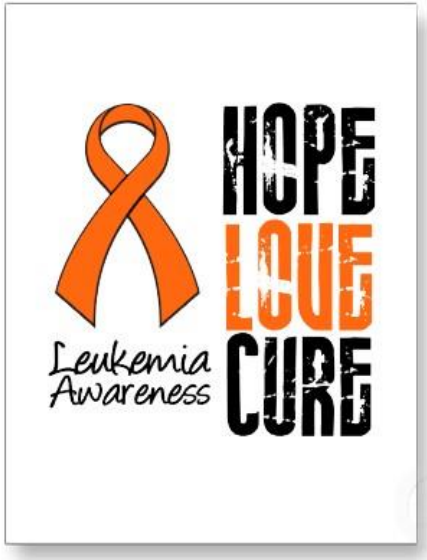
University of Puerto Rico
Medical Sciences Campus
Comprehensive Cancer Center

Clinical and Translational Correlation of Leukemia



Maribel Tirado Gomez, MD
Assistant Professor of Medicine

January 8, 2015

Agenda

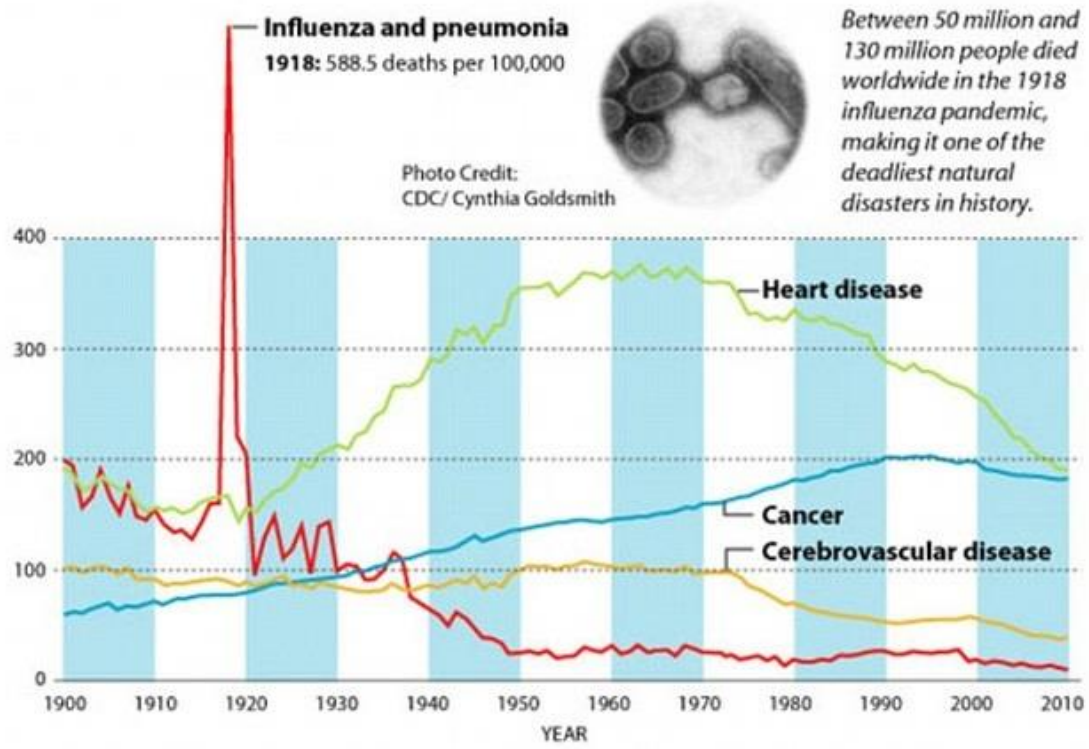
- Cancer Statistics
- Drug Development and Clinical Research
- Hematopoiesis and Leukemia
- Chronic Myelogenous Leukemia

Cancer Statistics

Leading causes of deaths in the U.S. since 1900

Number of deaths per 100,000

1900		1950		2010	
1. Influenza and pneumonia	202.2	**1.** Heart disease	355.5	**1.** Heart disease	192.9
2. Tuberculosis	194.4	**2.** Cancer	139.8	**2.** Cancer	185.9
3. Gastrointestinal infections	142.7	**3.** Cerebrovascular disease	104.0	**3.** Chronic airways disease	44.6
4. Heart disease	137.4	**4.** Diseases of early infancy	40.5	**4.** Cerebrovascular disease	41.8
5. Cerebrovascular disease	106.9	**5.** Non-motor-vehicle accidents	37.5	**5.** All accidents	38.2



Jones, DS. et. el. The Burden of Disease and the Changing Task of Medicine. N Engl J Med 2012; 366:2333-38

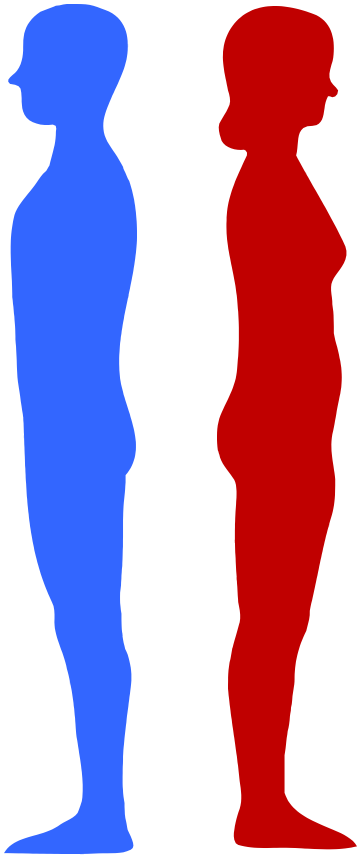
Why study Cancer?

- Cancer is a public health problem
  - Screening is limited
  - Most treatments are not curative in the metastatic setting
  - Costs
  - Influence of environment and ethnicity
  - Aging population

Cancer Statistics in Puerto Rico

Cancer Incidence in Puerto Rico, 2006-2010

Male (N=36,273)	%
Prostate	40.6
Colon and Rectum	13.1
Lung and Bronchus	6.1
Urinary Bladder	4.3
Oral Cavity and Pharynx	4.0
Non-Hodgkin Lymphoma	3.4
Liver and Intrahepatic Bile	2.9
Stomach	2.8
Kidney and Renal Pelvis	2.3
Leukemia	2.1
Other Locations	18.4



Female (N=29,734)	%
Breast	29.7
Colon and Rectum	13.2
Thyroid	9.1
Corpus and Uterus	7.5
Lung and Bronchus	4.1
Non-Hodgkin Lymphoma	3.9
Cervix Uteri	3.9
Stomach	2.5
Ovary	2.5
Leukemia	2.0
Other Locations	21.6

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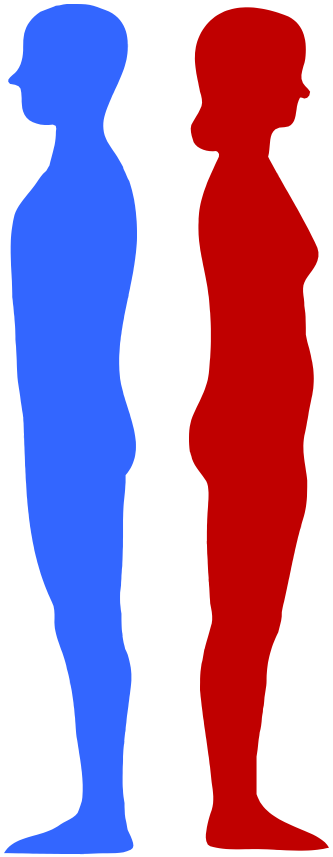
Cancer Mortality in Puerto Rico, 2006-2010

Male (N= 14,201)	%
Prostate	18.4
Lung and Bronchus	13.8
Colon and Rectum	13.1
Liver and Intrahepatic Bile Duct	6.5
Stomach	4.7
Pancreas	3.9
Oral Cavity and Pharynx	3.6
Esophagus	3.5
Leukemia	3.3
Non-Hodgkin Lymphoma	3.2
Other Locations	26.0



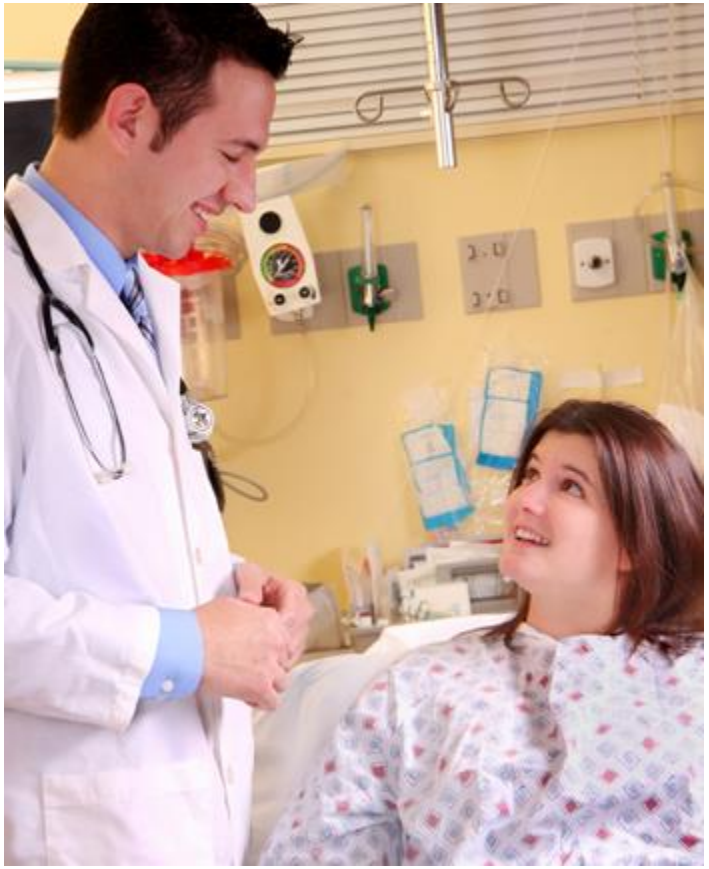
Female (N= 10,912)	%
Breast	18.9
Colon and Rectum	3.6
Lung and Bronchus	9.6
Pancreas	5.3
Liver and Intrahepatic Bile Duct	4.8
Corpus and uterus, NOS	4.6
Ovary	4.2
Stomach	3.9
Leukemia	3.5
Non-Hodgkin Lymphoma	3.4
Other Locations	28.2

Tortolero-Luna G, Zavala-Zegarra D, Pérez-Ríos N, Torres-Cintrón CR, Ortiz-Ortiz KJ, Traverso-Ortiz M, Román-Ruiz Y, Veguilla-Rosario I, Vázquez-Cubano N, Merced-Vélez MF, Ojeda-Reyes G, Hayes-Vélez FJ, Ramos-Cordero M, López-Rodríguez A, Pérez-Rosa N (2013). Cancer in Puerto Rico, 2006-2010. Puerto Rico Central Cancer Registry. San Juan, PR.

