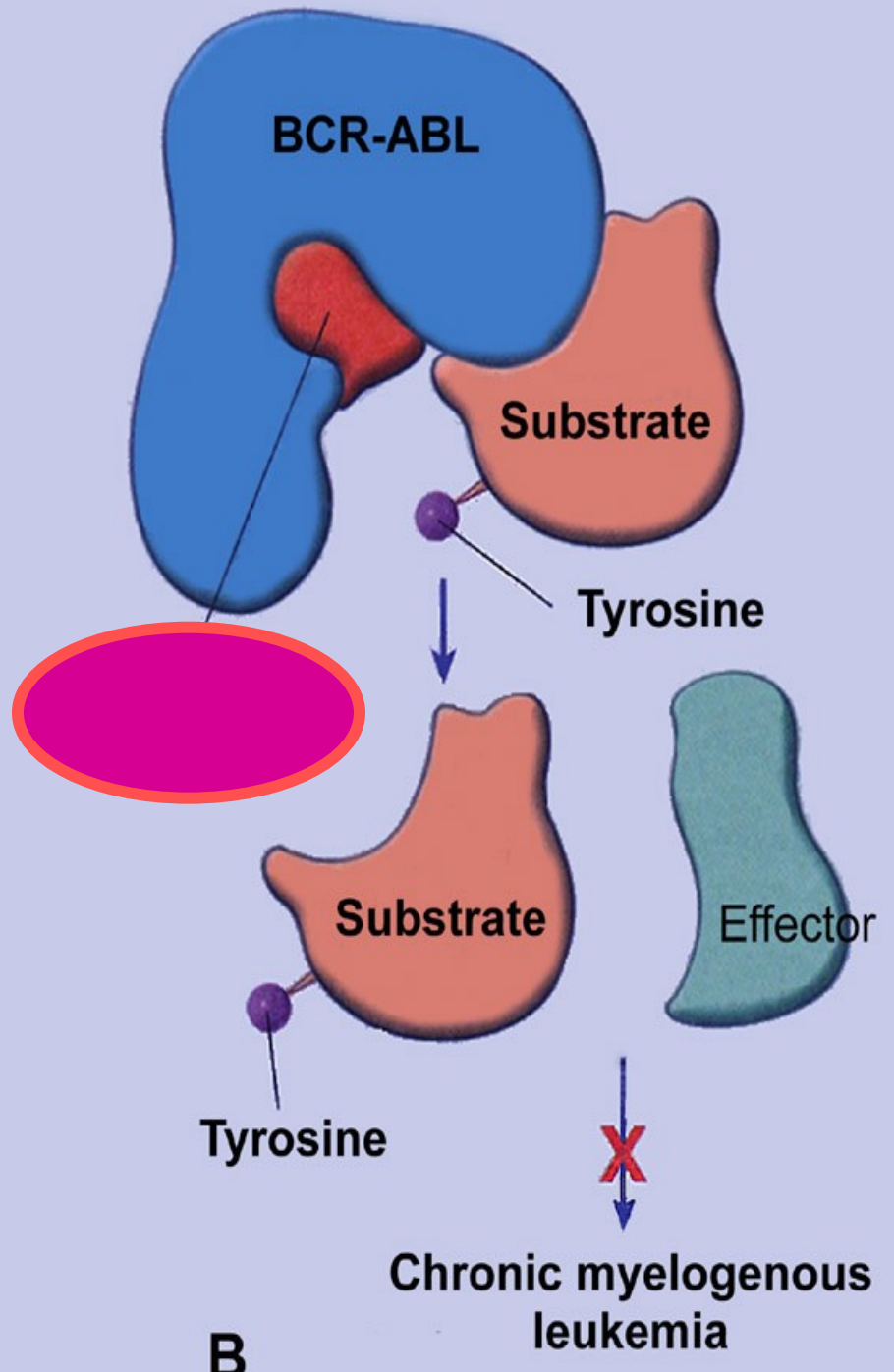
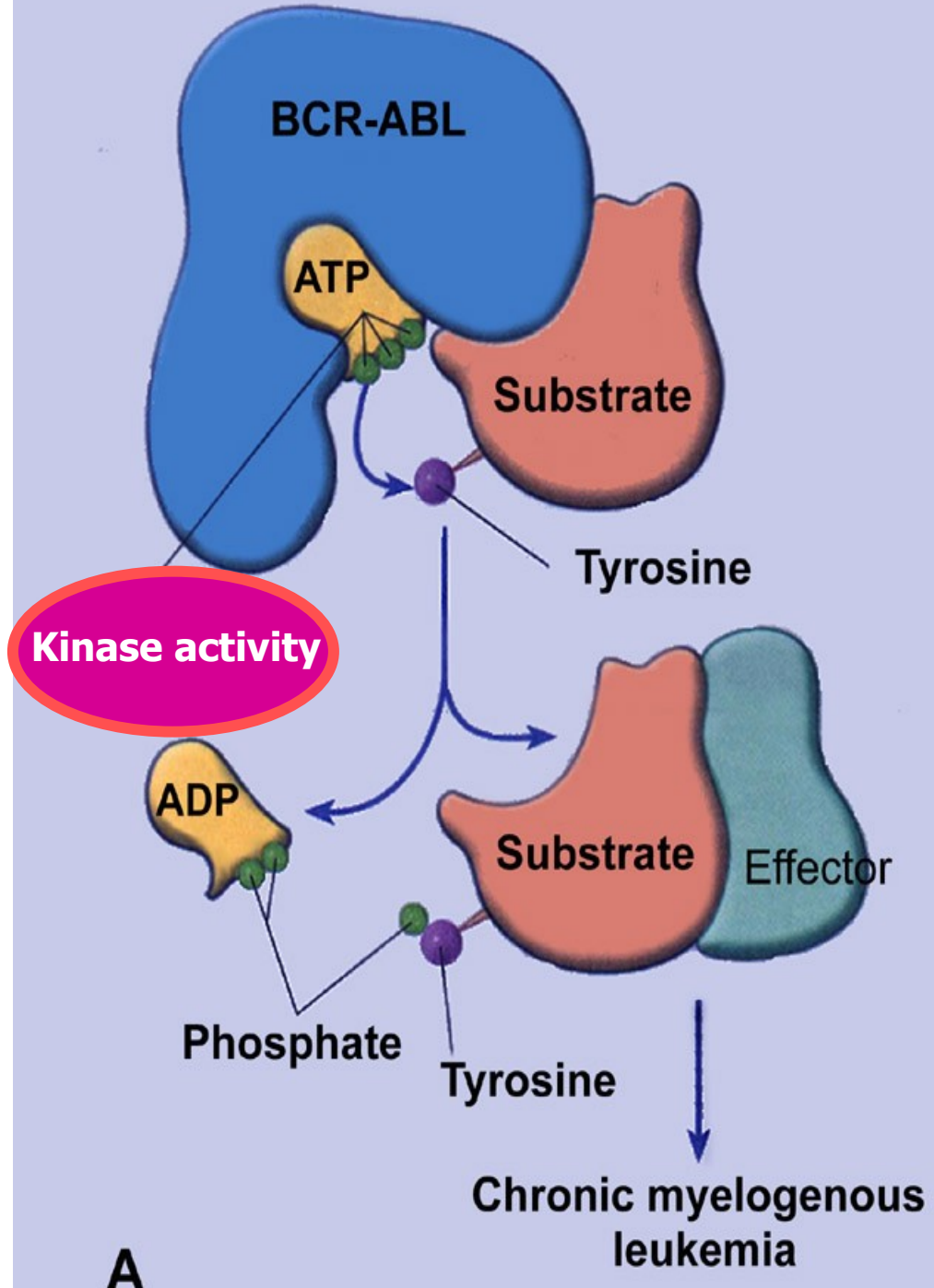
der(9)

1982: abl localized on chromosome 9

- *Heisterkamp N et al.: Chromosomal localization of human cellular homologues of two viral oncogenes. Nature 299, 1982, 747-749.*
 - ...we now show that the human equivalents of c-fes and **c-abl are localized on human chromosomes 15 and 9**, respectively. It is of interest that both of these **chromosomes are involved in specific rearrangements found in certain forms of human cancer...**
- *ABL gene = the human homologue of the v-abl oncogene of the Abelson murine leukemia virus. **Abelson HT**, Rabstein LS: Proc Am Assoc Cancer Res 10: 1, **1969***

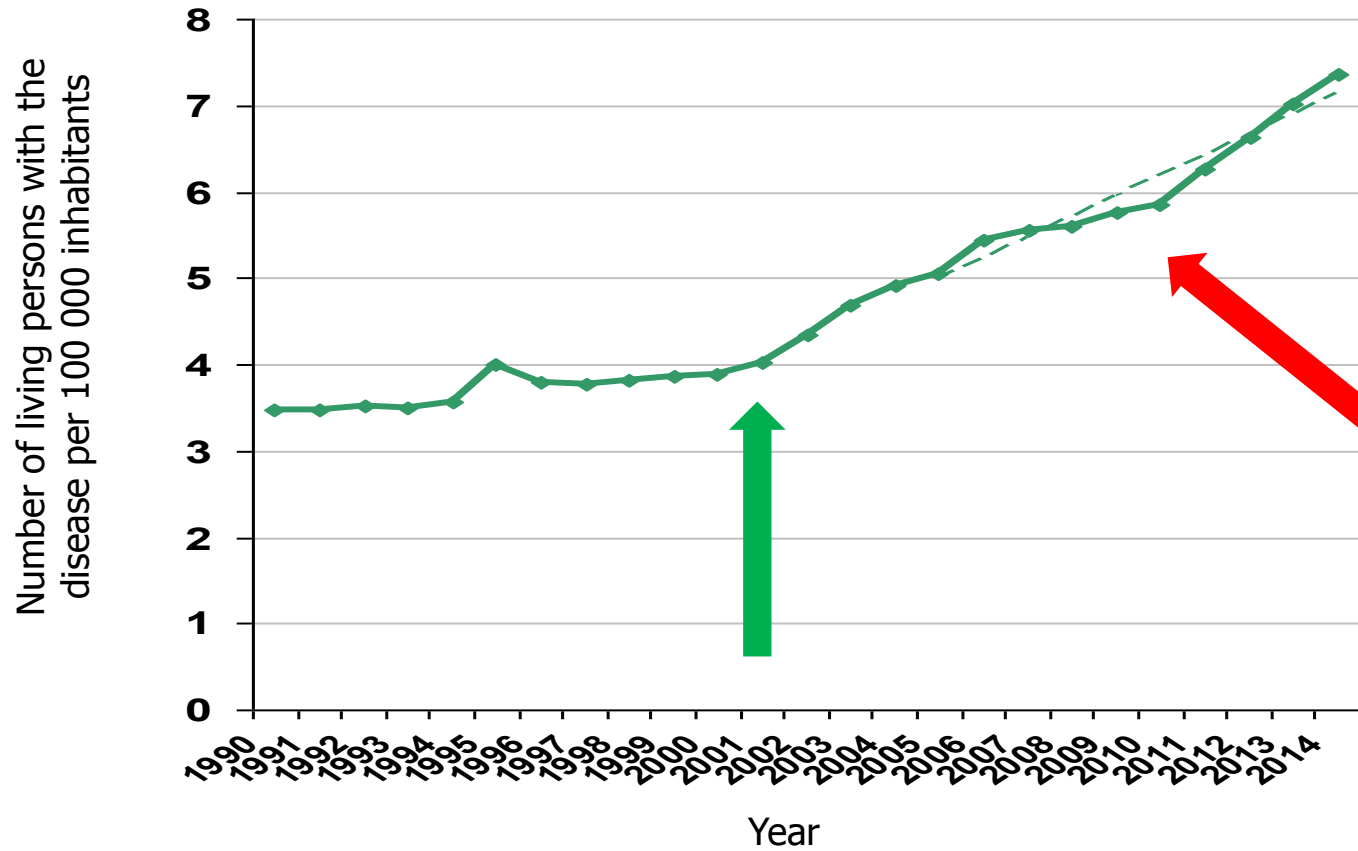
1985: fused protein BCR::ABL

- *Shtivelman E et al.: Fused transcript of abl and bcr genes in chronic myelogenous leukaemia. Nature 315, 1985, 550-554.*
- ...characterization of an 8-kilobase RNA specific to chronic myelogenous leukaemia shows it to be a FUSED transcript of the two genes. The FUSED protein that would be produced is probably involved in the malignant process...