Drug Development and Clinical Research

What are Clinical Studies?

- Prospective study where the effect of an intervention in humans is tested

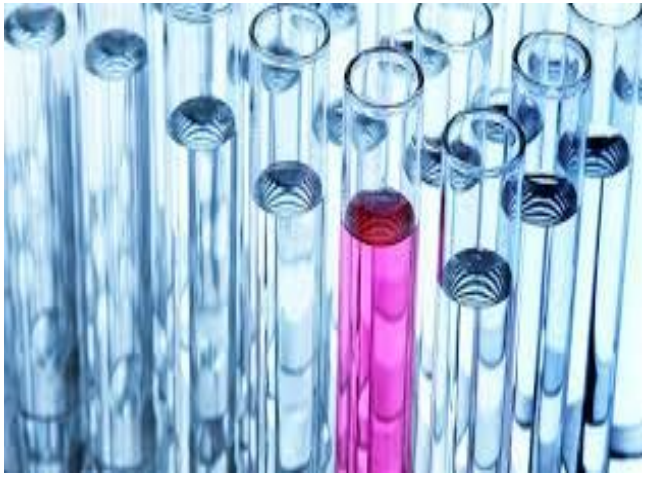


Types of Clinical Studies

- Prevention
  - Intervention to avoid cancer development
  - "Action Studies"
    - Do "something" to avoid cancer
  - "Agent studies"
    - Take "something" to avoid cacncer

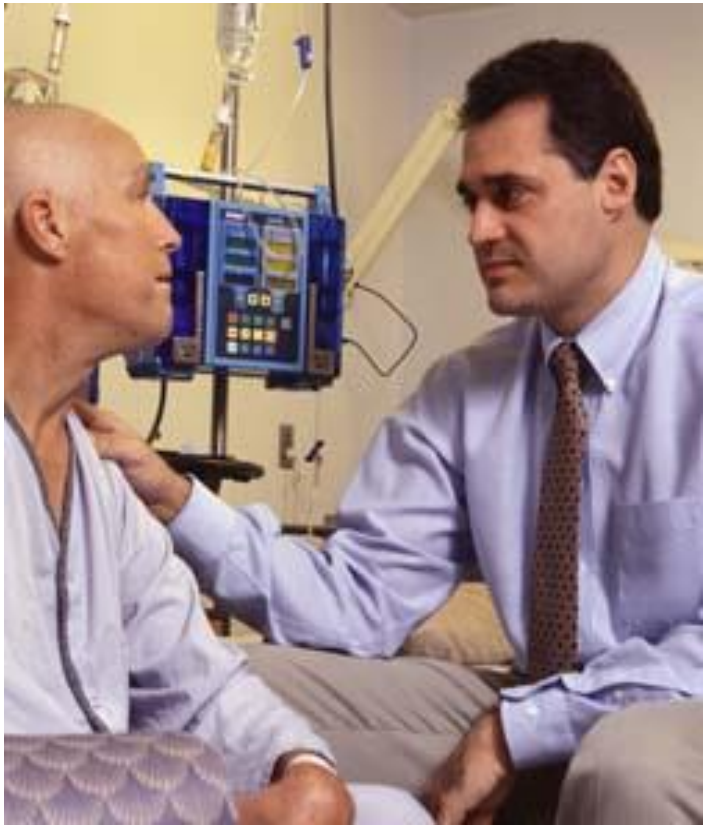
Types of Clinical Studies

- Screening and Early Detection
- Genetics
  - To understand how heritage influences the development of cancer
- Quality of Life
- Supportive Care



Types of Clinical Studies

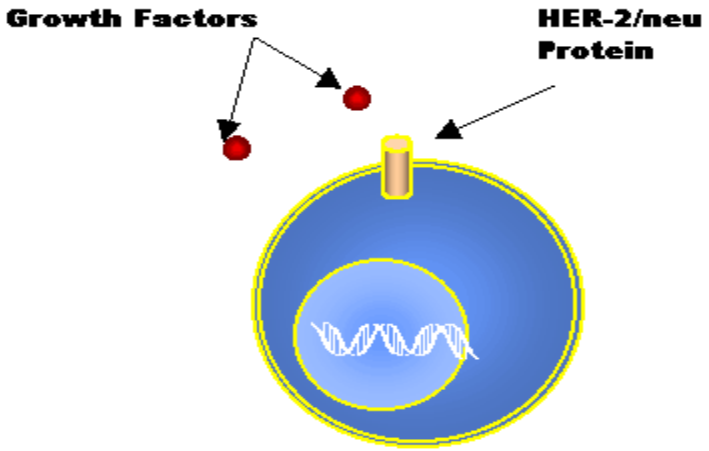
- Surgical Procedures
- Equipment
- Treatment
  - New drug testing
  - Which drug/combination of drugs are more effective

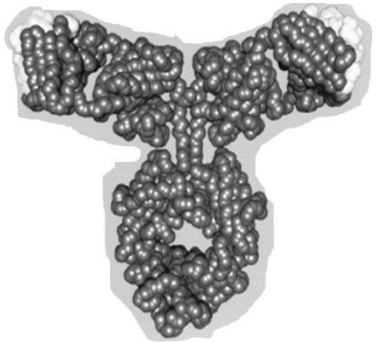


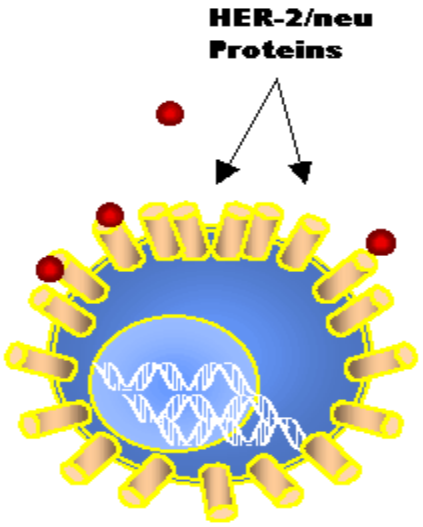
Drug Development

Preclinic Phase

- Understand the molecular basis of the disease
- Select a therapeutic target
- Link therapeutic target to a specific neoplastic event

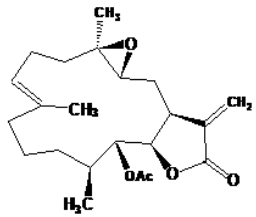






Extraction and Synthesis of New Drugs

- Extraction from plants or animal
- Synthesis



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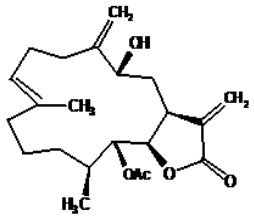
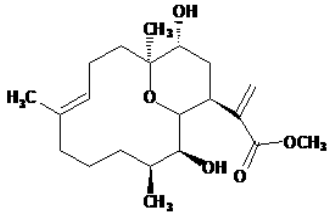
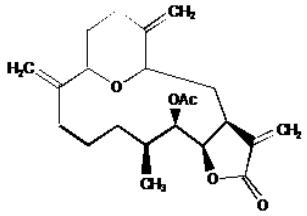