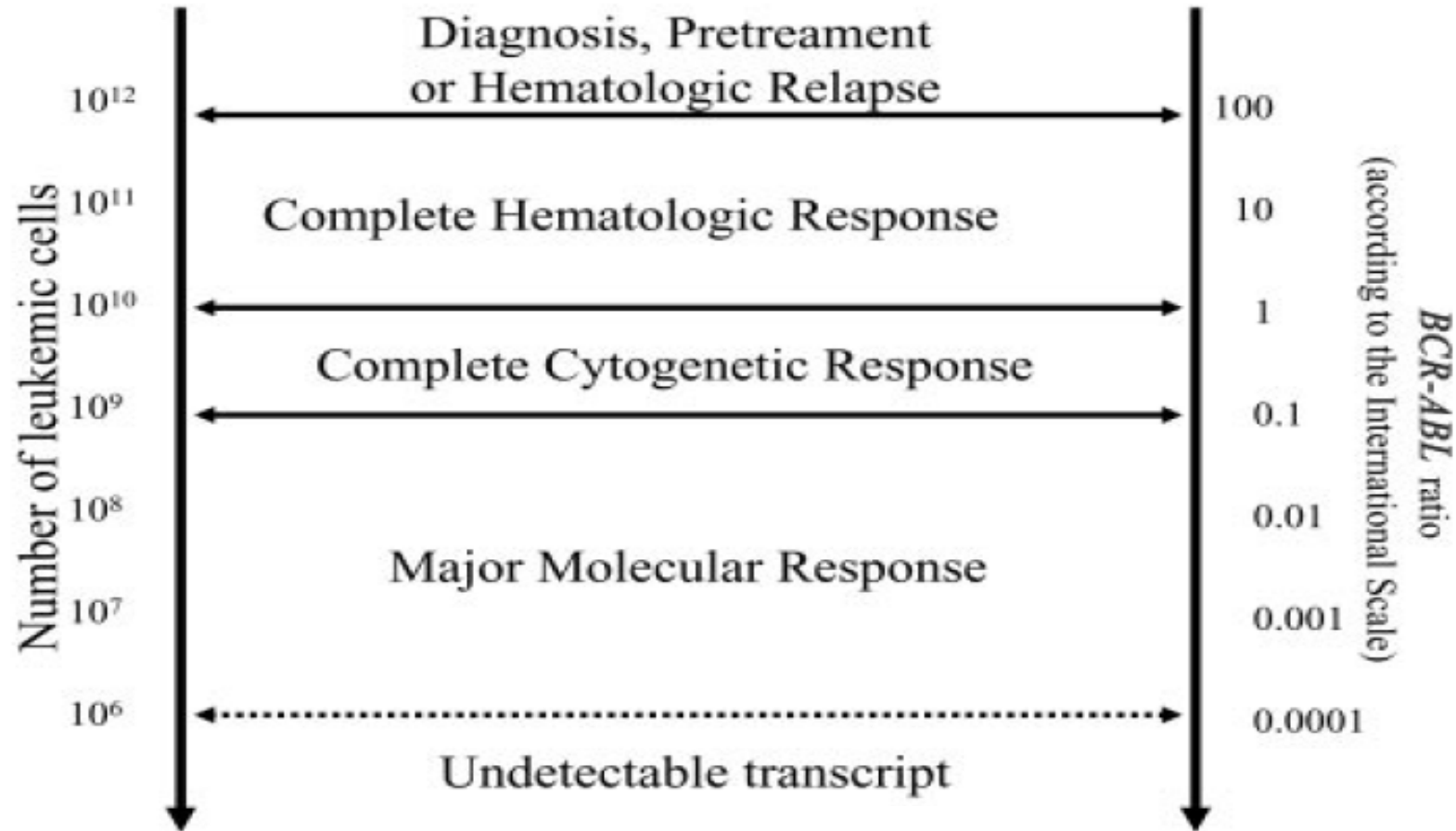
Epidemiology of CML in Czechia

Prevalence

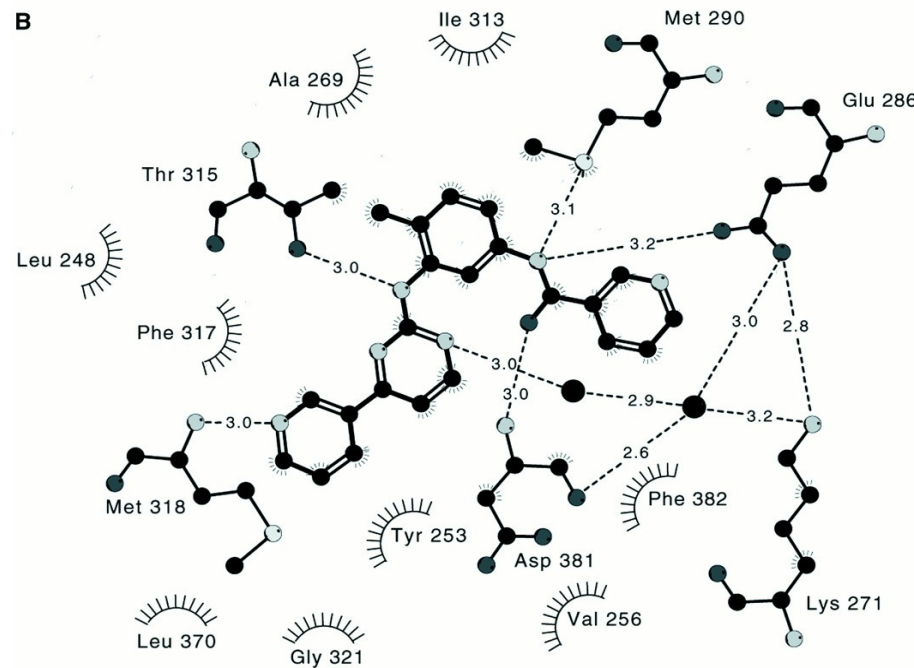
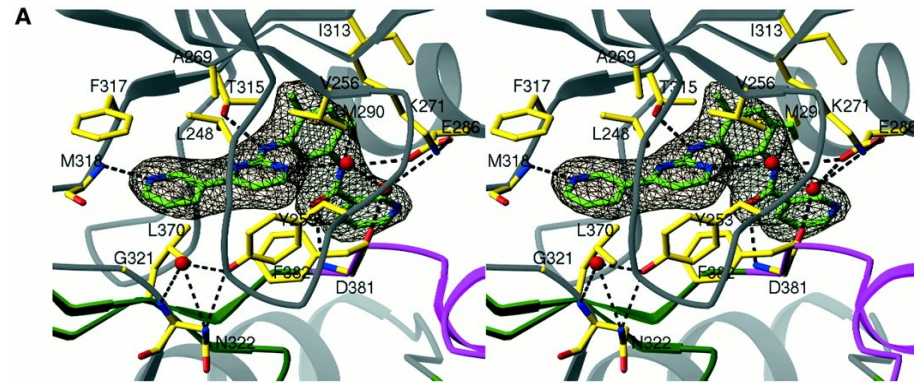


---- trend of 2005-2014

Relationship between the number of malignant cells, therapy response, and *BCR-ABL*



Crystal structure solved, but resistance described



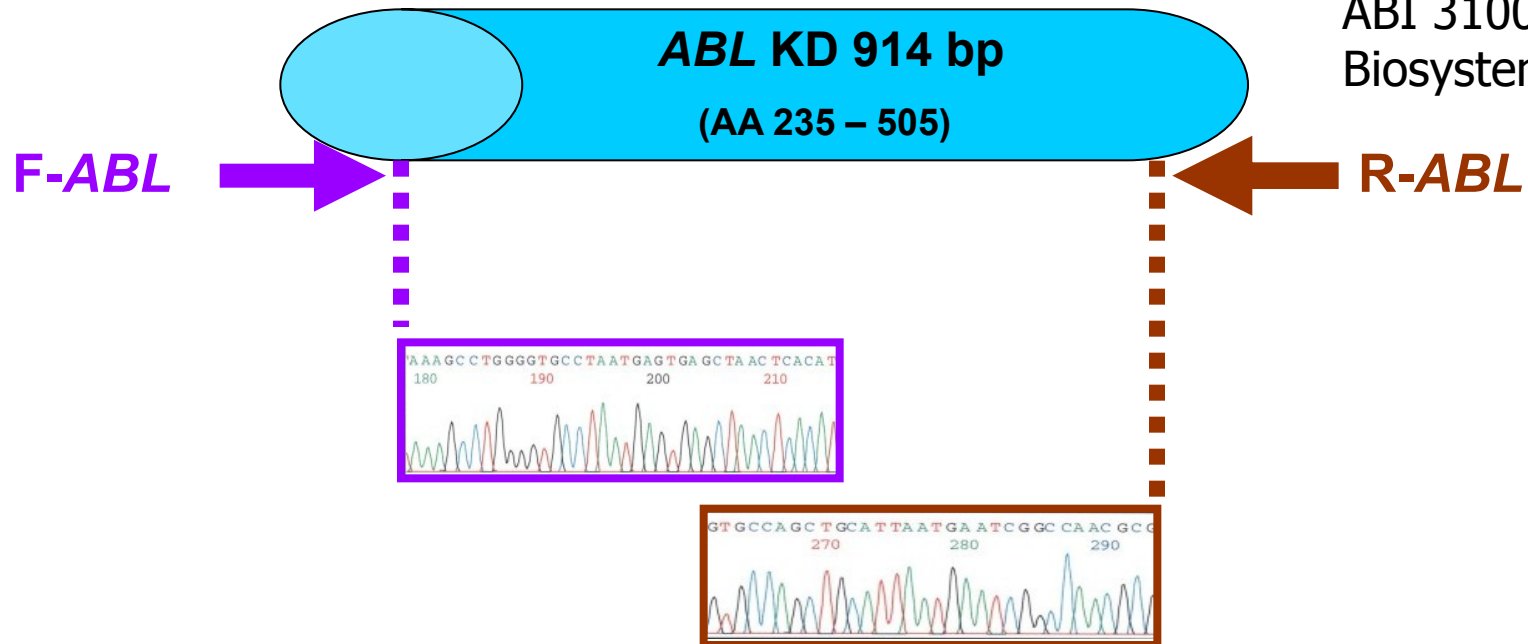
- Schindler T et al.: **Structural mechanism** for STI-571 inhibition of Abelson tyrosine kinase. Science 289, 2000, 1938-1942.
- Gorre ME et al.: **Clinical resistance** to STI-571 cancer therapy caused by BCR-ABL **GENE MUTATION** or amplification. Science 293, 2001, 876-880.

Direct sequencing

- BigDye v3.1 Termination kit (Applied Biosystems)



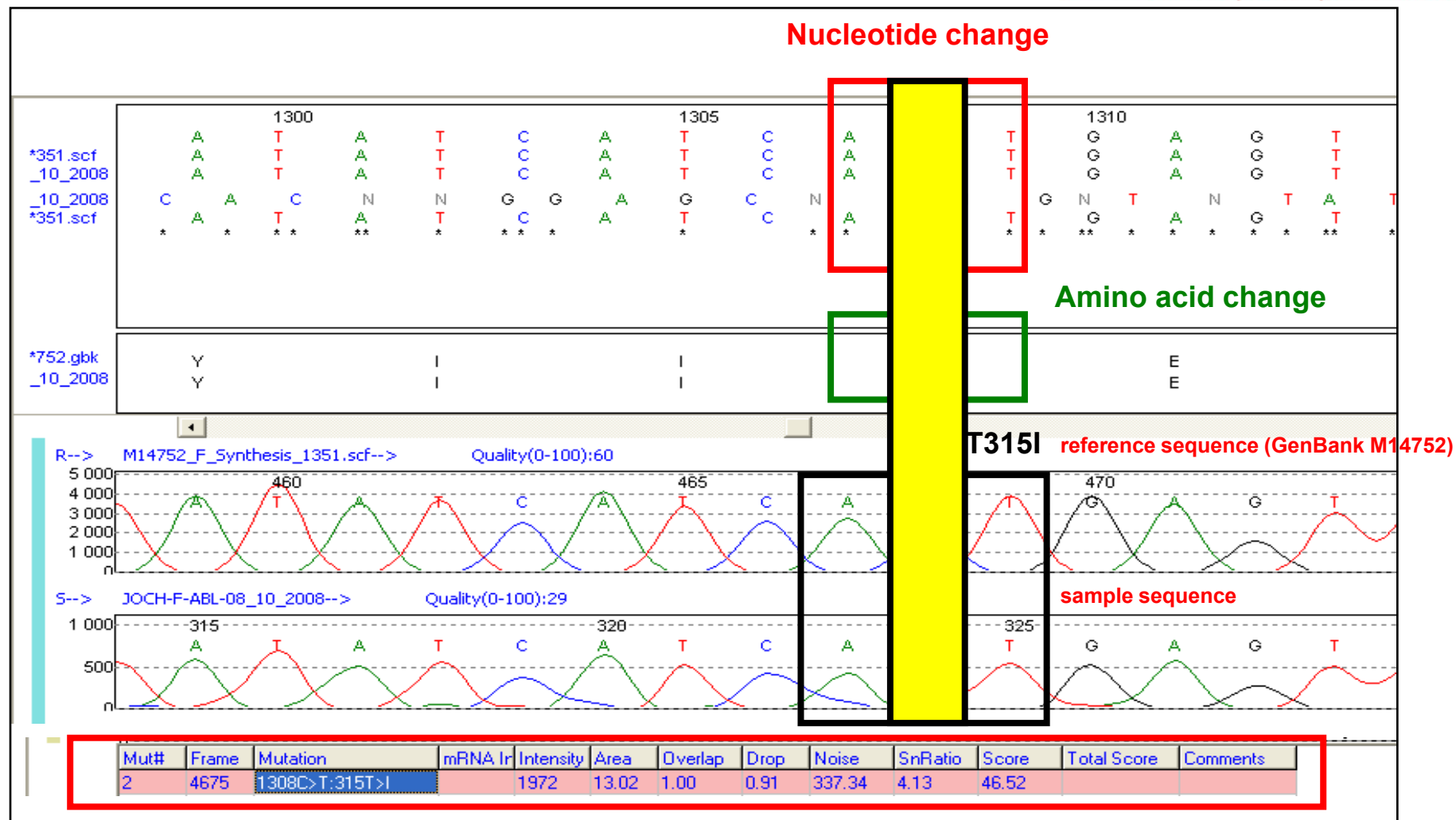
ABI 3100 (Applied Biosystems)



Mutation detection - MutationSurveyor® software (Softgenetics)



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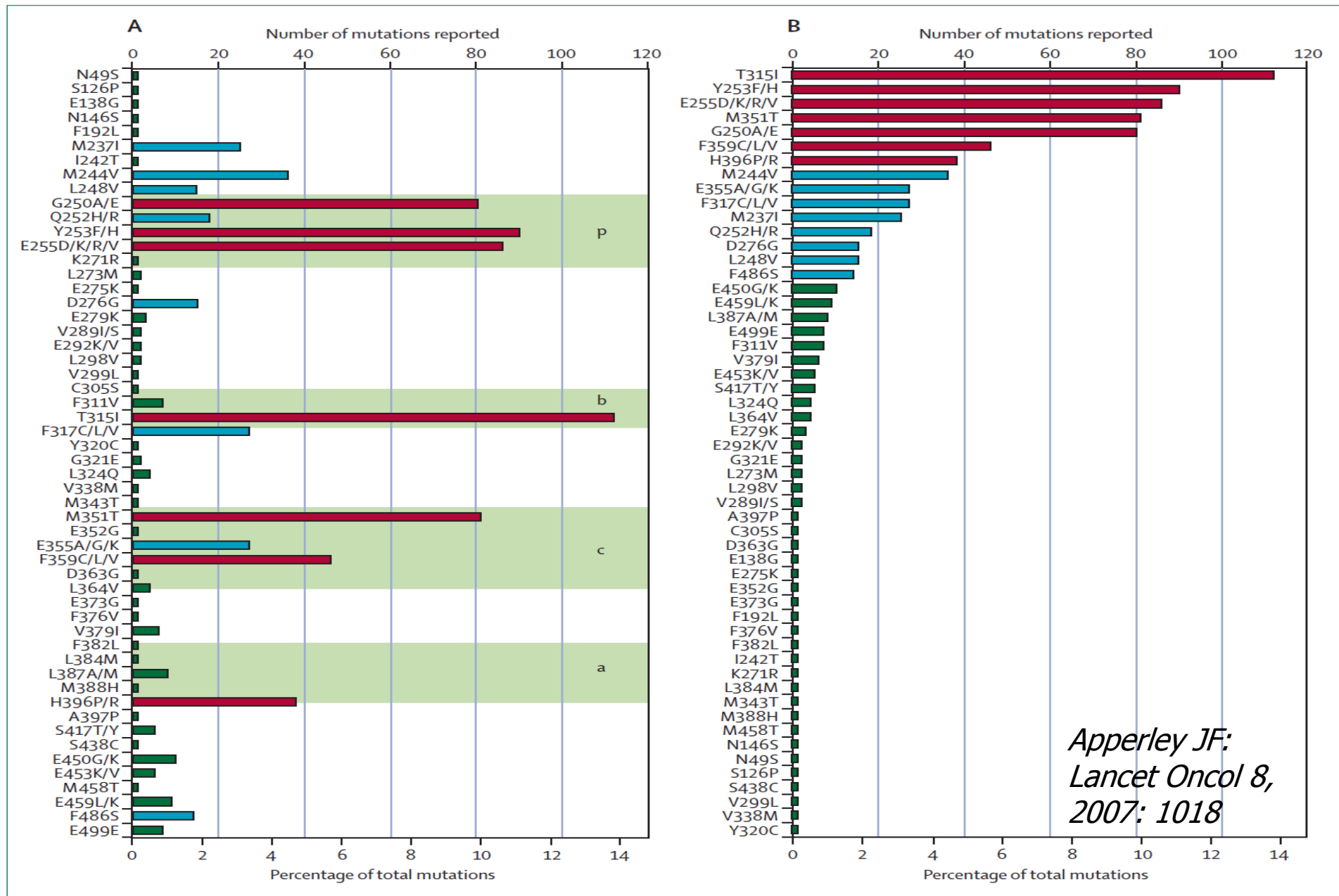


Figure 3: Incidence of mutations in clinical practice

(A) Incidence of mutations within the kinase domain by absolute number reported and by percentage of total. The seven most frequent mutations are depicted in red and the following eight most common mutations in blue. Specific regions of the kinase domain are indicated as P-loop or ATP binding site (p), imatinib binding site (b), catalytic domain (c) and activation loop (a). (B) Incidence of mutations in order of frequency; the seven most frequent mutations are depicted in red and the following eight most common mutations in blue.

CML Case

- **older** man, age 60
- history: hypertension, bronchial asthma
- drugs: sartan, CaC blocker
- occupation: office worker
- abusus: no alcohol, smokes 5 c./day
- current illnesses:
 - no symptoms
 - maybe a bit tired
 - sent by his **GP** – leukocytosis 26 found at a **routine check-up**

CML Case

- CBC
 - WBC **26** (4-10)
 - Hb 143 (135-176)
 - plt 207 (150-350)
- microscopic WBC differential count
 - neutrophils 53% (50-70)
 - lymphocytes 23% (20-40)
 - eosinophils 2% (0-5)
 - basophils **6%** (0-1)
 - metamyelocytes **5%** (0-0)
 - myelocytes **6%** (0-0)
 - blasts 0% (0-0)
- immature granulocytes = **myeloproliferative disorder** suspected

CML Case

- bone marrow
 - very increased cellularity
 - increased **granulocyte lineage**
 - blasts 1% (0.1-3.5)
 - promyelocytes 2% (0.5-5)
 - myelocytes **28%** (5-23)
 - metamyelocytes 6% (10-30)
 - bands **15%** (10-30)
 - segments **27%** (7-25)
 - = **myeloproliferative disorder** probable
- mutations: **BCR::ABL** found by PCR
- cytogenetics: 46,XY,t(9;22) = **Philadelphia chromosome**
- Dg.: **chronic myeloid leukemia** in chronic phase

CML Case

- CML is not an emergency
 - except hyperleukocytosis (e.g. priapism)
- standard treatment
 - **tyrosine kinase inhibitors (TKIs)**
 - 1st: **imatinib**
 - 2nd: dasatinib, nilotinib, bosutinib
 - 3rd: ponatinib
 - **one pill every day**, but forever
- patient alive in CR

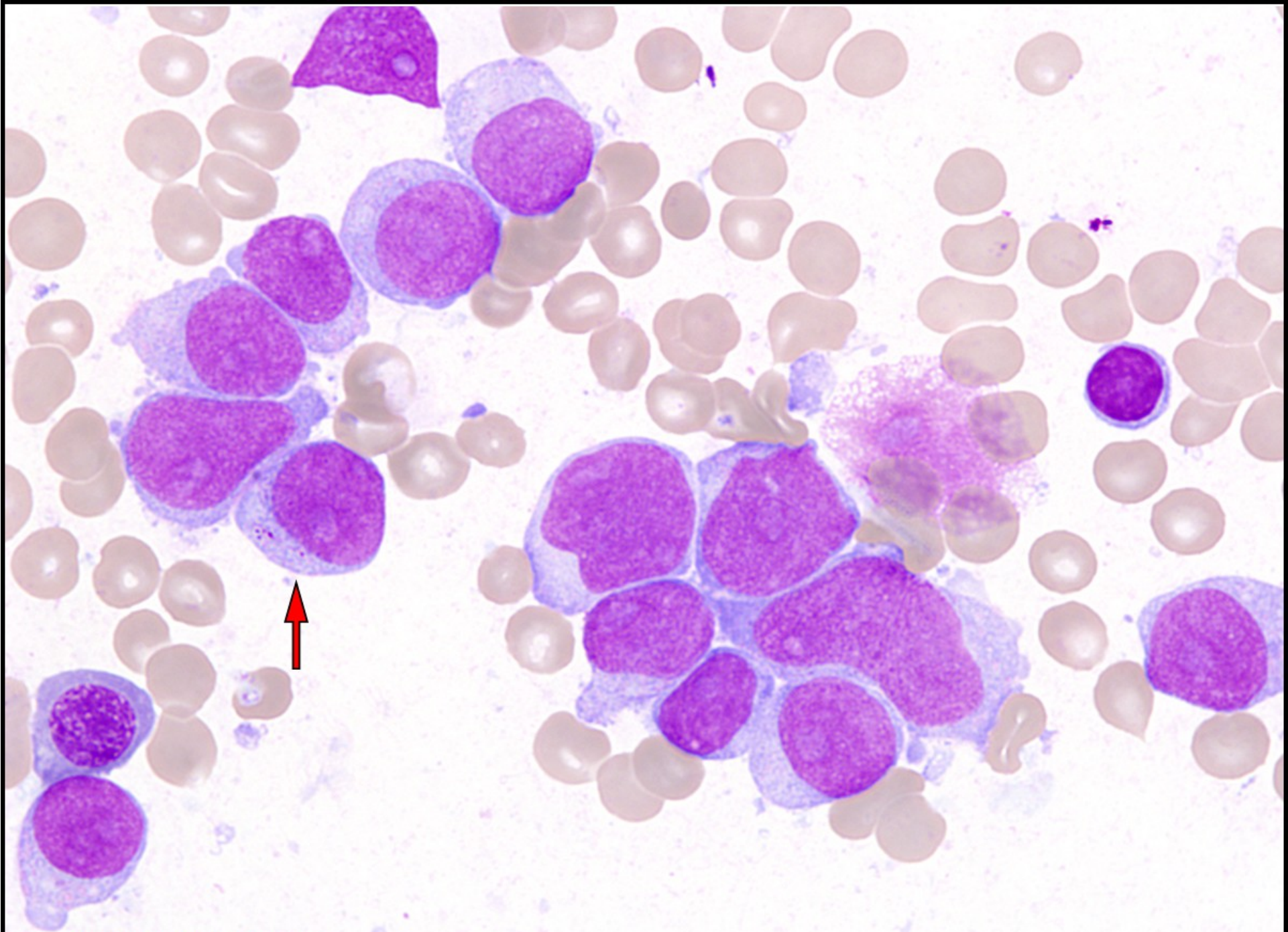
CML - Take home messages

- **chronic** disease
- usually found **incidentally**
- **Ph chromosome => BCR::ABL fusion gene**
- **TKI** = one pill a day
- **survival better than 95 %**
 - comparable to normal population

AML

Acute Myeloid Leukemia

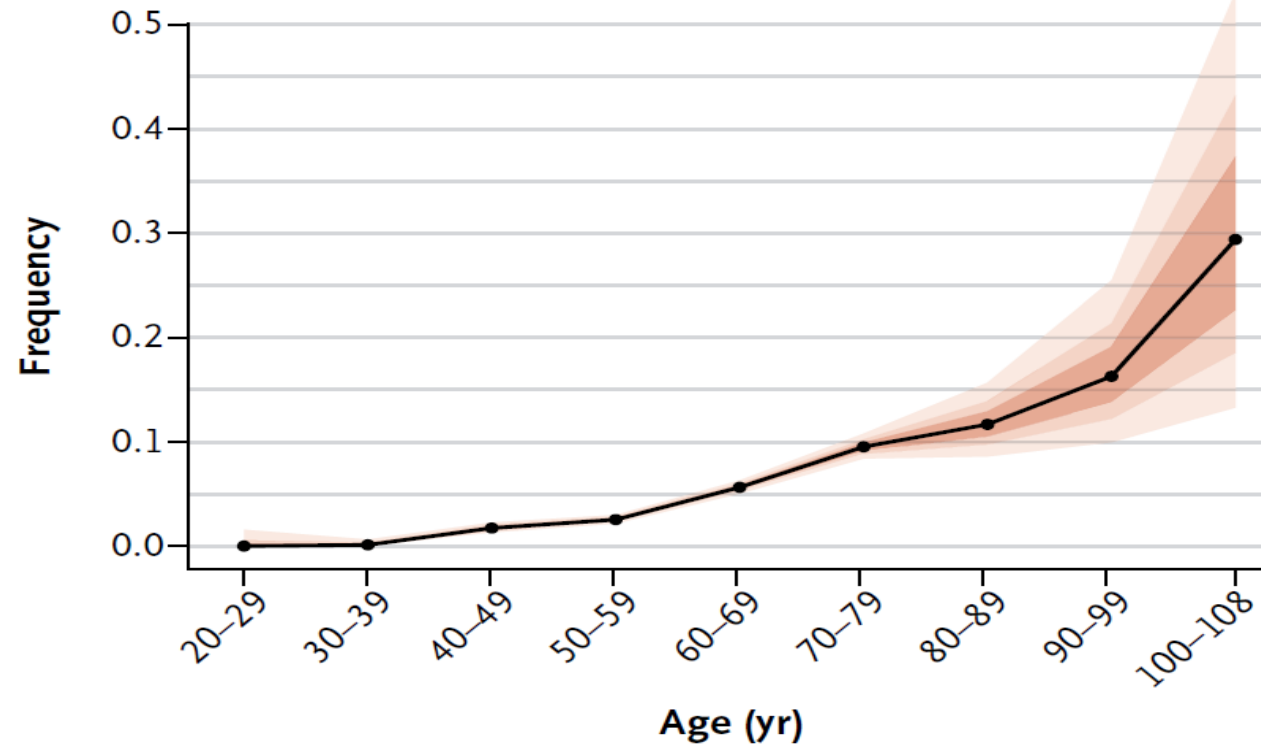
model disease of **heterogeneous** abnormalities
and **clonal evolution**



AML: outline

- **Myeloid pattern** of the malignant cells
- Variable maturation grade
- Amazing **genetic heterogeneity** significantly influencing the prognosis
- **Prognostic stratification** used in clinical practice for selecting the best therapeutic strategy
- New **molecular pathogenesis** findings lead to the development of new, targeted therapies very recently

Clonal hematopoiesis

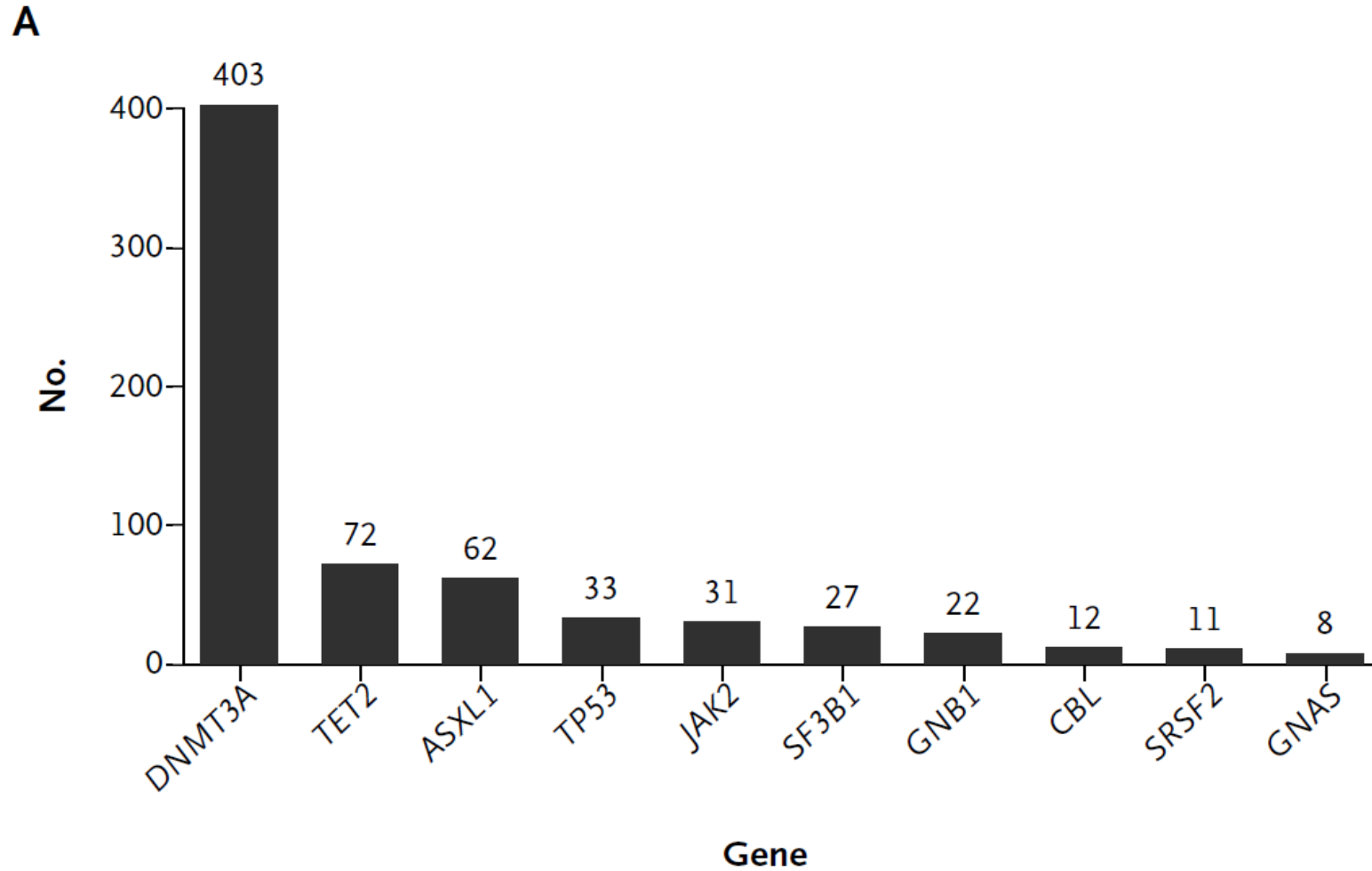


No. with Mutation	0	1	50	138	282	219	37	14	5
Total	240	855	2894	5441	5002	2300	317	86	17

Figure 1. Prevalence of Somatic Mutations, According to Age.

Colored bands, in increasingly lighter shades, represent the 50th, 75th, and 95th percentiles.