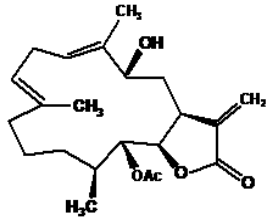
EPA-2



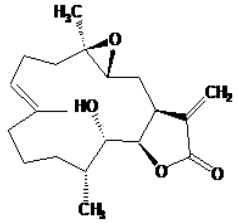
EPA-3



EPA-7



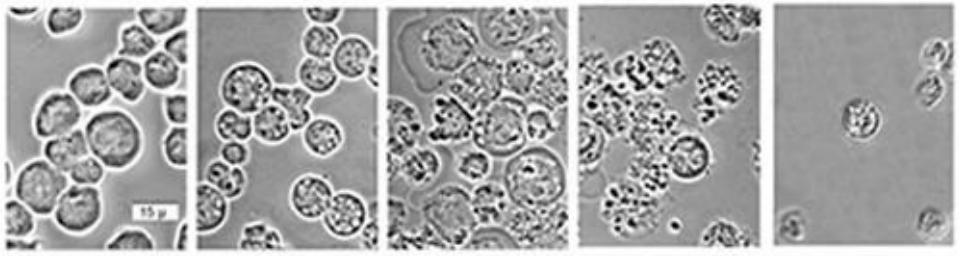
EPA-8

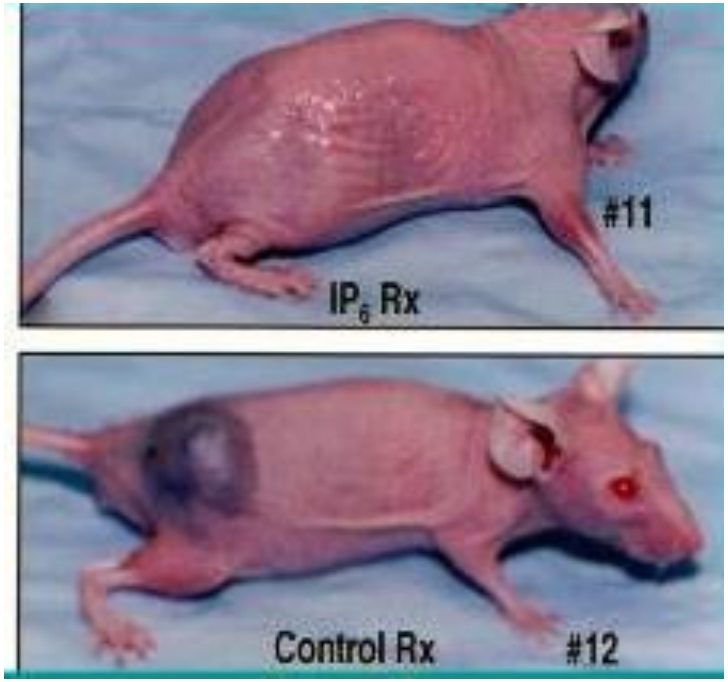


EPA-9

Screening of New Drugs

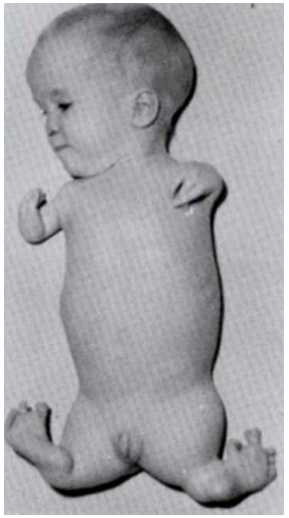
- Assessment of pharmacological and therapeutic activity
  - Cell lines culture
    - NCI Human Tumor Cell Line Panel
  - Animal Models





Use of Animals in Pre-Clinical Studies

- US Kefauver-Harris Act (1961)
  - Legislation developed as a result of the Thalidomide Experience
    - Phocomelia
  - FDA must request researchers test on the security and efficacy of new compounds



Formulation of Compounds

- Process to transform an active compound into one suitable for human use
  - Formulations
    - Liquid, tablet, capsules, creams, sprays, patchs…
  - “Excipients”
    - Improve flavor
    - Allow chemical stability
    - Manipulation of drug absorption
    - Prevention of bacterial growth
    - The effect of this excipients must be studied in the biological system

Investigational New Drug Application (IND)

- Animal Pharmacology and Toxicology Studies
- Previous experience with the drug in humans (often foreign use)
- Manufacturing Information
  - To ensure that the company can adequately produce and supply consistent batches of the drug

Investigational New Drug Application (IND)

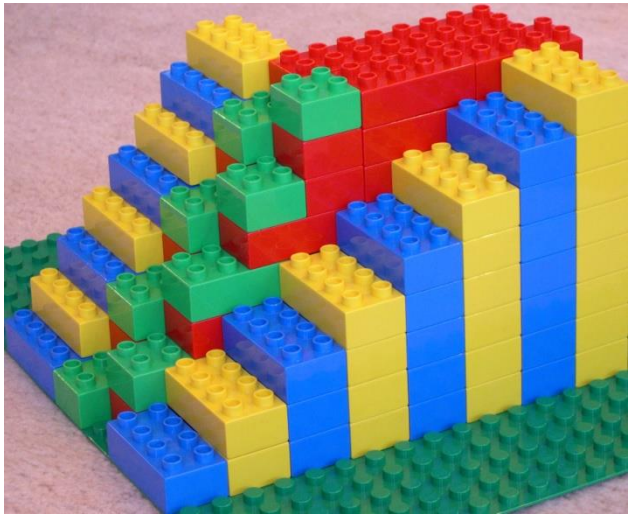
- Detailed protocols for proposed clinical studies to assess whether the initial-phase trials will expose subjects to unnecessary risks
- Information on the qualifications of clinical investigators
- Informed consent
- Review by an institutional review board (IRB)
- To adhere to the investigational new drug regulations
- Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials.

Investigator's Brochure

- Pre-Clinical Studies
  - Efficacy Models
  - Mechanistics Studies
  - Toxicologies at least in two species
  - PK and PD in animals

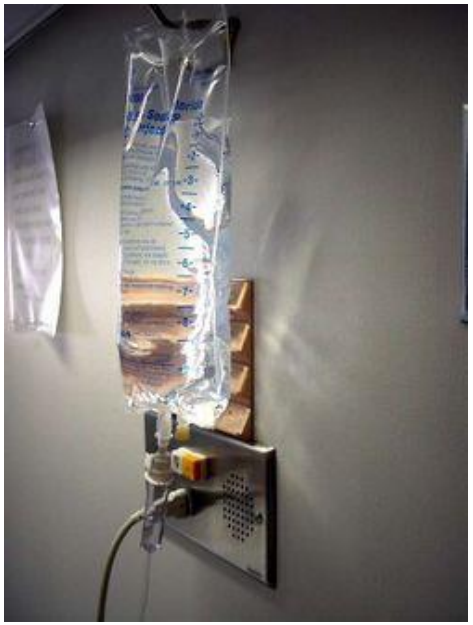
Phases of Clinical Studies

- “Steps”for the clinical development of a drug
- Each “phase” is designed to answer specific questions

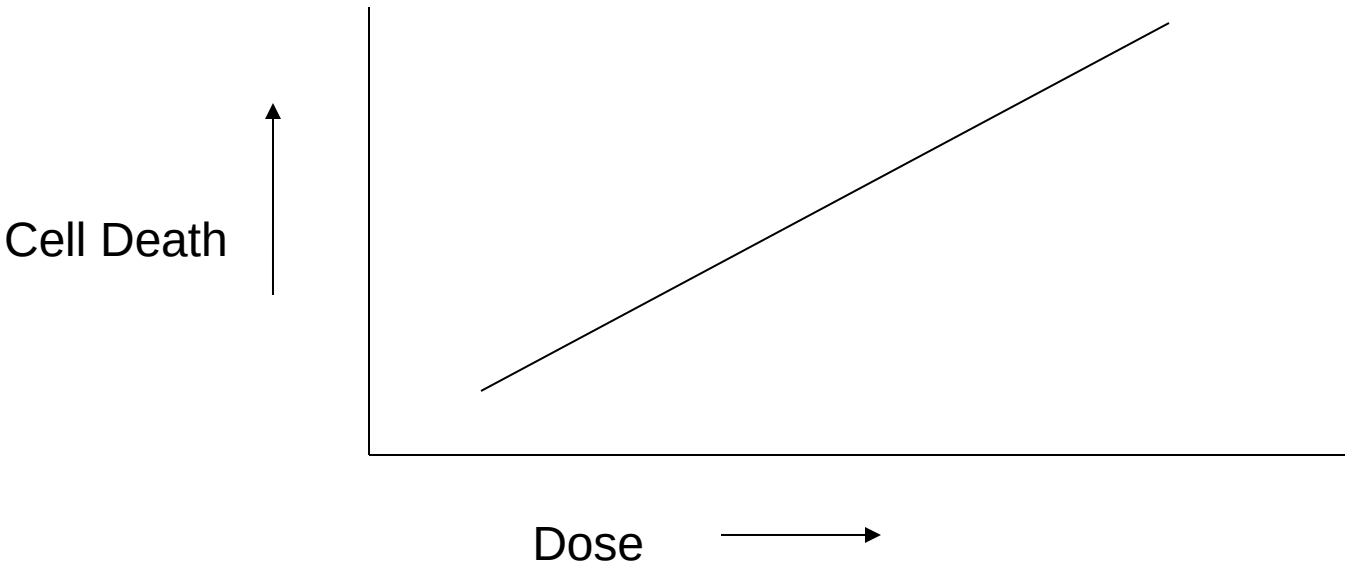


Phase I Clinical Trials

- Goals
  - Determined recommended dose for further evaluation
- Question
  - What maximum dose can be administered (PD)
  - What is pharmacokinetic behavior (PK)
- Design
  - Non-randomized
  - Dose Escalation
- Primary Endpoint
  - Toxic Effect using standard criteria



Phase I Trials
What maximum dose can be administered?



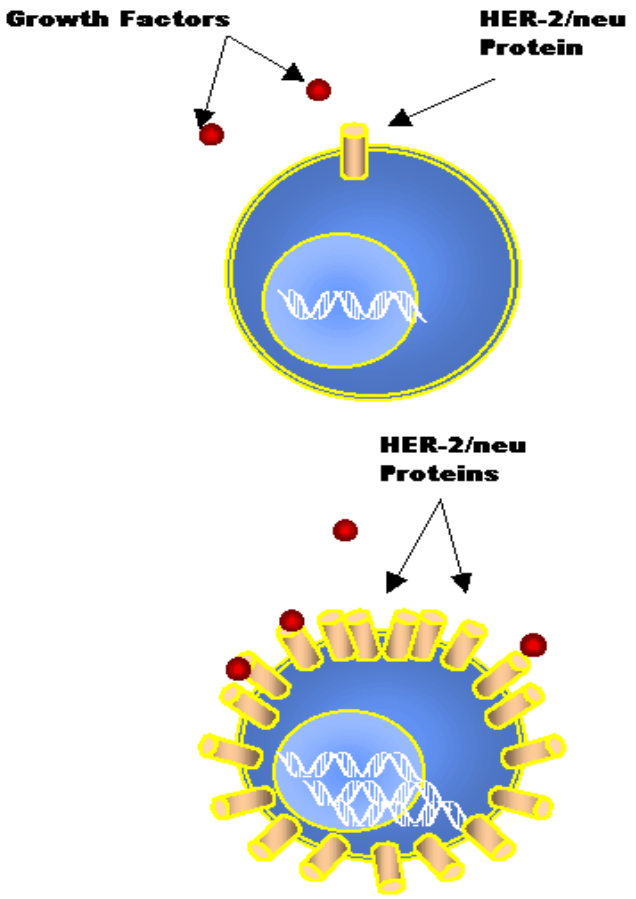
Chabner BA, Nat Rev Cancer 5:65-72

MTD (Maximum Tolerated Dose) and DLT (Dose Limiting Toxicity)

- The MTD is the highest dose that can be given with acceptable and reversible toxic effects
  - NCI CTCAE (NCI Common Terminology Criteria for Adverse Events, 2003)
    - Descriptive terminology to be used for adverse event reporting
    - Category (Broad classification of AE)
      - Adverse Event Terms
      - Grades 1-5
- Dose Limiting Toxicity (DLT)
  - Grade 3 or higher NCI CTCAE

Non-cytotoxic Drug Development

- Molecular Targeted Therapy
  - Drug design to affect specific intracellular and extracellular targets thought to be relevant to malignant transformation



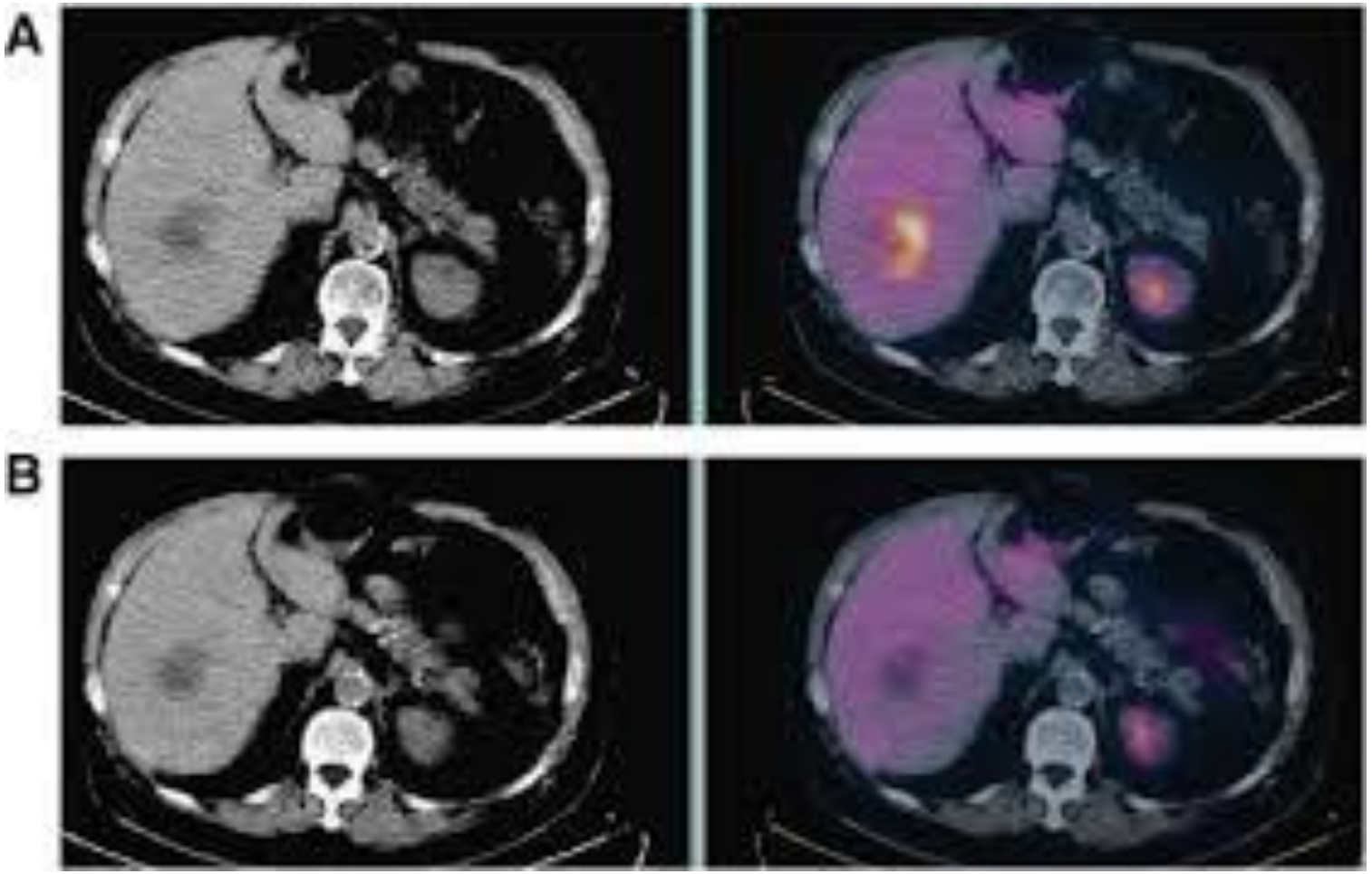
Non-cytotoxic Drug Development

- Agents devoid of traditional toxic effects
  - Is dosing to toxicity appropriate?
- May not cause tumor regression
  - RECIST (Response Evaluation Criteria in Solid Tumors)
    - http://ctep.cancer.gov/guidelines/recist.html
- May have effects only in molecularly defined populations
  - How to measure them?

Tumor “activity” rather than measurement

Baseline

Follow Up



Measure of Target Effect

- Tumor Biopsy before and after treatment
  - Does patient agrees on the biopsies?
  - Does patient have accesible tumor?
  - What if the biopsies are non-diagnostic?
- Normal Tissues to Measure Molecular effects
  - Skin
  - Peripheral blood leukocytes
  - Swab of Bucca mucosa

Patient Population

- Cancer patients for whom no curative or standard therapy remains
- Why not normal, healthy subjects?
  - Most anticancer agents have toxic effects
  - Pharmacokinetics

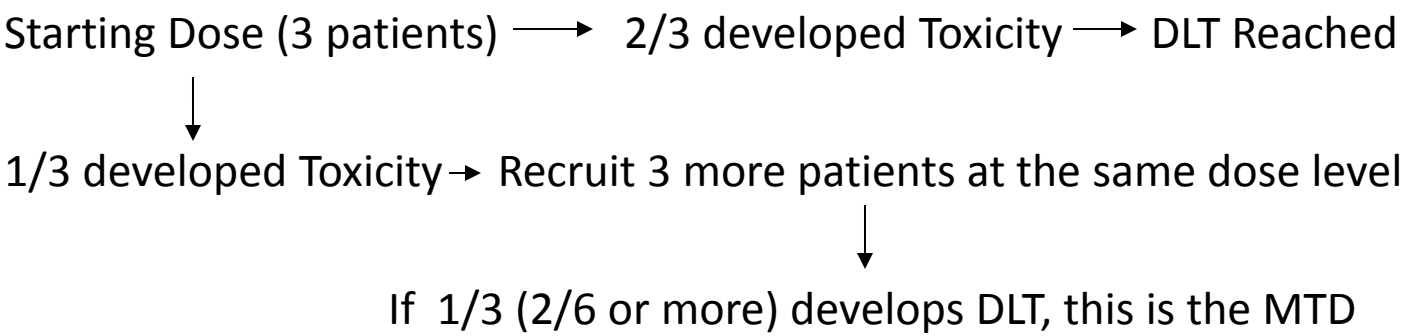
Patients / Marimastat	Healthy Patients	Cancer Patients
Dose	50-200 mg po bid	100 mg po bid
Mean Trough Plasma Level	59.4 ug/l	286.2 ug/l
Toxicity	None	Arthralgia and myalgia

Starting Dose

- Based on animal toxicology where the drug has been given in the same schedule as will be assesed in humans
  - LD10 (One tenth of the dose that causes 10% lethality in mice)

Escalation Plan

- Fibonacci Scheme
  - Cohorts of three patients are enrolled at the same dose level
    - If one of three develop toxicity, then three more are recruited at the same level