Clonal hematopoiesis



DNMT3A

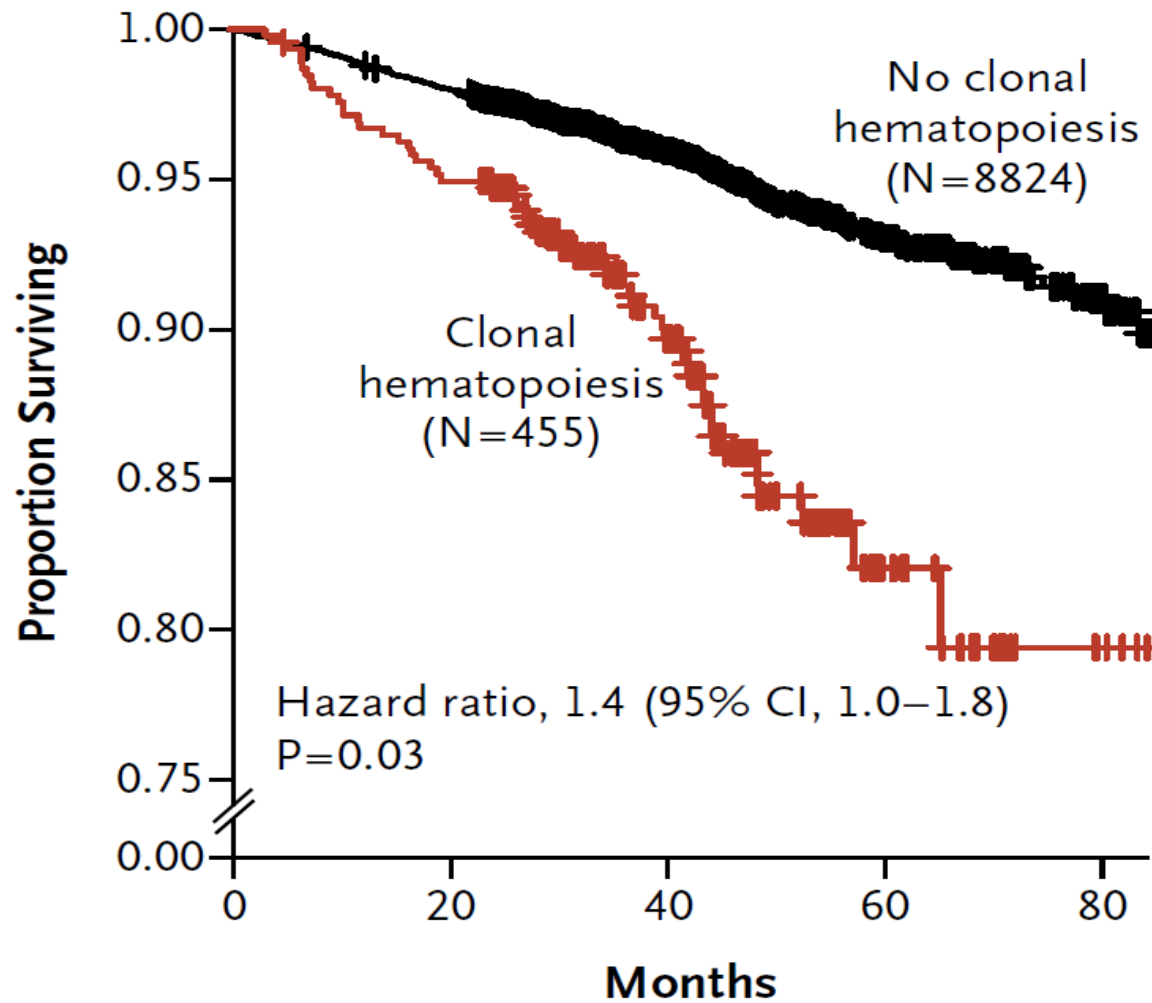
- DNA (cytosine-5)-methyltransferase 3A is an enzyme that catalyzes the transfer of methyl groups to specific CpG structures in DNA, a process called **DNA methylation**. The enzyme is encoded in humans by the DNMT3A gene.
- It is responsible for de novo DNA methylation. DNMT3A forms part of the family of DNA methyltransferase enzymes.
- While de novo DNA methylation modifies the information passed on by the parent to the progeny, it enables **key epigenetic modifications essential for processes such as cellular differentiation and embryonic development, transcriptional regulation, heterochromatin formation, X-inactivation, imprinting and genome stability**.

TET2

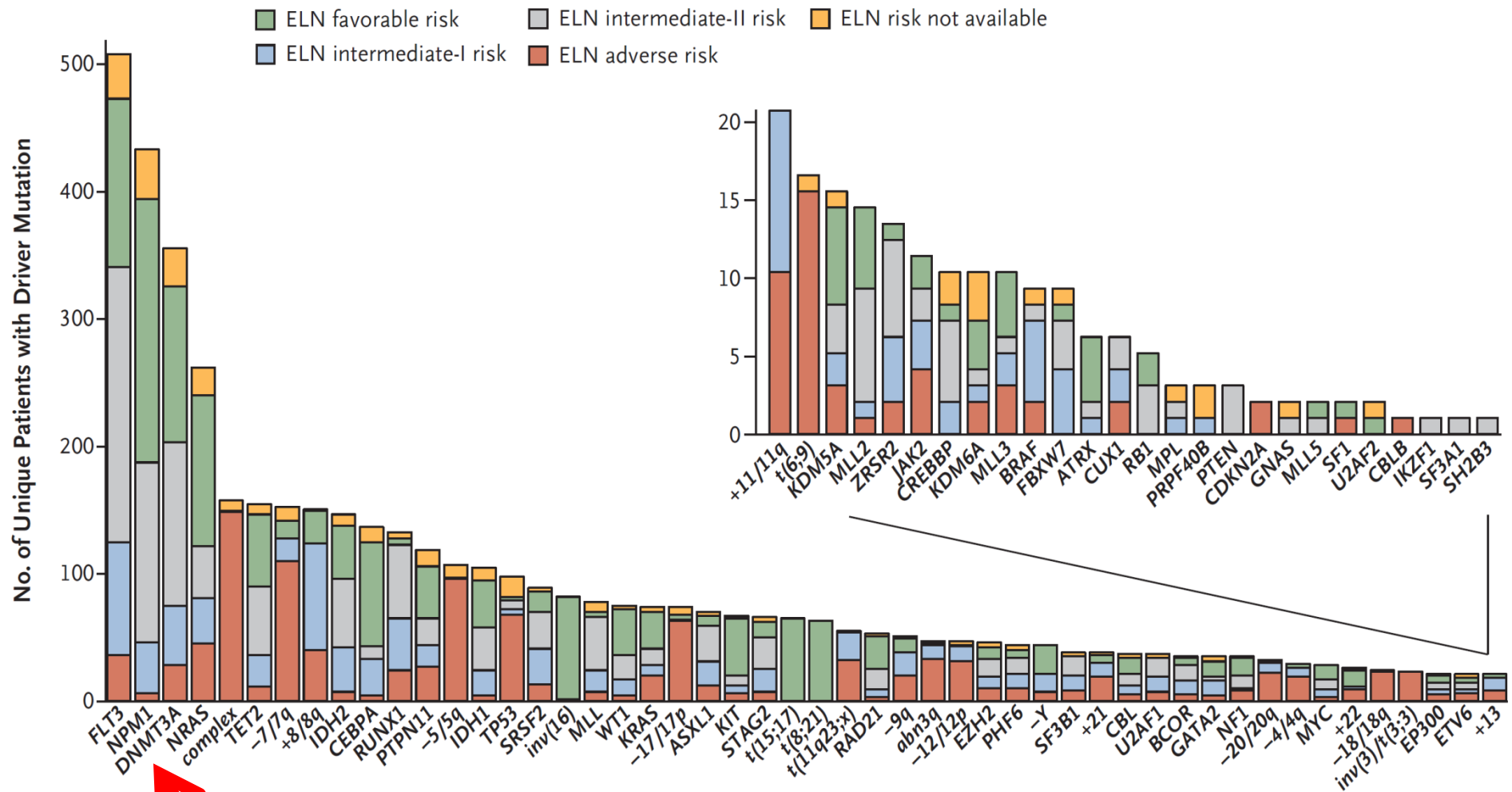
- TET2 tet methylcytosine dioxygenase 2
- The protein is a methylcytosine dioxygenase that catalyzes the **conversion of methylcytosine to 5-hydroxymethylcytosine**.
- The encoded protein is involved in **myelopoiesis**, and defects in this gene have been associated with several myeloproliferative disorders.

ASXL1

- The ASXL1 gene provides instructions for making a protein that is involved in a process known as **chromatin remodeling**.
- Through its role in chromatin remodeling, the ASXL1 protein **regulates the expression of many genes**, including a group of genes known as HOX genes.
- The ASXL1 protein may have an additional role in gene regulation by signaling to molecules to add a methyl group (a process called methylation) to an area near a gene called the promoter region, which controls gene activity. When a promoter region is methylated, gene activity is repressed, and when a promoter region is not methylated, the gene is active.

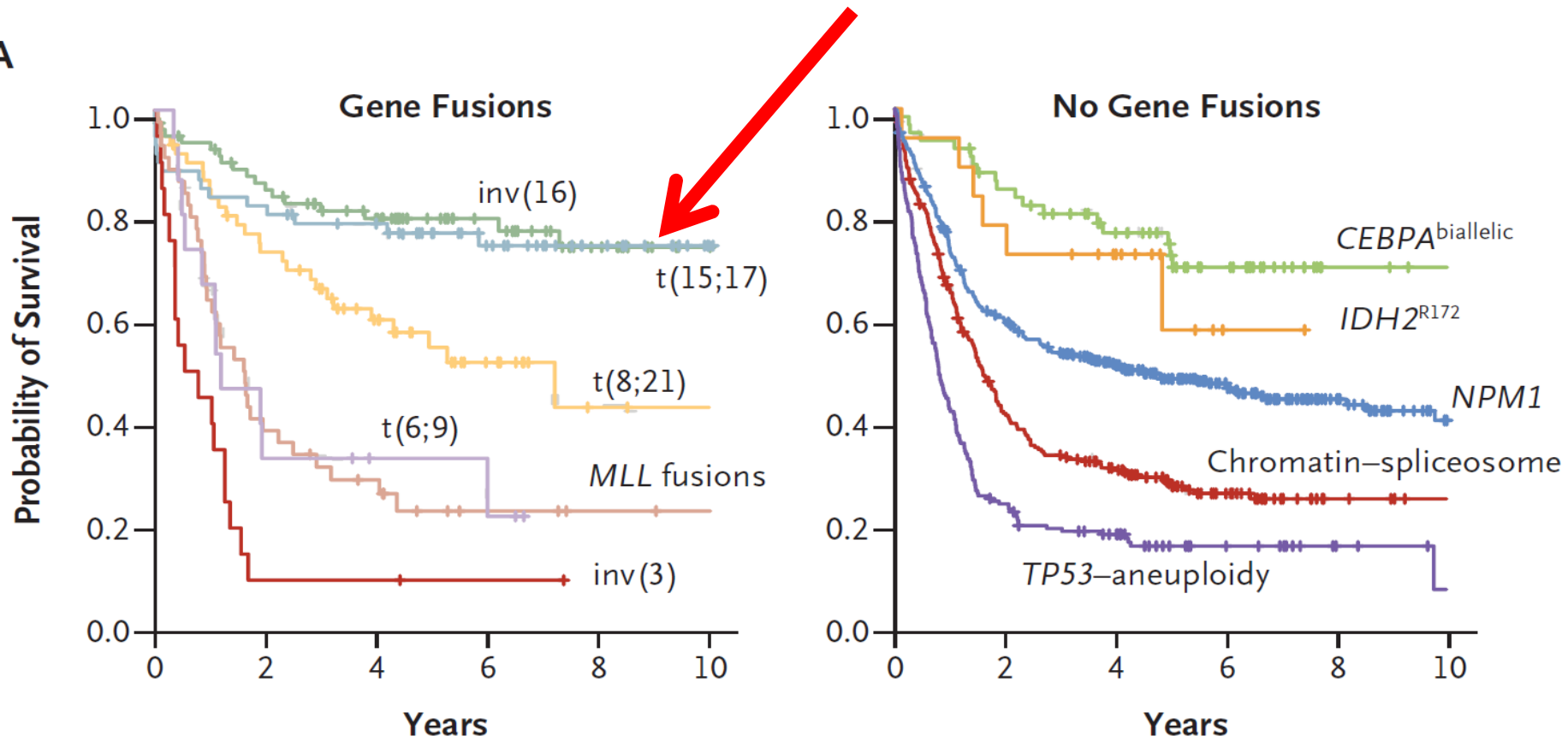


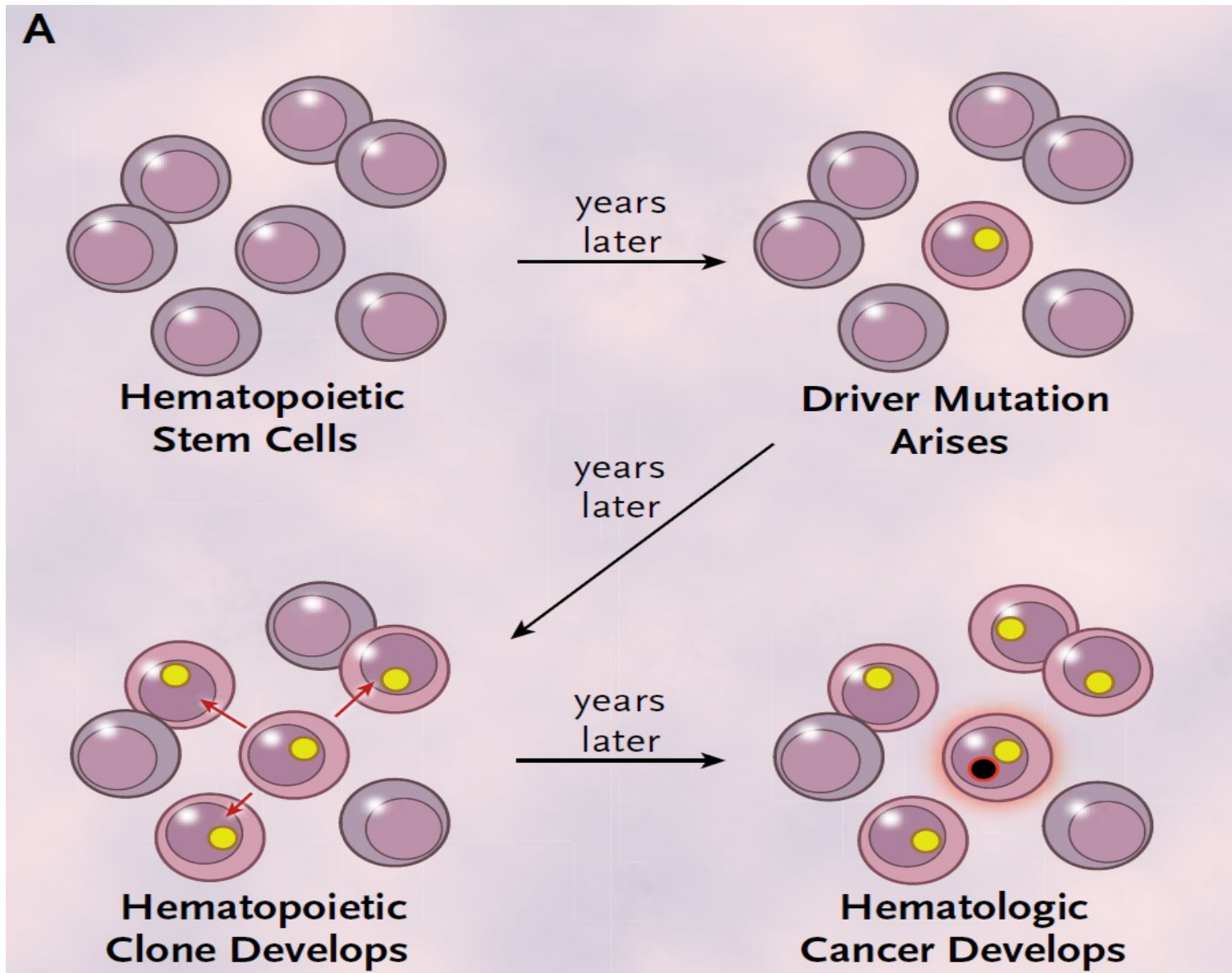
Clonal hematopoiesis: more frequent than hematological malignancies, as well as cardiovascular diseases! Increase in total mortality.