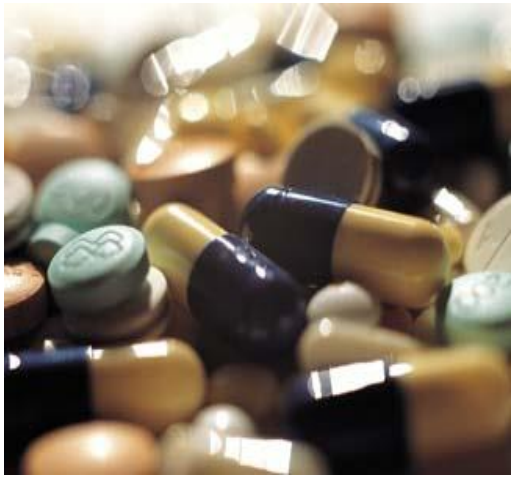


Phase II Clinical Trials

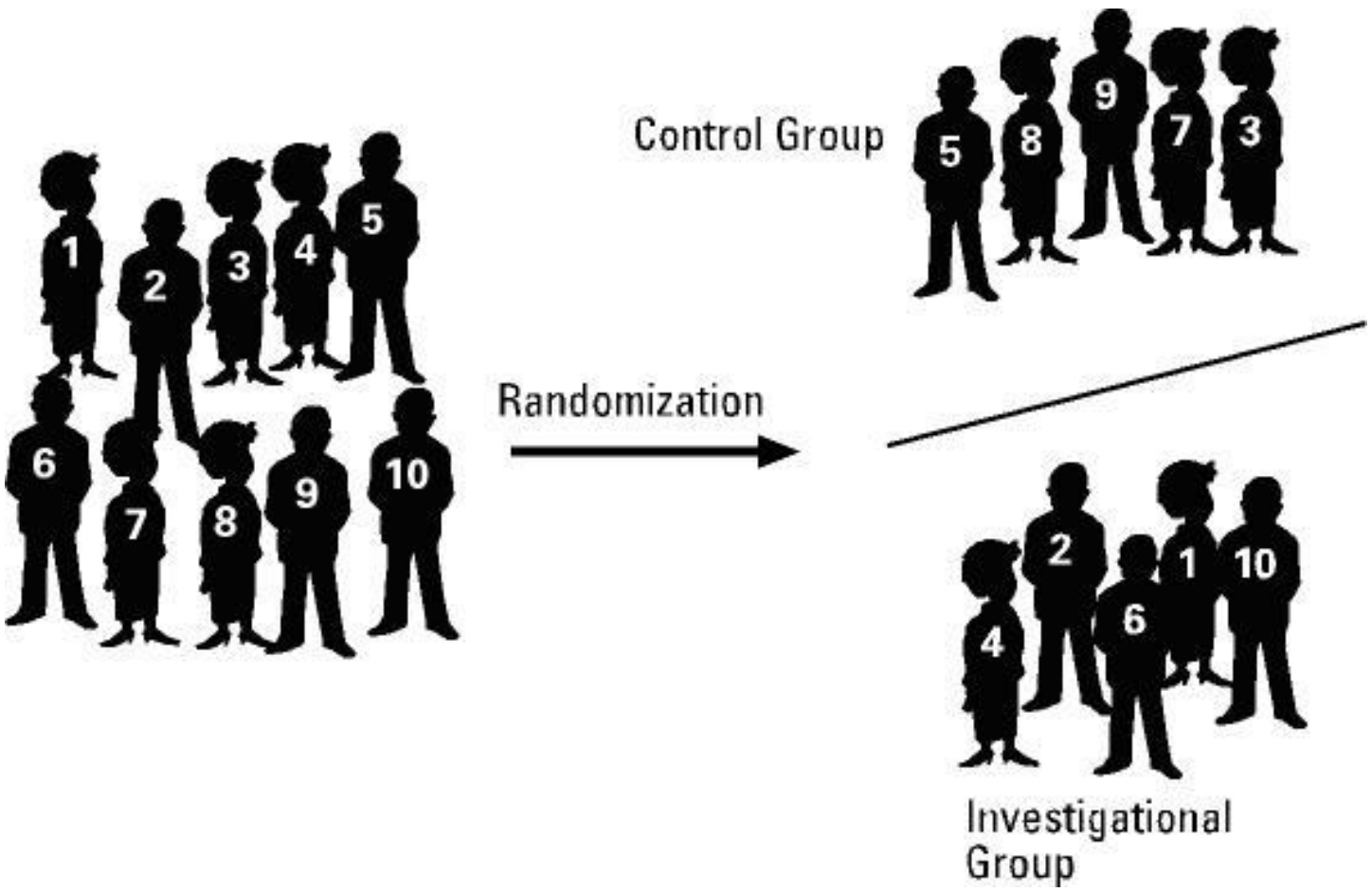
- Phase II
  - Defines the efficacy of a ddrug in a specific type of cancer
  - Evaluates short term side effects
  - Around 50-100 participants

Phase III

- Phase III
  - Comparison of a new drug or treatment against the standard of care
  - Study that usually precedes FDA approval
  - Over 100 participants



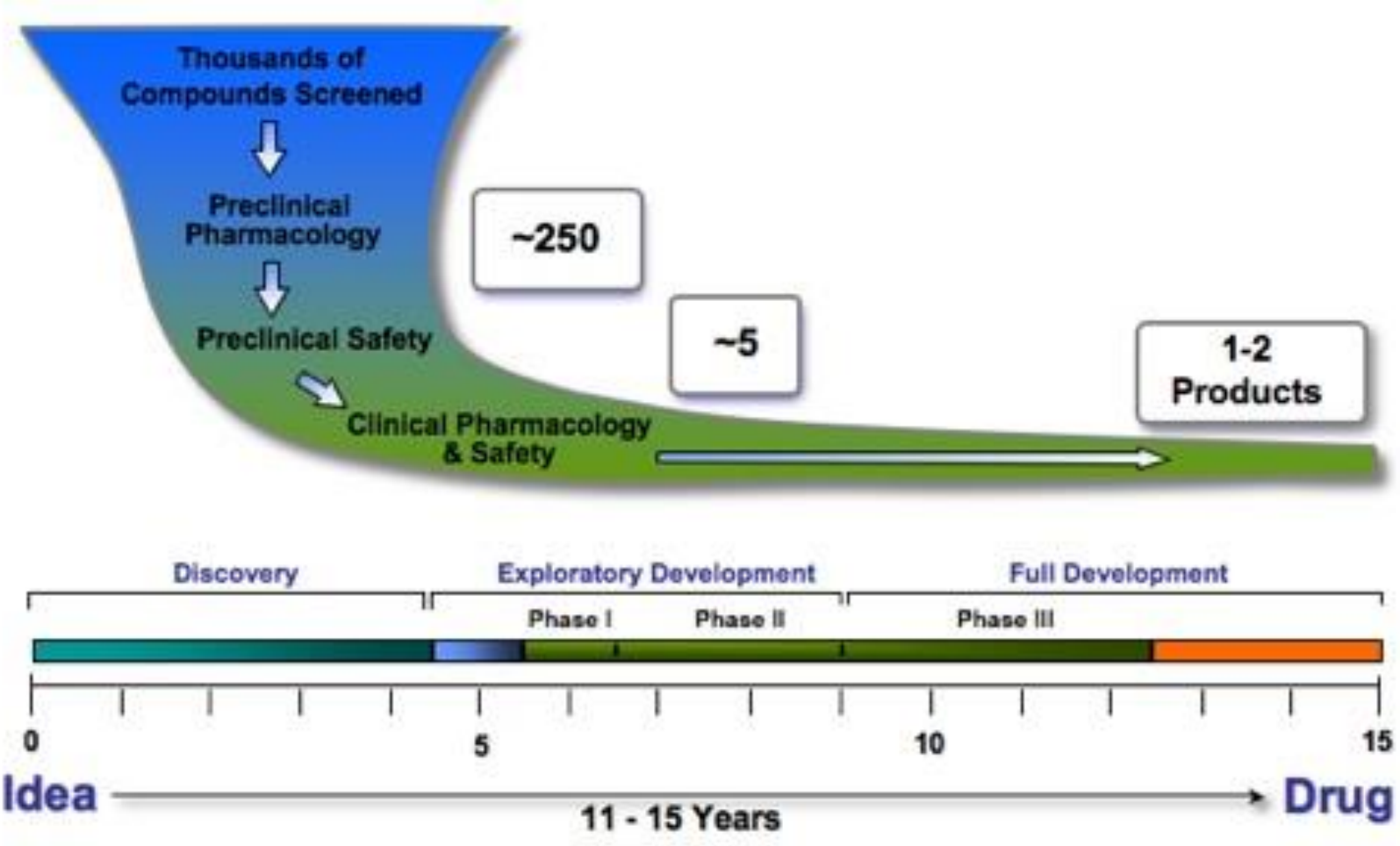
Randomization



Phase IV

- Phase IV
  - Studies performed once the drug is available for "general use"
  - This studies offer information of the efficacy and side effects of drugs in populations not included in initial studies

Clinical Studies



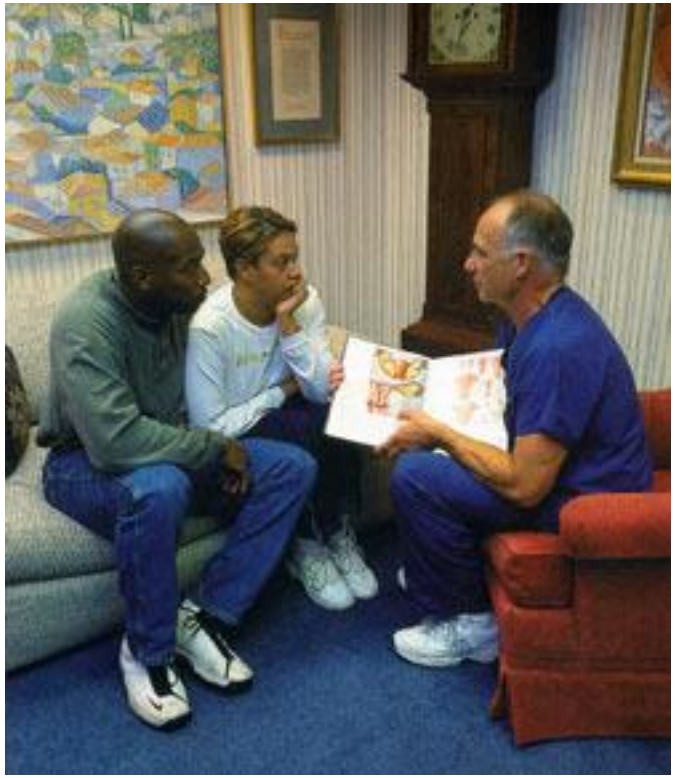
How are participants protected in clinical studies?