2016, n=1540

A





AML Case

- **young** man, age 24
- history: none, no drugs taken
- occupation: 1st factory worker, 2nd bartender
- abusus: alcohol, 10-20 cigarettes/day
- current illnesses:
 - **weight loss** 5 kg in last month
 - 3 weeks **fatigue**
 - 2 weeks **fever**
 - **gum bleeding** – stomatologist: gingivitis, insufficient hygiene
 - 1,5 weeks **cough** – GP: bronchitis – started ATB
 - 1 week ago **blurry vision** left eye, then both eyes – ophthalmologist: retinal hemorrhage – sent to infectious dep.
 - infectious: WBC 320
 - hematologist: urgent transfer to our centre

AML Case

- CBC
 - WBC **321** x10e9/l (normal range 4-10)
 - Hb **66** g/l (135-176)
 - plt **89** x10e9/l (150-350) after transfusion
- microscopic WBC differential count
 - neutrophils 0.5% (50-70)
 - lymphocytes 1.5% (20-40)
 - monocytes 0.0% (2-12)
 - blasts **98.0%** (0-0) = Dg. **acute leukemia**
- coagulation
 - D dimers **14** ug/ml (0-0.5), otherwise normal
- biochemistry
 - LDH **9.88** ukat/l (2.25-3.75), otherwise normal

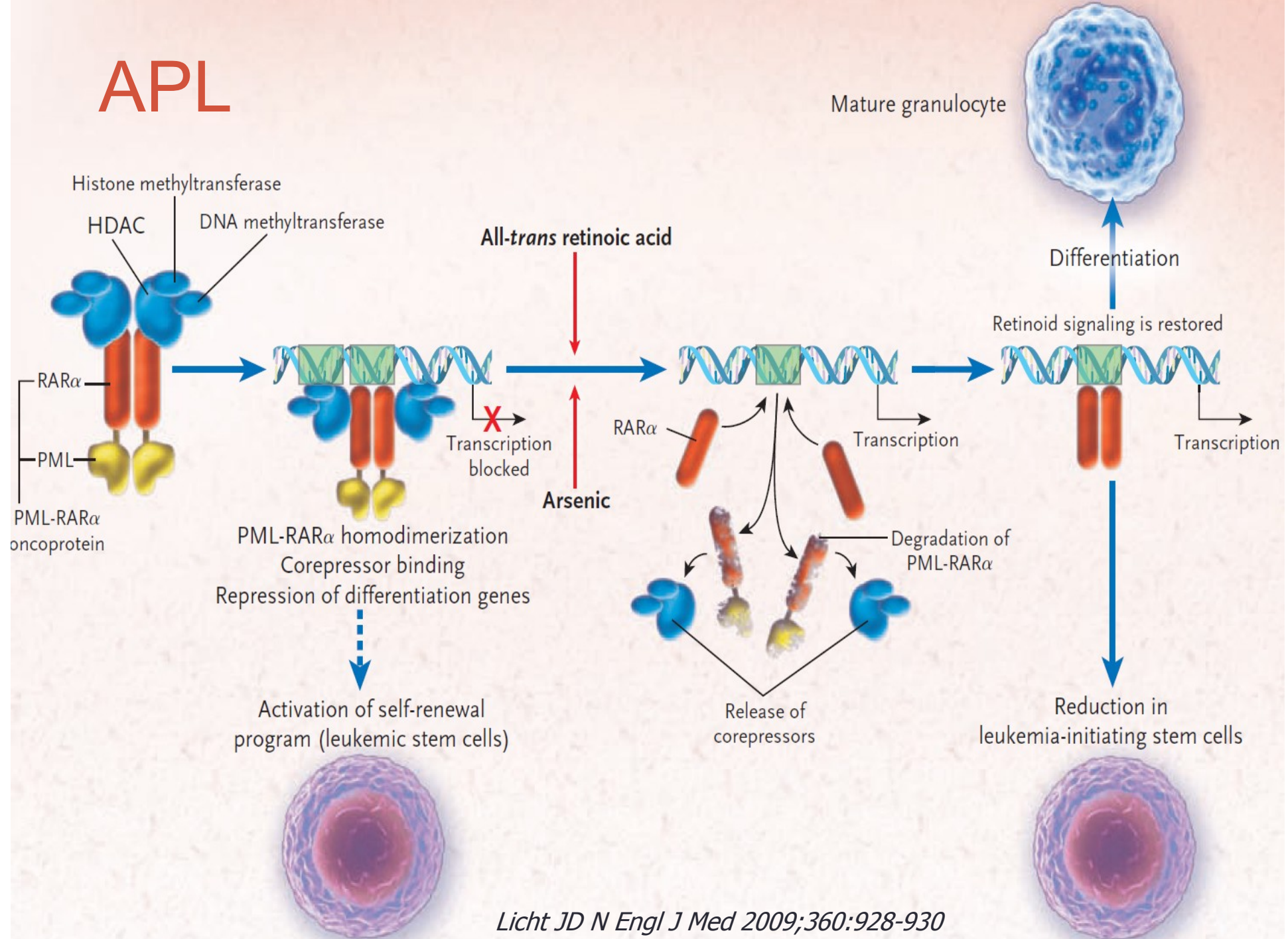
AML Case

- bone marrow assessment
 - increased cellularity
 - low % of normal cells 0-1%
 - blasts **93%** (0-5)
- cytochemistry
 - **POX** (myeloperoxidase) positive
- Diagnosis: **acute myeloid leukemia**
- work-up:
 - mutations: none found
 - cytogenetics: several chromosome abnormalities (**complex karyotype**)
- risk group: **very high risk** (of relapse)
 - hyperleukocytosis + adverse karyotype

AML Case

- hyperleukocytosis + leukostasis = **hematological emergency**
- emergency treatment
 - **leukapheresis**
 - leuk- = leukocytes
 - -apheresis = removal
 - supportive measures
- treatment
 - **induction**: 1 cycle – complete remission
 - Webster: to induce = to cause (something) to happen or exist
 - **consolidation**: 2 cycles
 - Webster: to consolidate = to make (something) stronger
 - allogeneic stem cell **transplantation**
- died due to transplant related toxicity (infection)

APL



APL Case

- **elderly** man, age 70
- history: non-STEMI, type 2 diabetes, cataract
- drugs: ACE-i, BB, ASA, statin, 3 PADs, eye drops
- occupation: retired
- abusus: non-smoker, alcohol seldom
- current illnesses:
 - 2 weeks **shortness of breath**
 - thought of heart problems
 - cardiologist: CBC – pancytopenia
 - no other symptoms

APL Case

- CBC
 - WBC 2.10 (normal range 4-10)
 - Hb 74 (135-176)
 - plt 24 (150-350)
 - = **pancytopenia**
- microscopic WBC differential count
 - neutrophils 8% (50-70)
 - lymphocytes 41% (20-40)
 - monocytes 0.5% (2-12)
 - blasts **50%** (0-0) = Dg. **acute leukemia**
- coagulation
 - D dimers **11.5** (0-0.5), INR **1.35** (0.8-1.2), fbg **1.7** (1.8-4.2) = **DIC**
- biochemistry: normal

APL Case

- pancytopenia + DIC = APL suspected = **hematological emergency**
- bone marrow assessment
 - increased cellularity
 - low % of normal cells
 - blasts **26%** (0-5)
 - promyelocytes **43%** (0.1-5) = APL probable
- cytochemistry
 - POX positive
- work-up:
 - mutations: **PML::RARa** detected PCR = Dg. APL
 - cytogenetics: 46,XY,t(**15;17**)
- risk group: **favorable** = very low risk of relapse

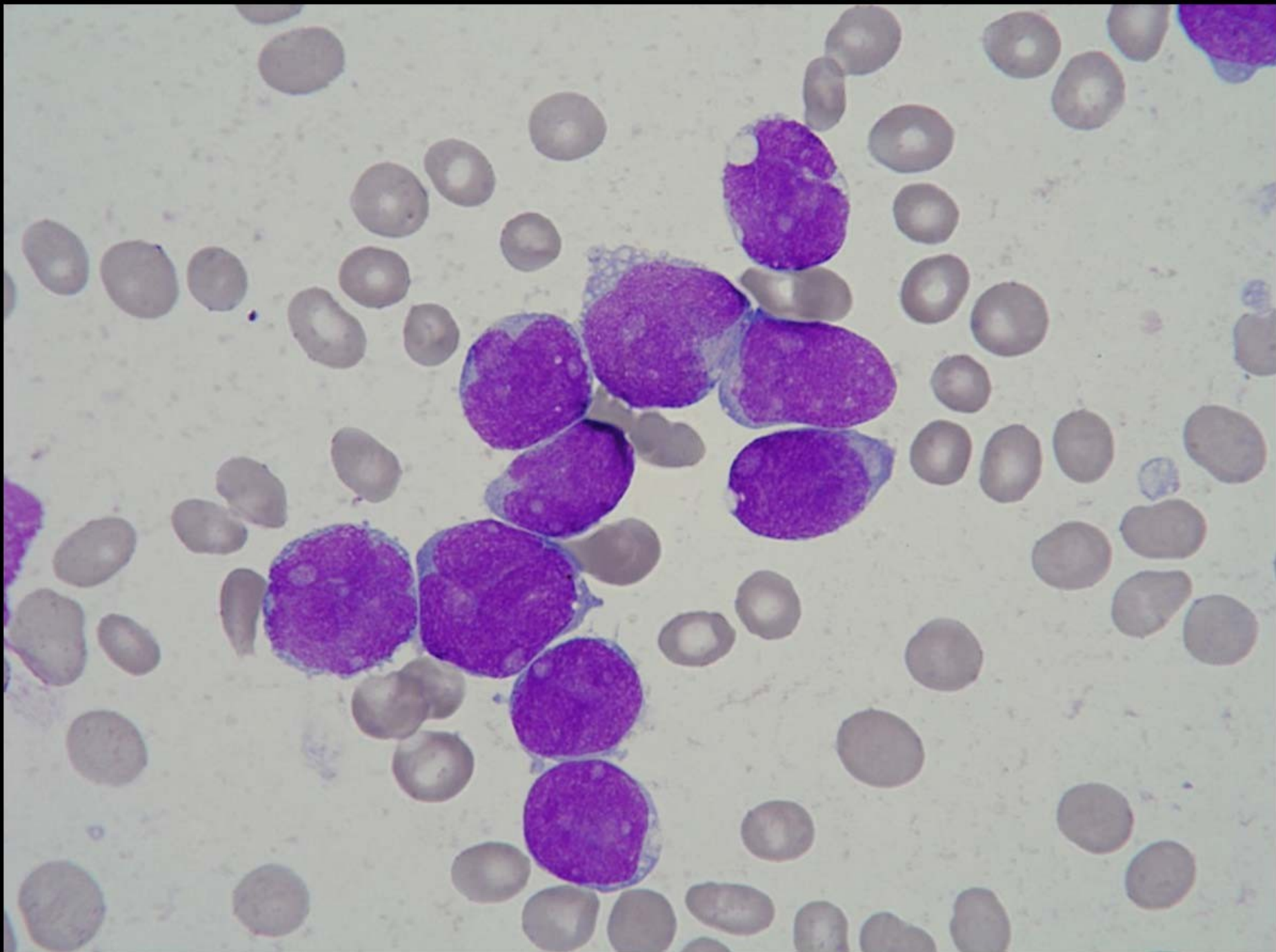
APL Case

- emergency treatment
 - **ATRA** as soon as possible
 - All-Trans Retinoic Acid (vitamin A derivative)
- standard treatment
 - induction: **ATRA** + chemo
 - consolidation: **ATRA** + chemo
 - maintenance: **ATRA** alone
 - no transplant necessary
- option for chemo-free therapy: ATRA + ATO (As_2O_3)
- **remission**

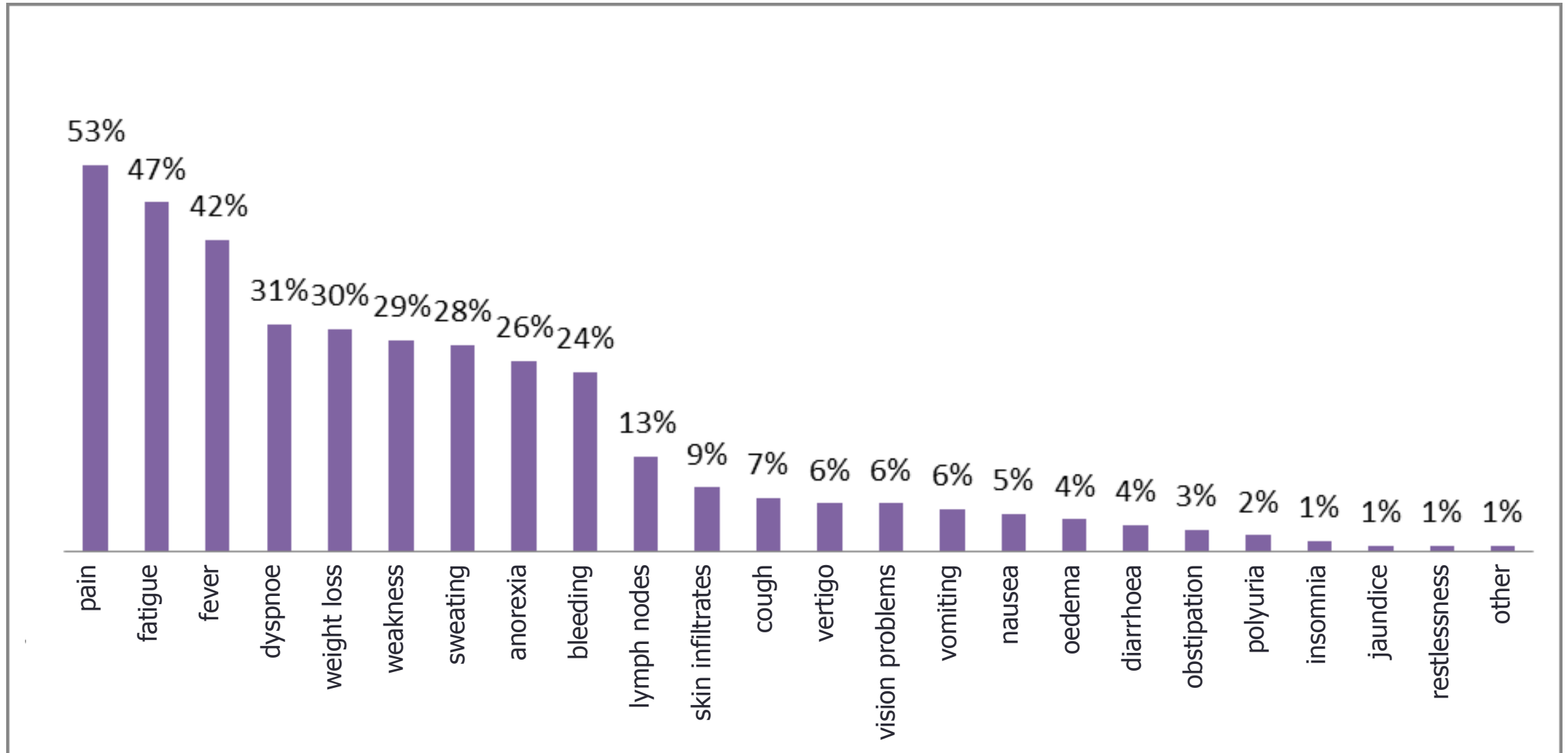
ALL

Acute Lymphoblastic Leukemia

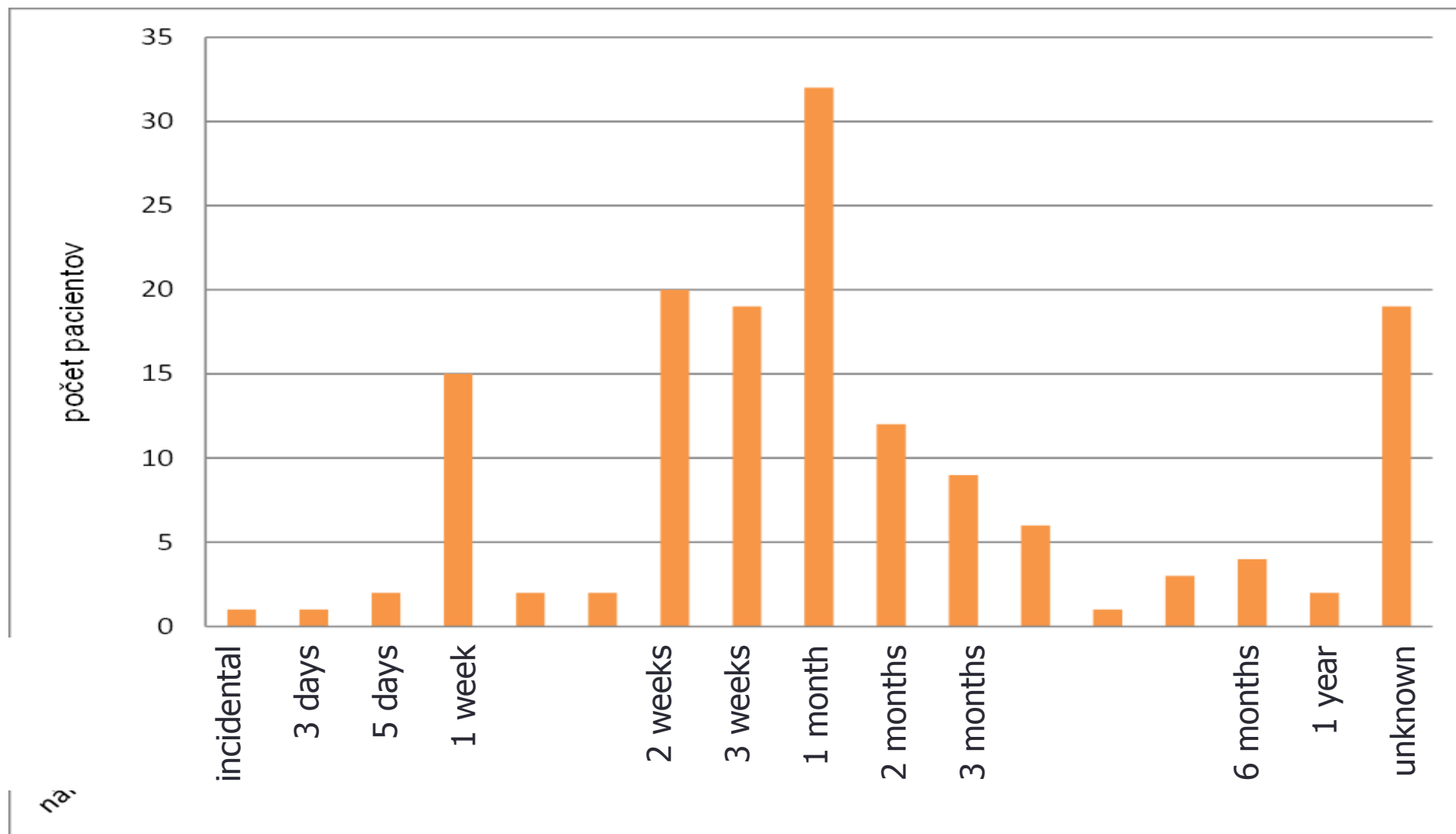
model disease of child malignancies with **first and second hit**



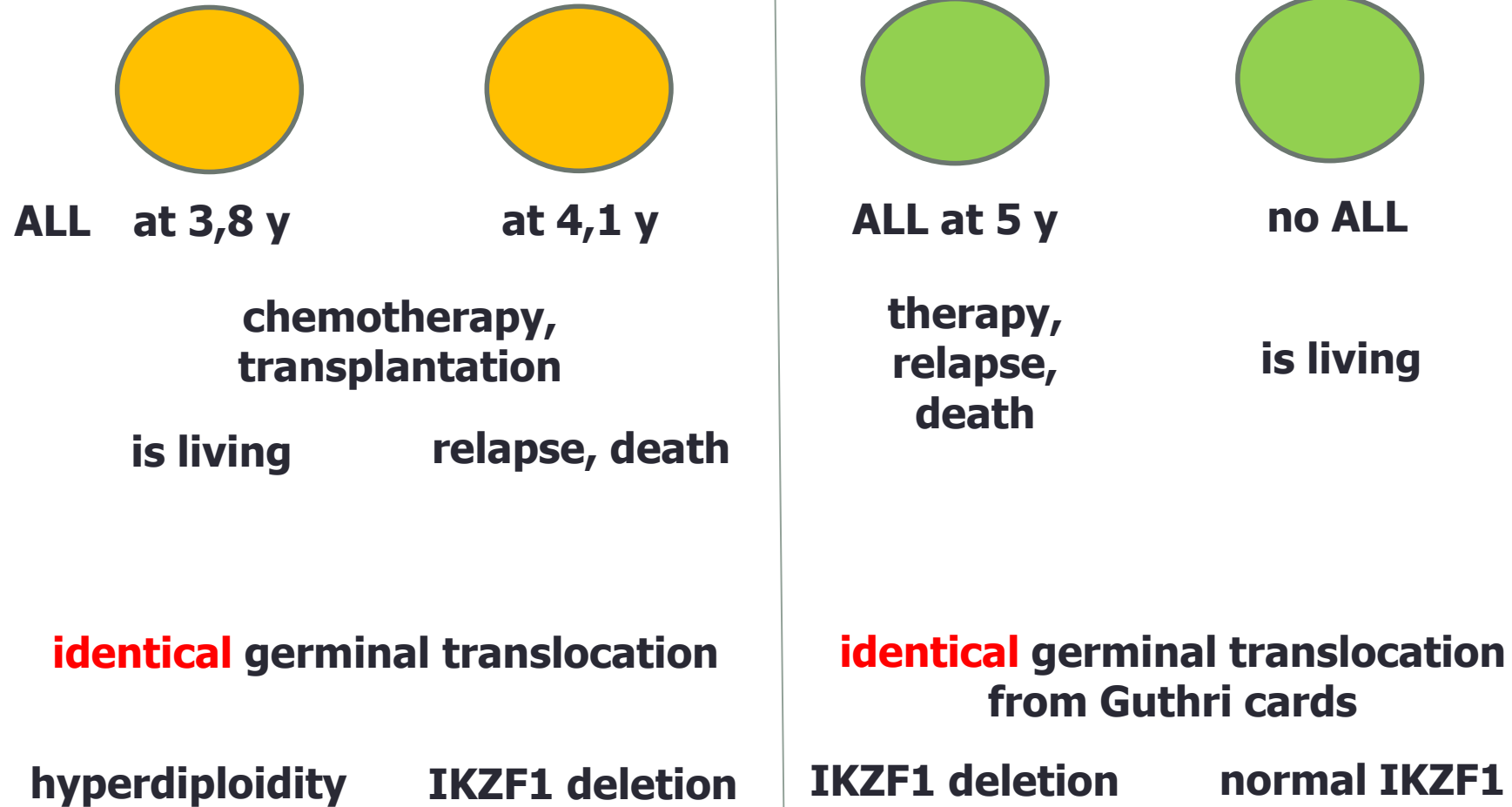
ALL: Clinical symptoms at diagnosis



ALL: Time from first symptoms to diagnosis



Monozygotic twins



IKZF1

- DNA-binding protein Ikaros also known as **Ikaros family zinc finger protein 1** is a protein that in humans is encoded by the IKZF1 gene.
- This gene encodes a **transcription factor** that belongs to the family of zinc-finger DNA-binding proteins associated with chromatin remodeling.
- Ikaros displays **crucial functions in the hematopoietic system** and its loss of function has been linked to the development of lymphoid leukemia.
- Ikaros point mutant **mice are embryonic lethal** due to anemia; they have severe defects in terminal erythrocyte and granulocyte differentiation, and excessive macrophage formation.
- The expression of this protein is **restricted to the fetal and adult hemolymphopoietic** system, and it functions as a **regulator of lymphocyte differentiation**.

ALL Case

- **young adult** man, age 25
- history: none, no drugs
- occupation: construction worker
- abusus: alcohol sometimes, smokes 10/day
- current illnesses:
 - **weight loss** 10 kg in last 6 months
 - several weeks **fatigue**
 - 10 days feeling **common cold, cough**
 - 3 days ago **fainting** – local internal dept.: orthostasis
 - yesterday at GP: „bad“ blood count – sent to local internal dept.
 - anemia, lymphocytosis, blasts: transferred to our centre

ALL Case

- CBC
 - WBC **7.49** (4-10)
 - automated diff: Lympho **49%** (20-40)
 - Hb 75 (135-175)
 - plt 134 (150-350)
- **microscopic** WBC differential count
 - neutrophils 31.5% (47-70)
 - lymphocytes **10%** (20-45)
 - monocytes 0% (2-12)
 - blasts **55%** (0-0) = Dg. **acute leukemia**
- coagulation: normal
- biochemistry: normal

ALL Case

- bone marrow
 - increased cellularity
 - low % of normal cells
 - blasts 60% (0-5)
- cytochemistry
 - POX negative
- flowcytometry (immunophenotyping)
 - **CD10-19+20-22+34+38+c79a+cTdT+clgM-slgM- = pro-B immunophenotype**
 - = Dg. **Acute B-lymphoblastic leukemia**
- mutations: none found
- cytogenetics: 46,XY = normal karyotype
- risk group: **high risk**

ALL Case

- no emergency treatment necessary
- standard treatment
 - **prephase:** steroids
 - **induction:** 2 cycles, achieved **CR**
 - **consolidation:** 1 cycle (now)
- **allogeneic stem cell transplant**
 - no sibling donor
 - found 10/10 matched unrelated donor
 - still alive in CR