How are participants protected in clinical studies?

- Institutional Review Boards (IRB)
  - Health professionals and community representatives
  - Evaluate scientific merit but overall, patient safety
  - Frequently review studies and has the power to stop or allow them to continue

How are participants protected in clinical studies?

- Informed Consent
  - Purpose
  - Procedures
  - Risks and potential benefits
    - Emergency Contact Information
    - Contact for Complaints
  - Participant's Rights



Data Safety Monitoring Board

- Independent group of experts that periodically evaluate the progress of a clinical study
  - Adverse event evaluation
  - Clinical efficacy evaluation
  - Recommends whether the study must continue or being stopped

Clinical Trial Database

National Institute of Health

www.clinicaltrials.gov


ClinicalTrials.gov
A service of the U.S. National Institutes of Health
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Search
ClinicalTrials.gov is a registry of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov gives you information about a trial's purpose, who may participate, locations, and phone numbers for more details. This information should be used in conjunction with advice from health care professionals. Read more...
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Get instructions for clinical trial investigators/sponsors on how to register trials in ClinicalTrials.gov.
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Learn about clinical trials and how to use ClinicalTrials.gov, or access other consumer health information from the US National Institutes of Health.
Background Information:
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What's New
Glossary
Study Topics:
List by Condition
List by Drug Intervention
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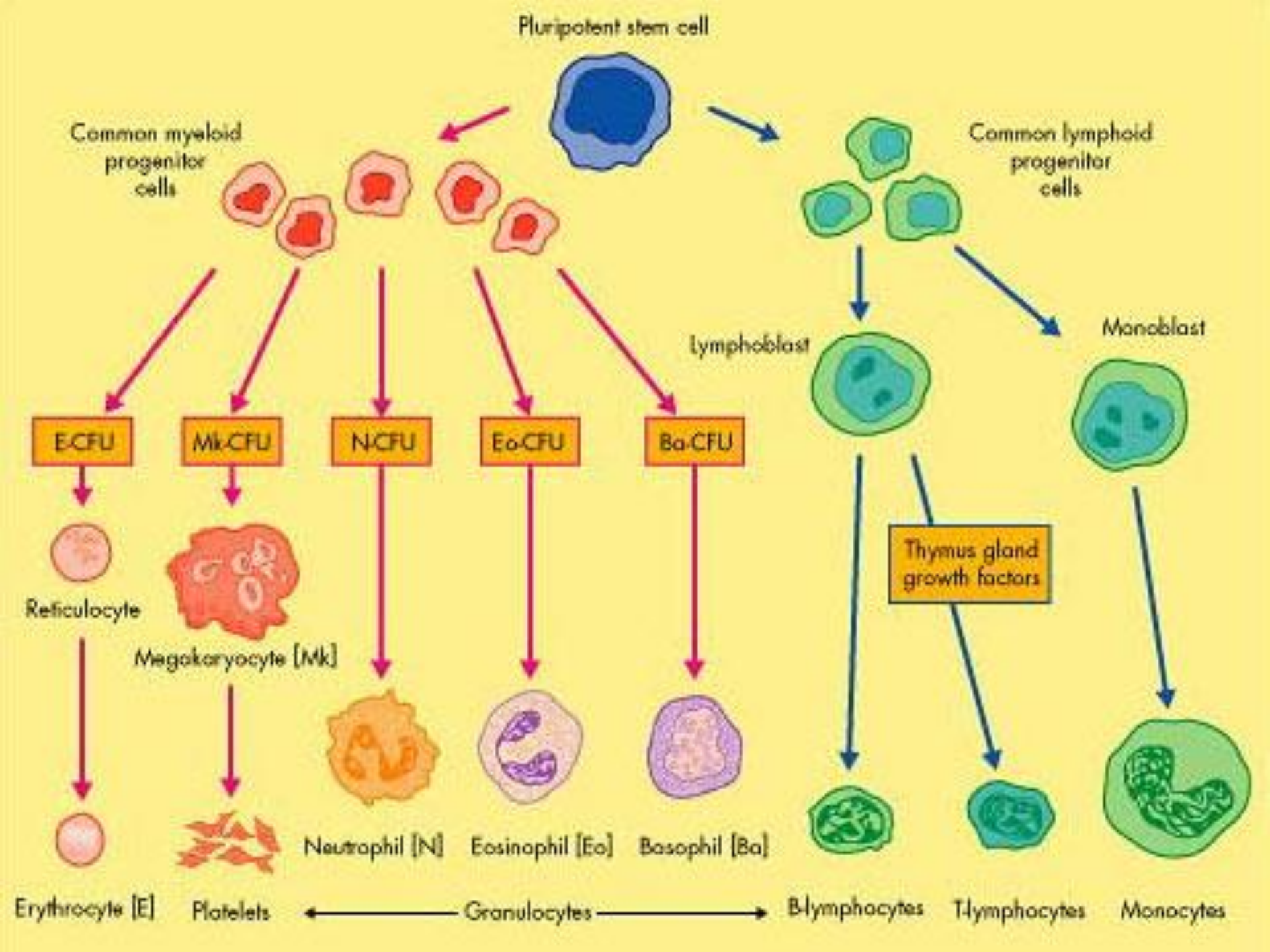
USA.gov, Copyright, Privacy, Accessibility, Freedom of Information Act

Hematopoiesis and Leukemia

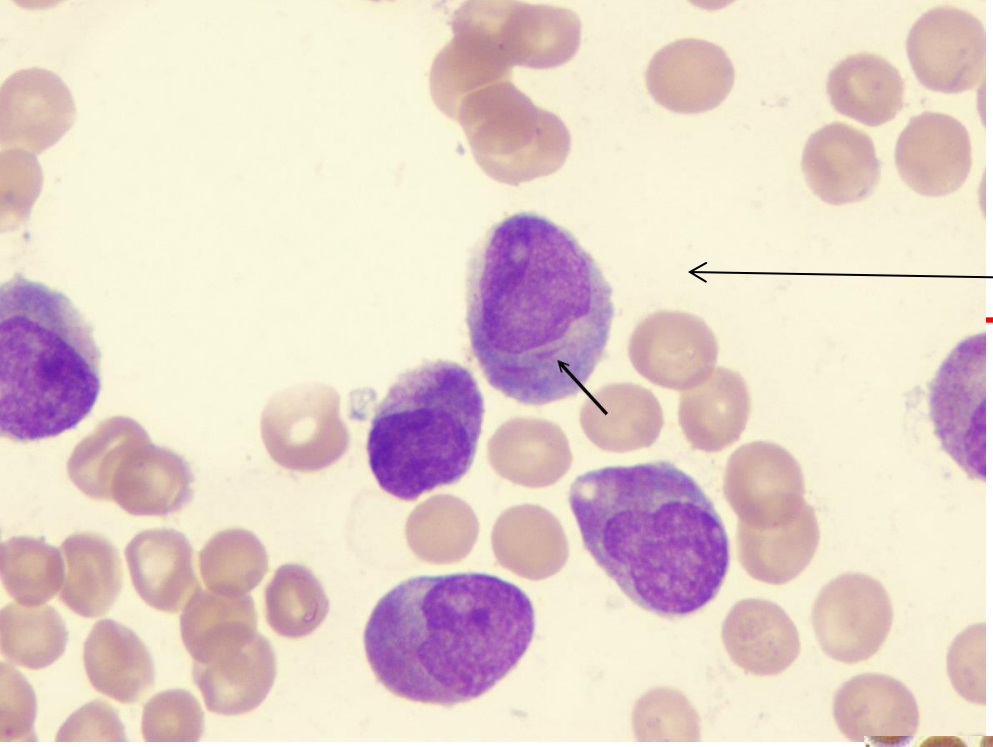
Hematopoiesis

- The production of all types of blood cells generated by a self-regulated system that is responsive to the demands put on it such as infections, allergic reactions, etc.
- All types of blood cells are derived from primitive stem cells
  - Undifferentiated precursor cells which give rise to the mature differentiated cells of the tissue
  - Properties of Stem Cells
    - capable of self-renewing
    - can give rise to specialized cell types (multipotency)
    - Small quiescent cells


Pluripotent stem cell
Common myeloid progenitor cells
Common lymphoid progenitor cells
E-CFU
Mk-CFU
N-CFU
Eo-CFU
Ba-CFU
Lymphoblast
Monoblast
Thymus gland growth factors
Reticulocyte
Megakaryocyte [Mk]
Neutrophil [N]
Eosinophil [Eo]
Basophil [Ba]
Erythrocyte [E]
Platelets
Granulocytes
B-lymphocytes
T-lymphocytes
Monocytes