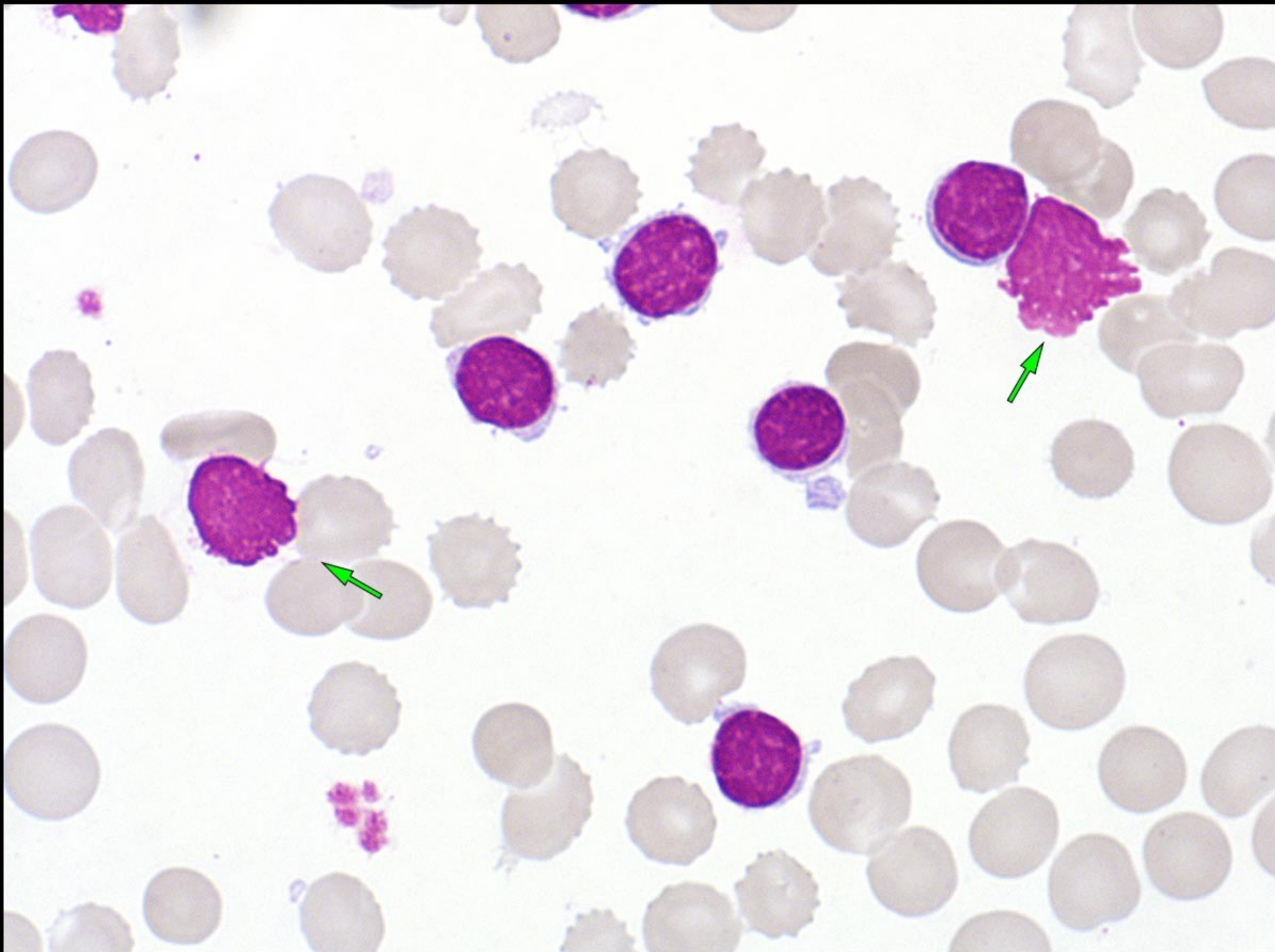
Acute leukemias - Take home messages

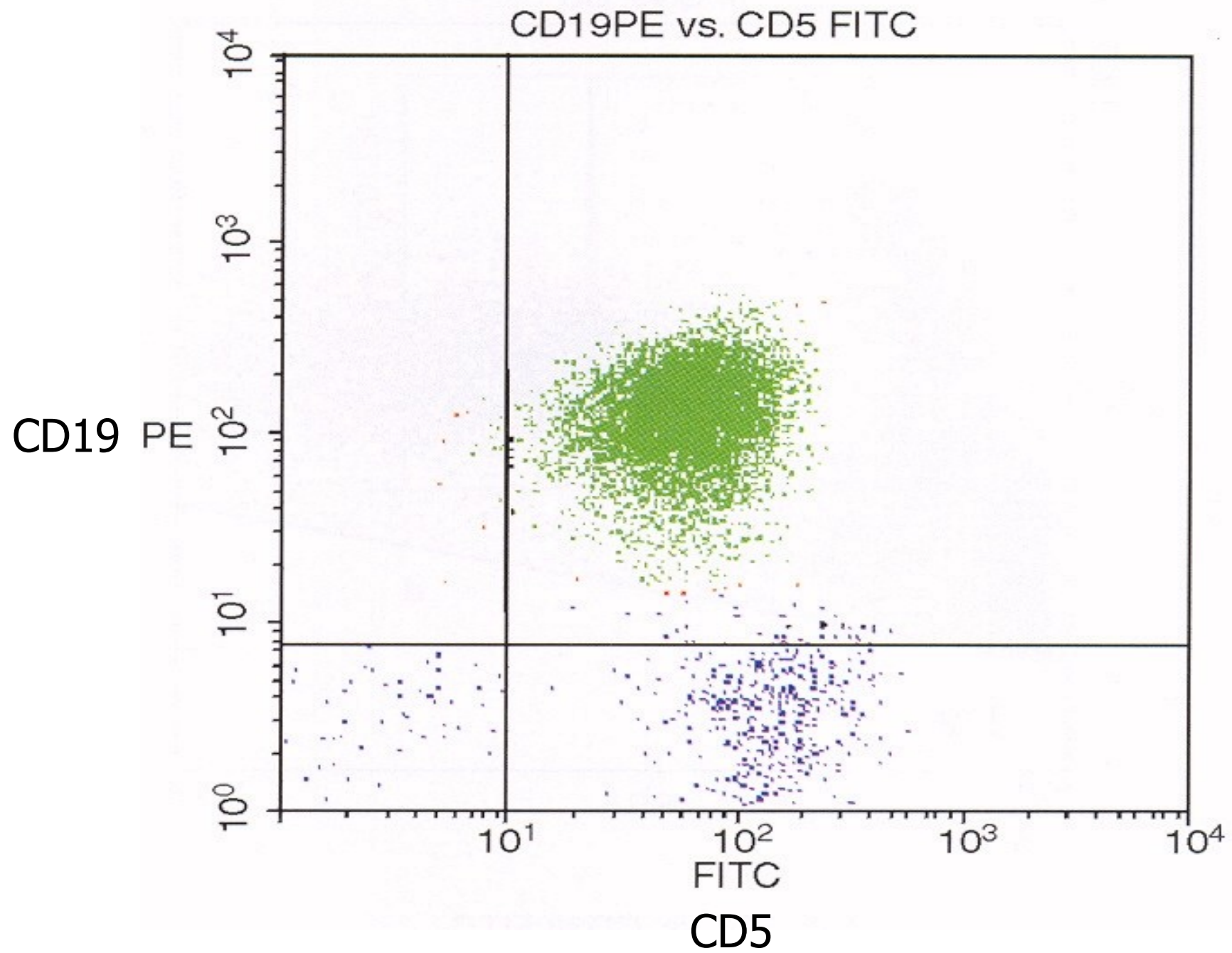
- **acute leukemia: 20 or more % of blasts** in blood and/or bone marrow
- acute = short history, rapid progression: **days or weeks**
- acute **myeloid** leukemia: POX positive (or negative)
- hyperleukocytosis: **emergency**
- acute **promyelocytic** leukemia: pancytopenia, DIC, **emergency**
- acute **lymphoblastic** leukemia: POX neg., immunophenotype
- survival depends on **risk factors**

CLL

Chronic Lymphocytic Leukemia

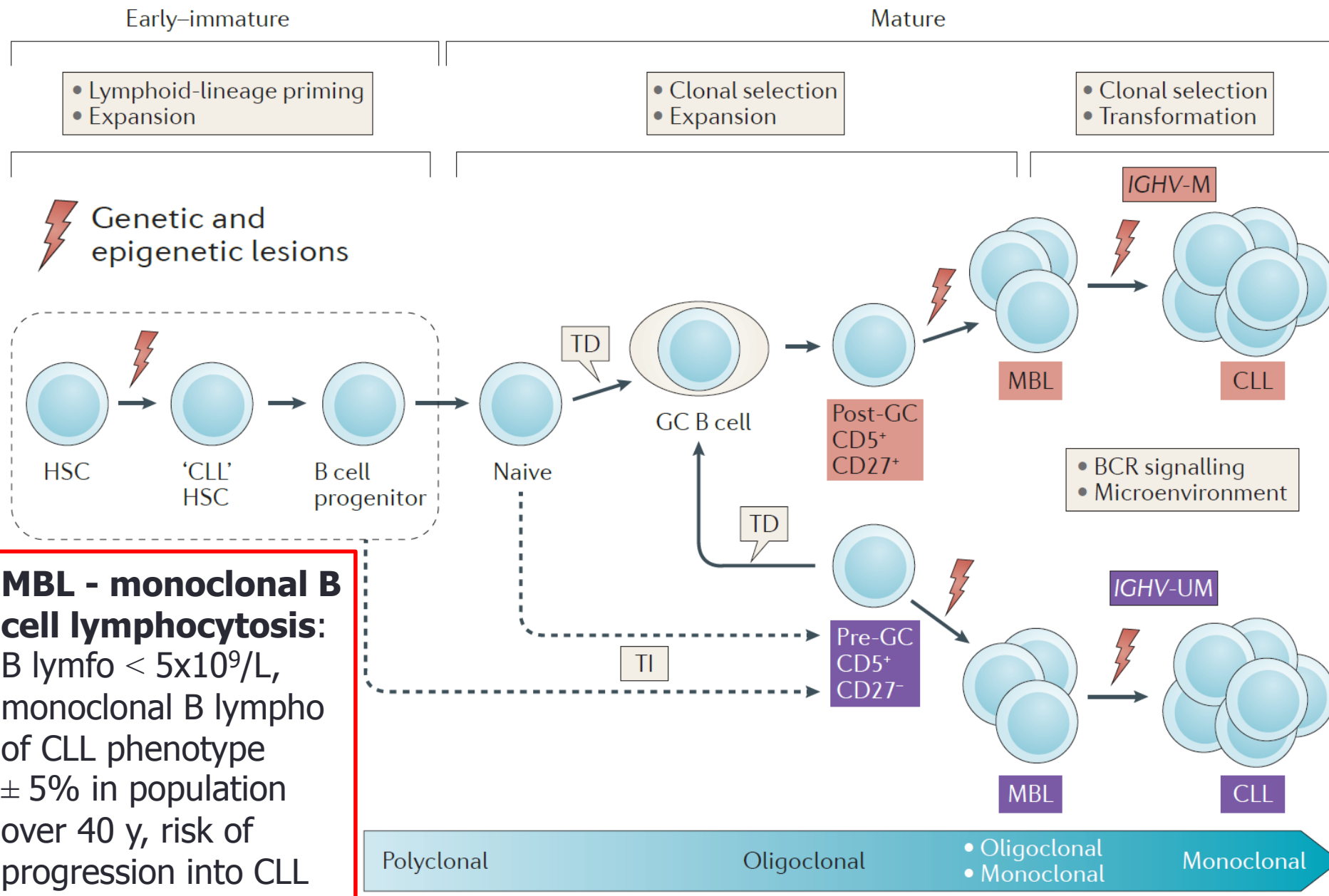
model disease of complex pathogenesis involving
signalling pathways and **tumor microenvironment**



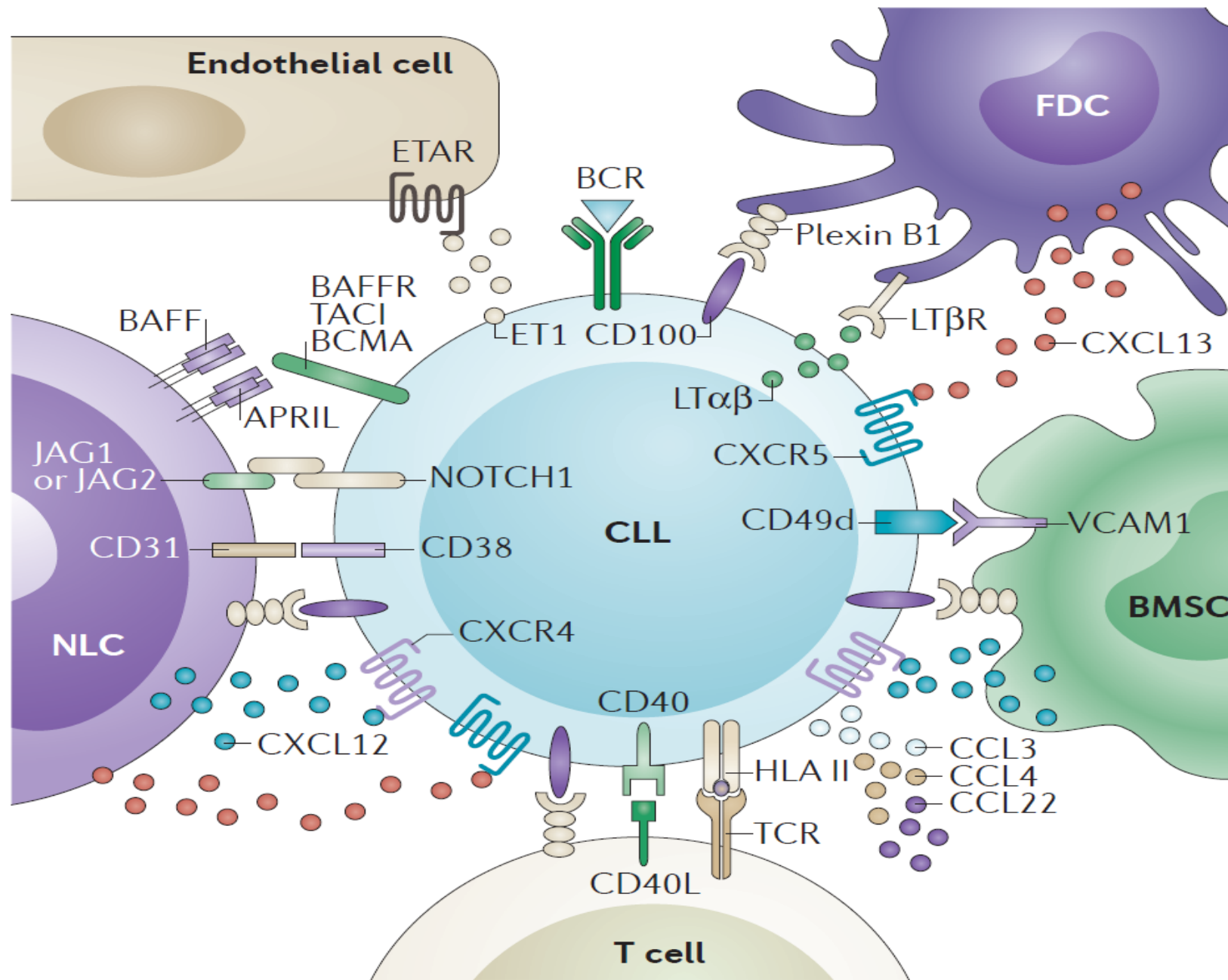


CLL - hallmarks

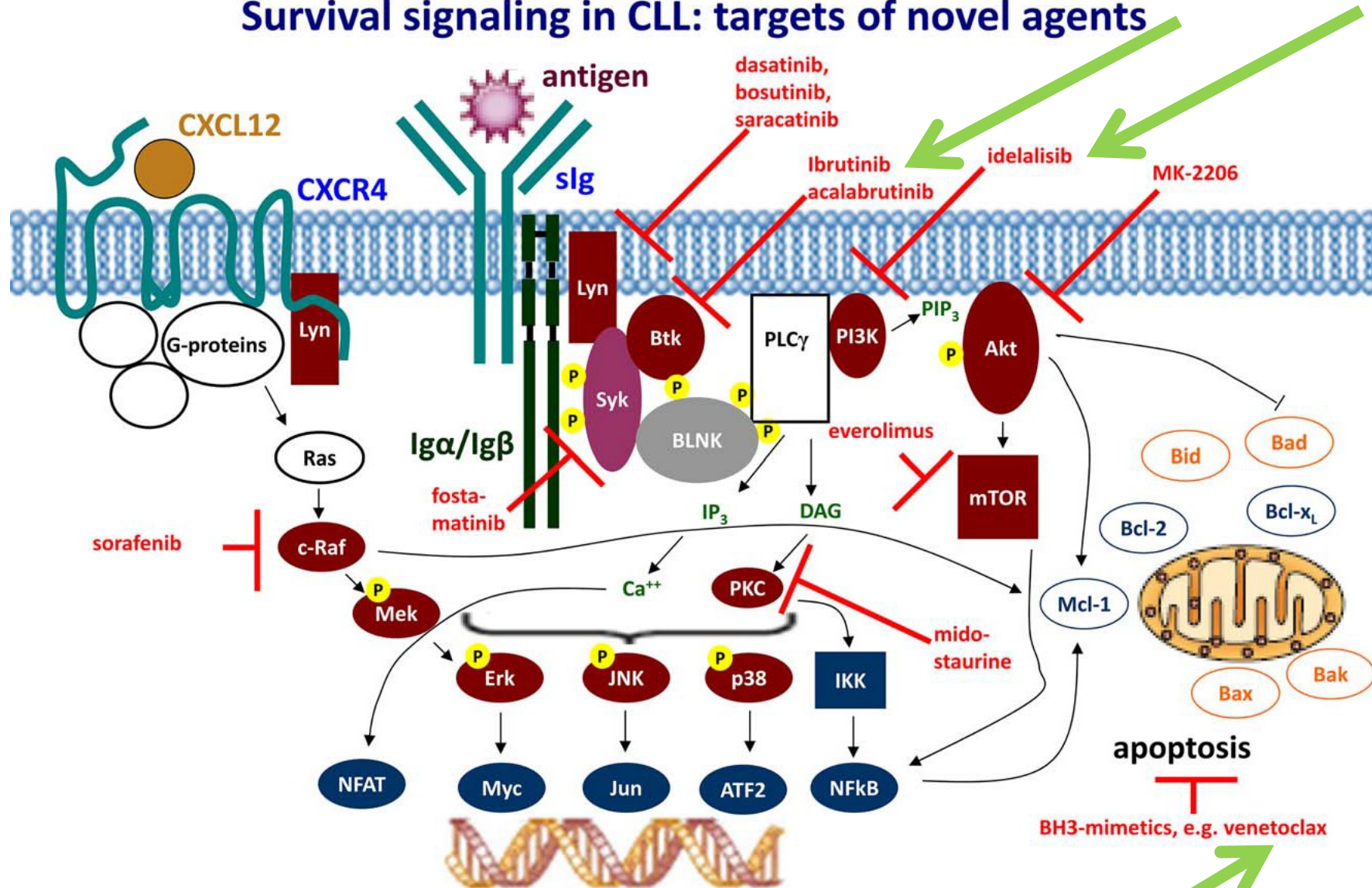
- **Different** behavior than AML, ALL, or CML
- Significant proportion of patients **never** require therapy (smoldering disease)
- According to our data, in 60% of patients just observation, **watchful waiting**
- The pathogenesis is extraordinarily **complex**, not yet fully understood, but big progress in **recent** years
- Not just the malignant cells are involved, also the interactions with **microenvironment** are crucial (vs AML)
- Due to recent progress, new therapies are **emerging**
- However, **still incurable (but treatable)** disease

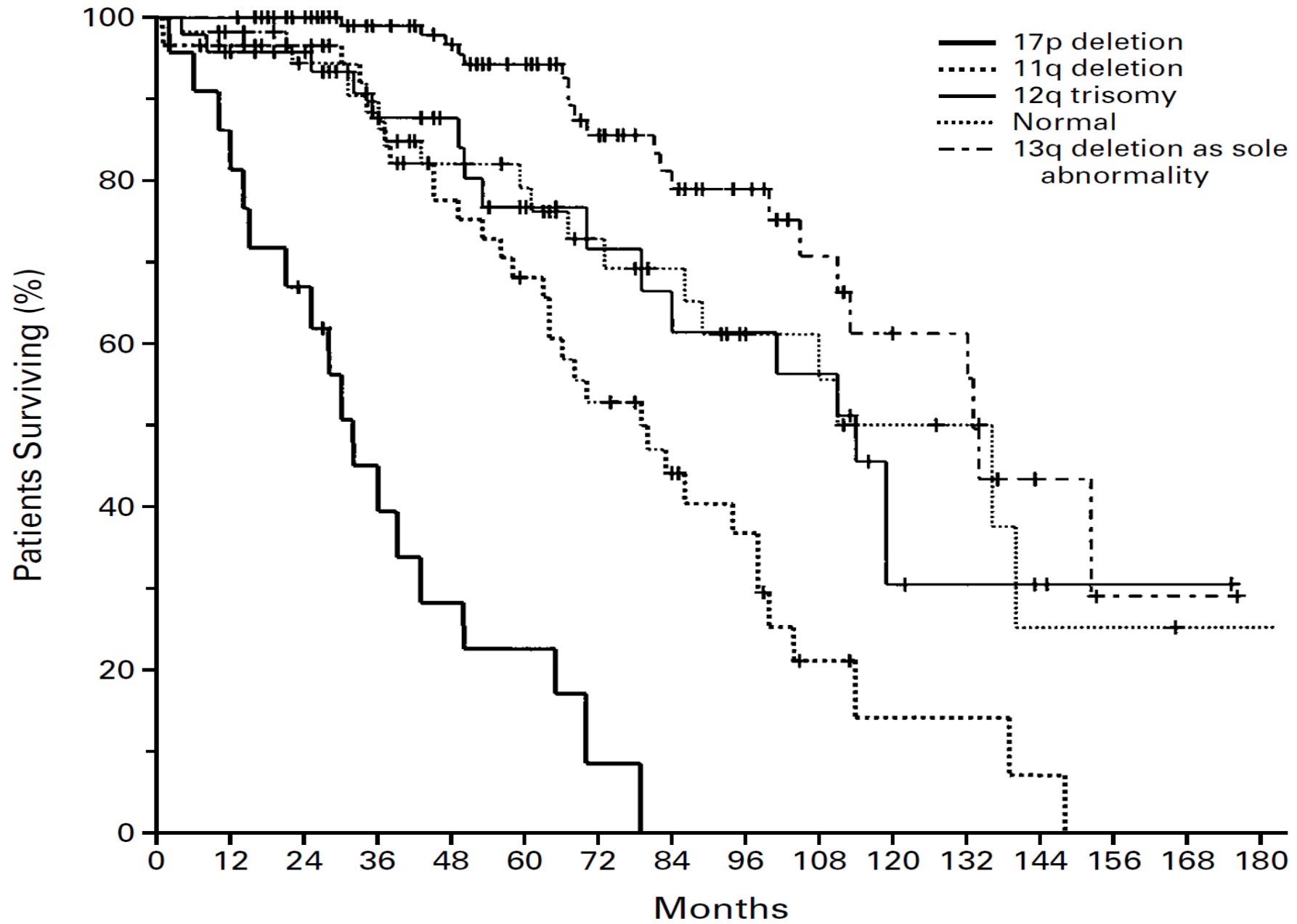


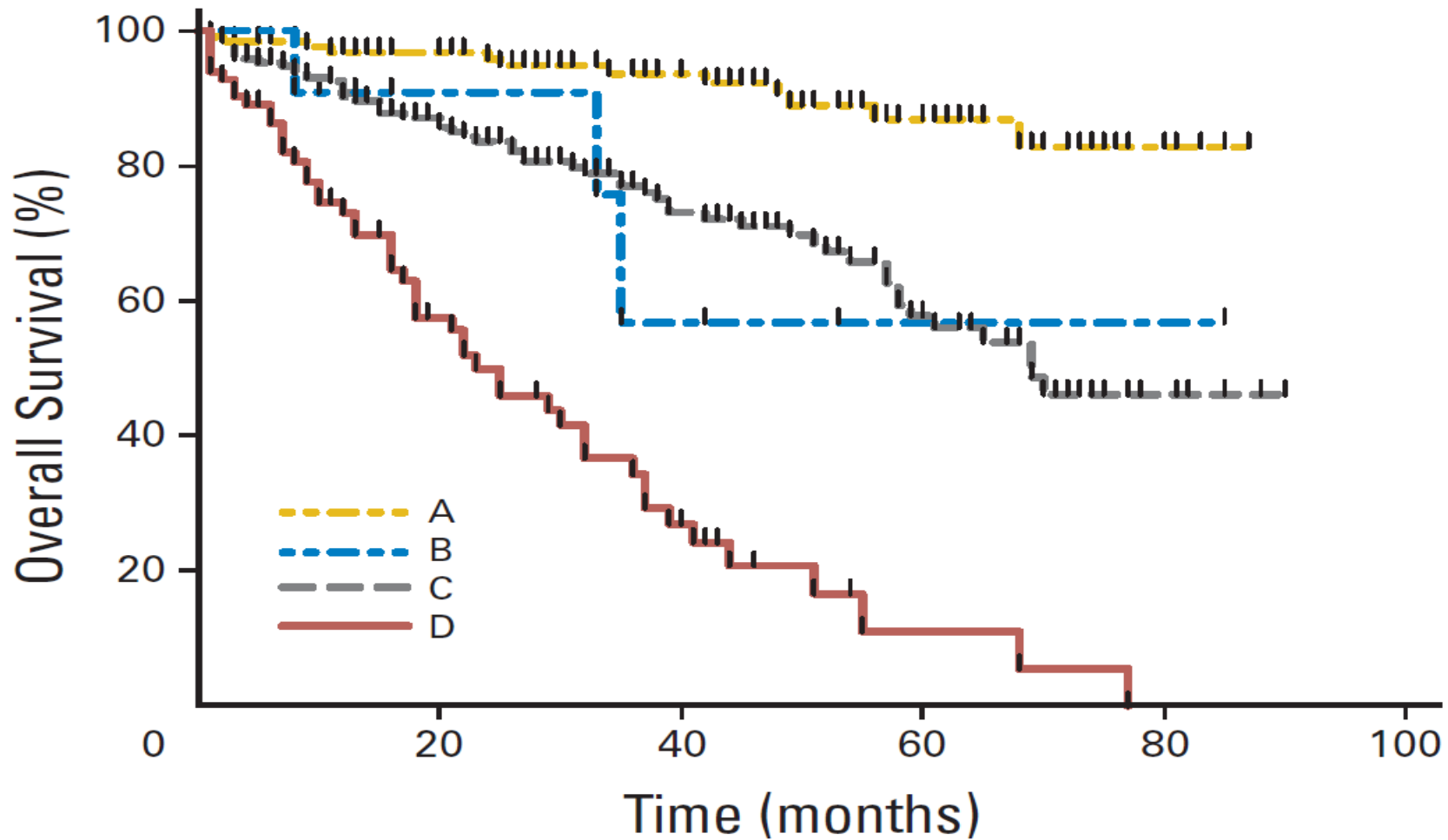
- **MBL - monoclonal B cell lymphocytosis:**
- B lymfo < 5x10⁹/L, monoclonal B lympho of CLL phenotype
- ± 5% in population over 40 y, risk of progression into CLL



Survival signaling in CLL: targets of novel agents







- A, wild-type p53 and mutated IgVH
- B, p53 defect and mutated IgVH
- C, wild-type p53 and unmutated IgVH
- D, p53 defect and unmutated IgVH

CLL Case

- **elderly** man, age 80
- history: hypertension, chronic cardiac disease
- drugs: ACE-i, BB, ASA, statin
- occupation: retired
- abusus: alcohol sometimes, non-smoker
- current illnesses:
 - **weight loss** 10 kg per last year
 - a bit **tired**
 - **night sweating**
 - no other problems
 - 1 month **fever**: up to 38 °C
 - sent by his GP = fever, lymph nodes and WBC 40

CLL Case

- CBC
 - WBC **44** (4-10)
 - Hb 105 (130-176)
 - plt 182 (150-350)
 - lymphocytes 93% (20-40)
- microscopic WBC differential count
 - neutrophils 5% (50-70)
 - lymphocytes **94%** (20-40)
 - monocytes 0% (2-12)
 - blasts 0% (0-0)
- coagulation and biochemistry: normal
- lymphocytosis = **lymphoproliferative disorder** probable

CLL Case

- bone marrow
 - increased cellularity
 - no blasts
 - lymphocytes **53%** (5-20)
- immunophenotyping
 - **CD5+10-19+20dim23+200+79a-FMC7-** = typical for **B-CLL**
- Dg.: **Chronic lymphocytic leukemia**
- work-up: mutations, cytogenetics
- indication for treatment
 - symptoms: fever, sweating, weight loss
- patient is alive, now 2nd relapse

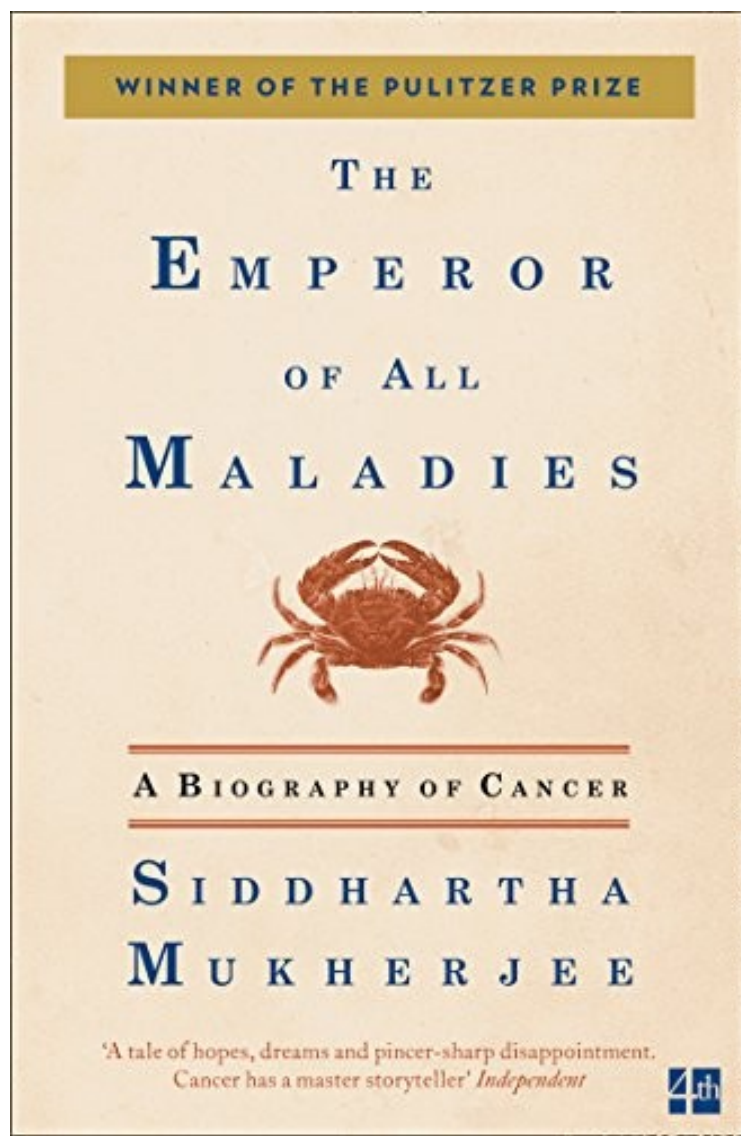
CLL - Take home messages

- chronic disease
- similar to indolent lymphomas
- no symptoms for many months or years
- **leukocytosis with lymphocytosis**
- **specific immunophenotype (CD5+19+23+)**
- **no treatment** when no symptoms nor problems
- **treatment necessary only in advanced cases**
 - go go = younger, healthy patients
 - slow go = elderly patients
 - no go = frail patients with comorbidities
- repeated **remissions and relapses**, incurable

Summary

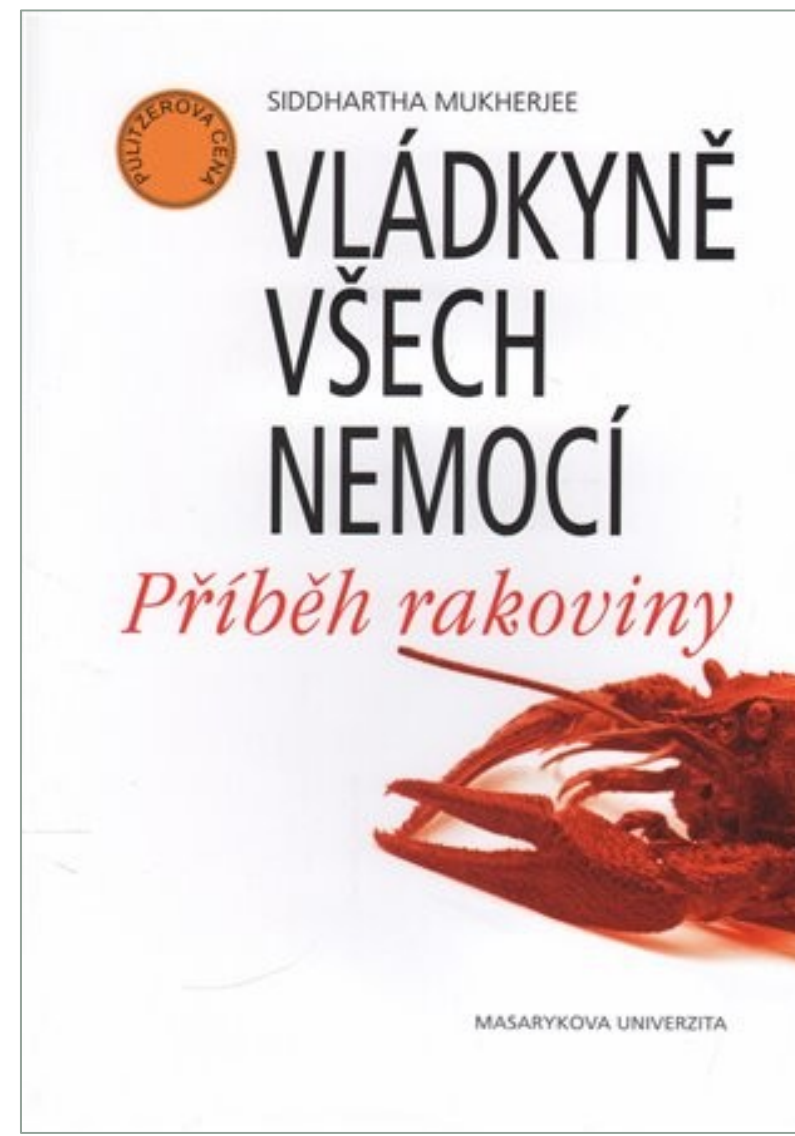
- After more than 150 years, the term **leukemia** still survives
- Leukemias have **different clinical behavior**, yet with some similar patterns
- Where the pathogenesis is relatively simple, just one **targeted therapy** may show miraculous effect (CML)
- **Complex genetic changes** in other types of leukemia, especially in advanced stages, preclude simple therapeutic strategy
- In CLL, disrupting the interactions with **tumor microenvironment** seems to be very important
- Classical non-specific chemotherapy, in combination with monoclonal antibodies, or BMT, still serve as therapeutic option in many cases

The Emperor of All Maladies



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