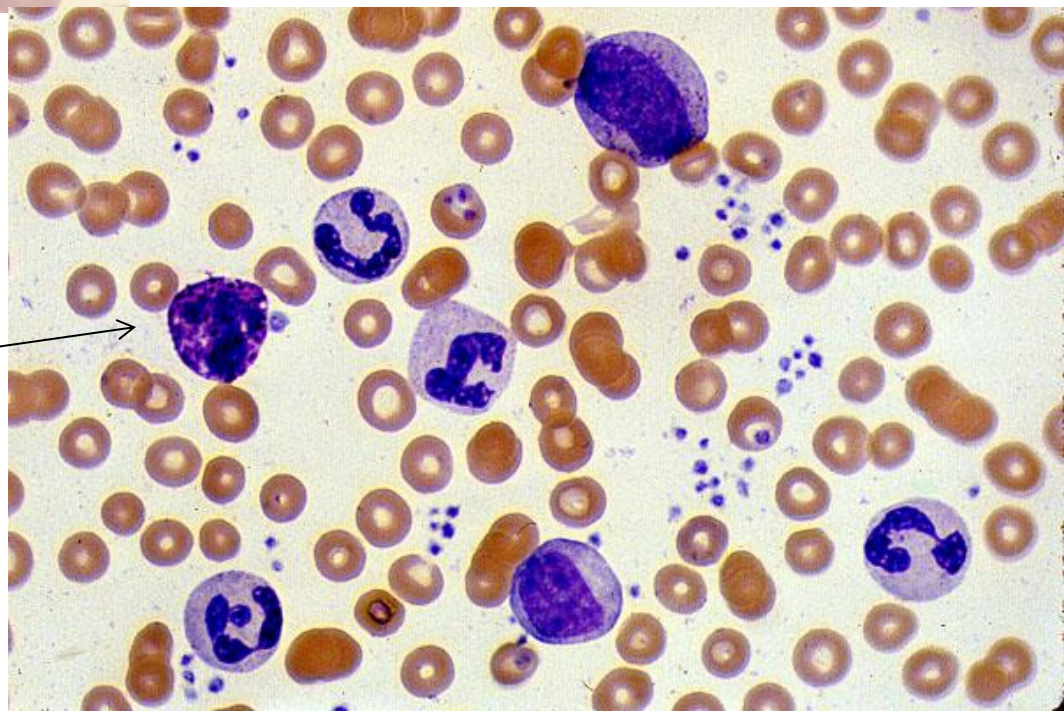
Acute vs Chronic

- Acute leukemias
  - Block in differentiation resulting in a massive accumulation of immature cells (blasts) in the bone marrow or other organs
- Chronic Leukemias
  - Unregulated proliferation or disordered programmed cell death (apoptosis), resulting in a marked accumulation of a spectrum of differentiated cells



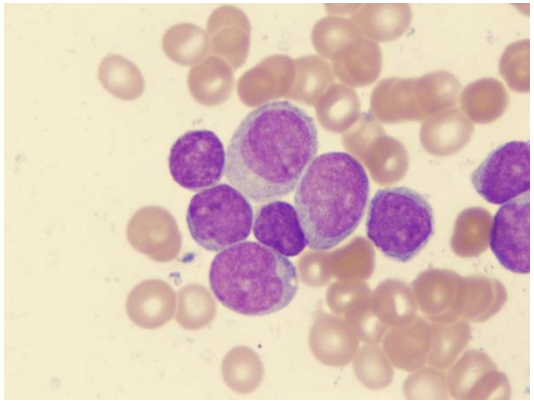
Acute Myelogenous Leukemia

Chronic Myelogenous Leukemia

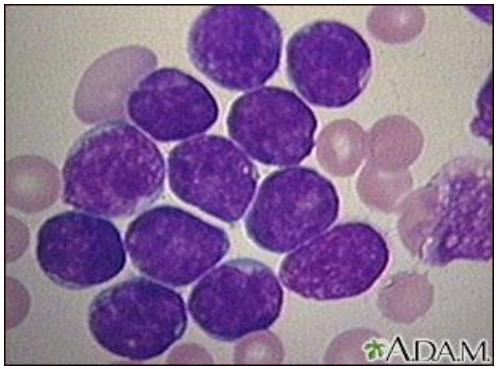


Myelogenous vs Lymphocytic

- Acute Myeloid Leukemia
  - Involves myeloid precursors
  - Median age: 65 years



- Acute Lymphocytic Leukemia
  - Involves cells of lymphoid lineage
  - 80% of ALL is seen in children
  - Median age: 10 years

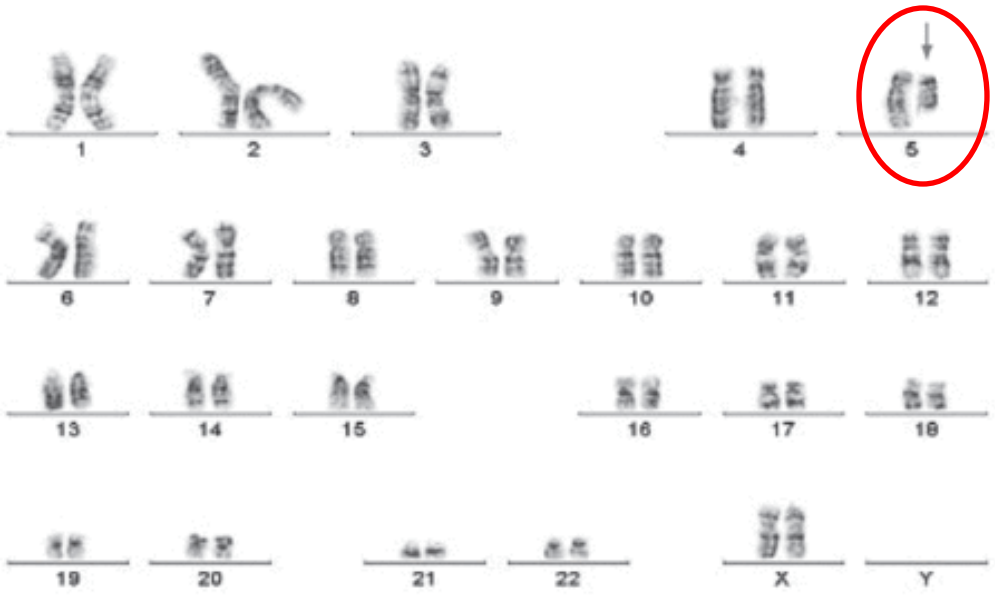


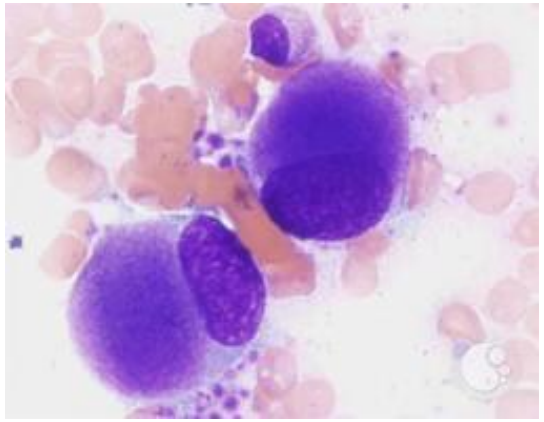
Cytogenetics

- Study of normal and abnormal chromosomes
  - Examination of chromosome structure
    - Deletions, additions, translocations, inversion, trisomies
  - Relationships between chromosome structure and phenotype
    - Translocation (8;14) → Burkitt's Lymphoma

Chromosome Structure

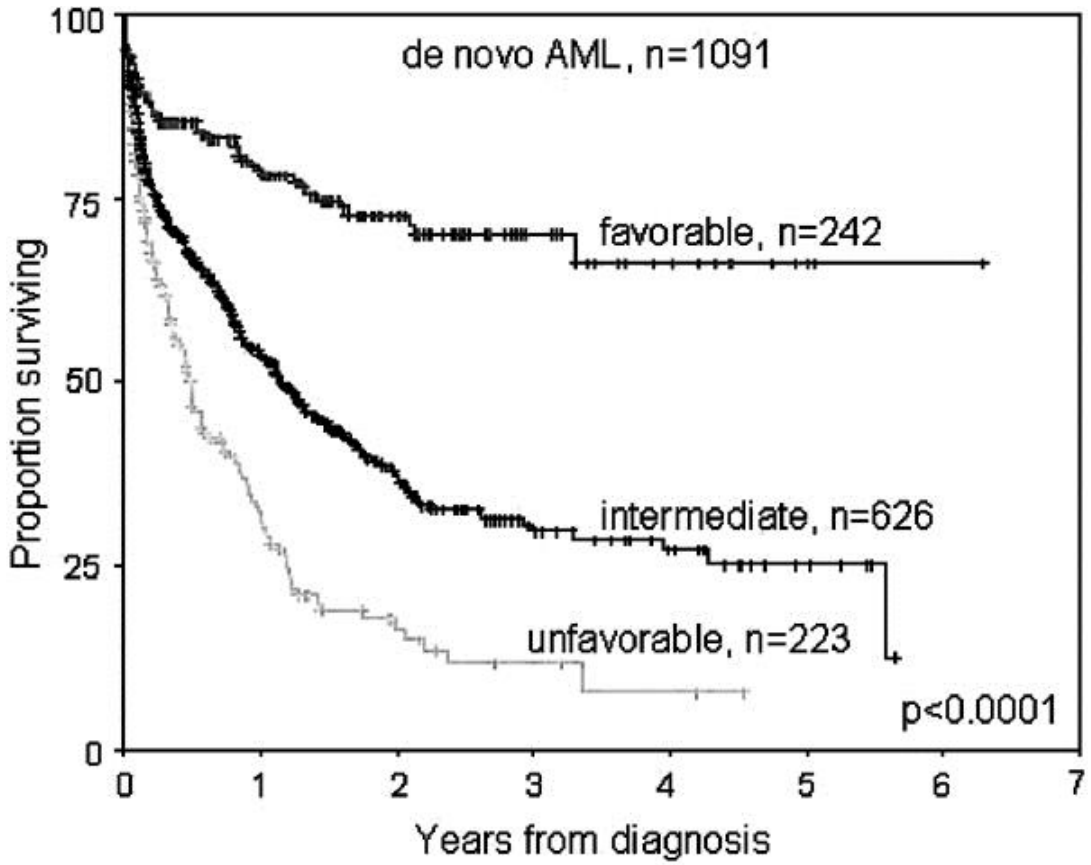
Myelodysplastic Syndrome with Isolated 5q deletion





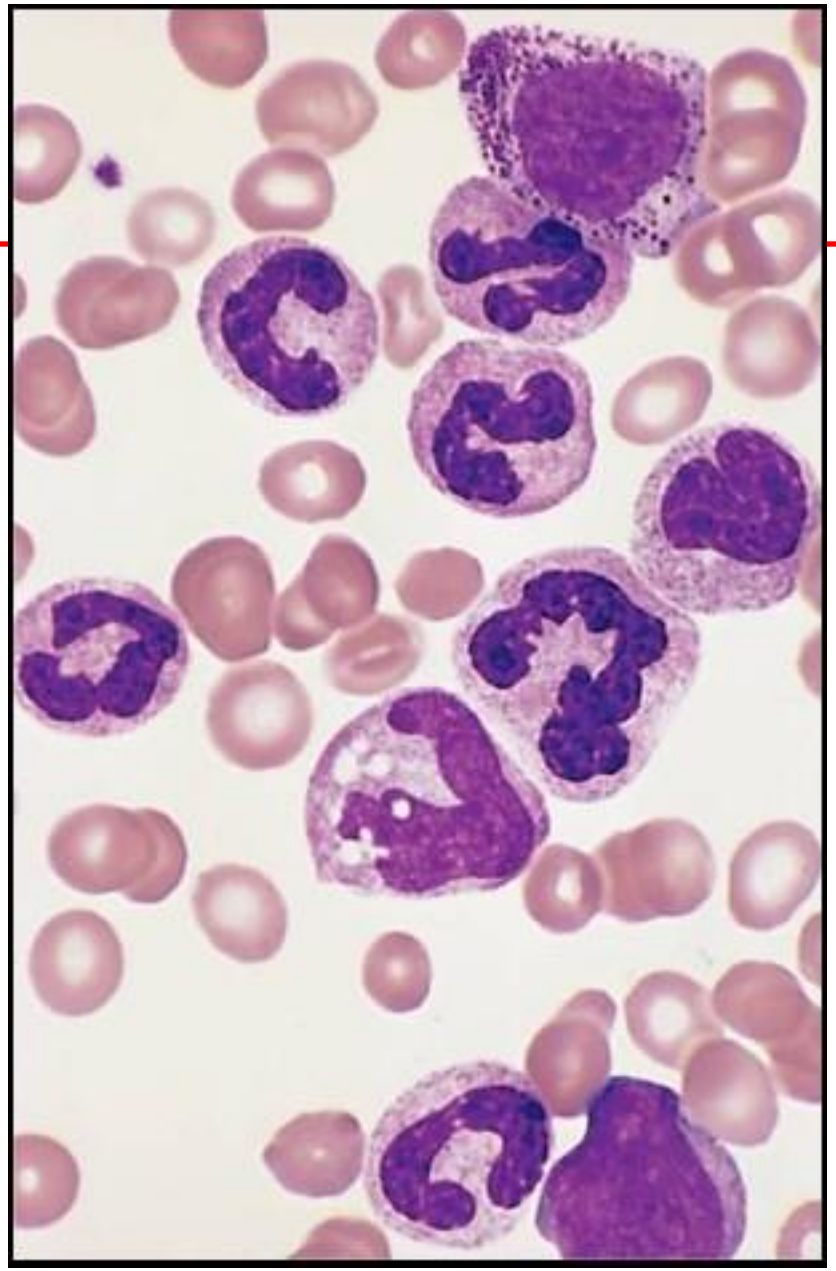
Cytogenetics Risk Groups in Acute Myelogenous Leukemia

- Favorable (low risk)
  - Inv/del 16
  - t (15; 17)
  - t (8:21)
- Intermediate Risk
  - Diploid (normal)
  - Trisomy 8
  - Trisomy 6
  - -Y
- Unfavorable (high risk)
  - Deletion 5
  - Deletion 7
  - t (9; 22)



Schoch S et. al. *Leukemia* (2004) 18:20–125

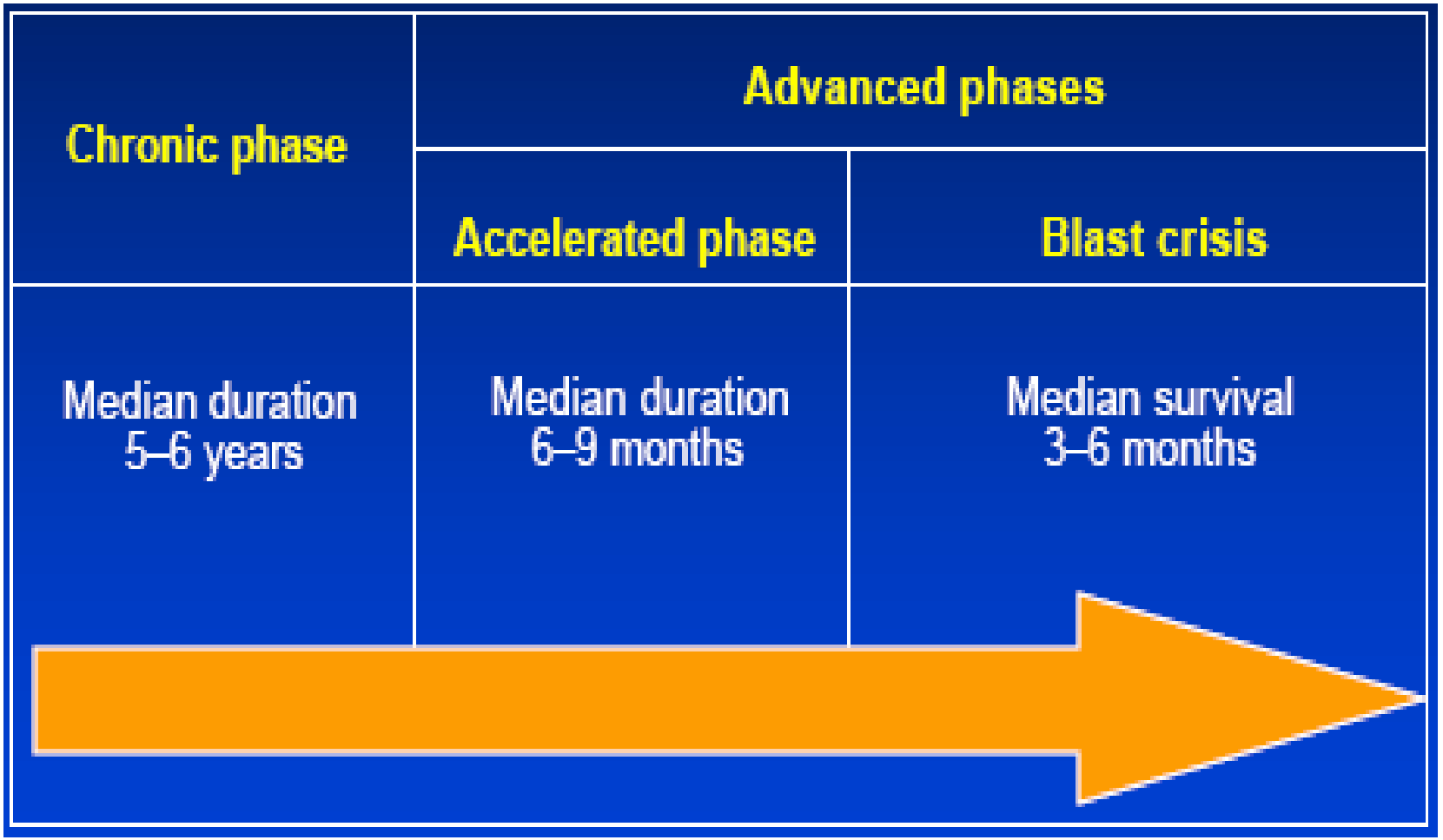
Chronic Myelogenous Leukemia



Chronic Myelogenous Leukemia (CML)

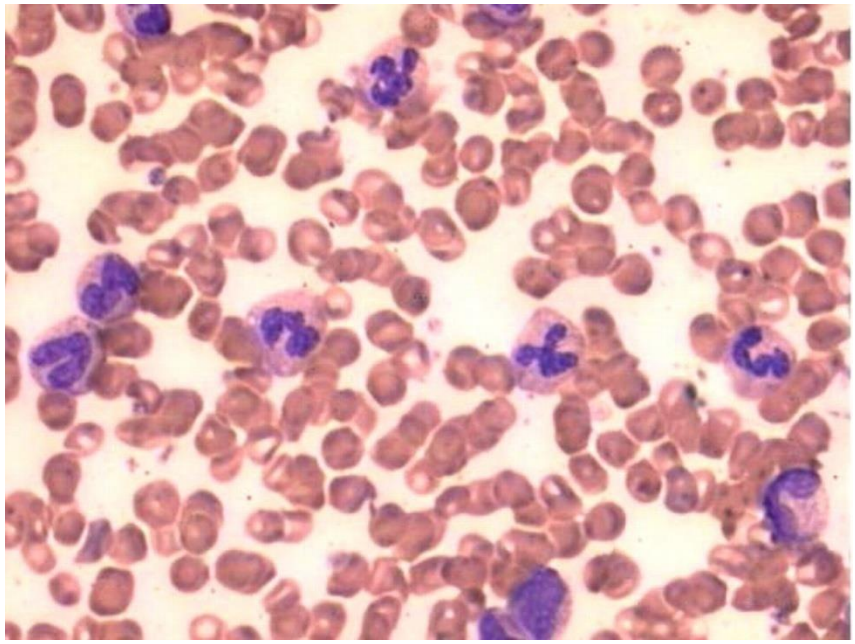
- Clonal myeloproliferative disorder resulting from the neoplastic transformation of the primitive hematopoietic stem cell
  - Affects myeloid, monocytic, erythroid and megakaryocytic cell lineage
  - 15% of all cases of leukemia in adults
  - Median age at diagnosis: 67 years

CML Natural History



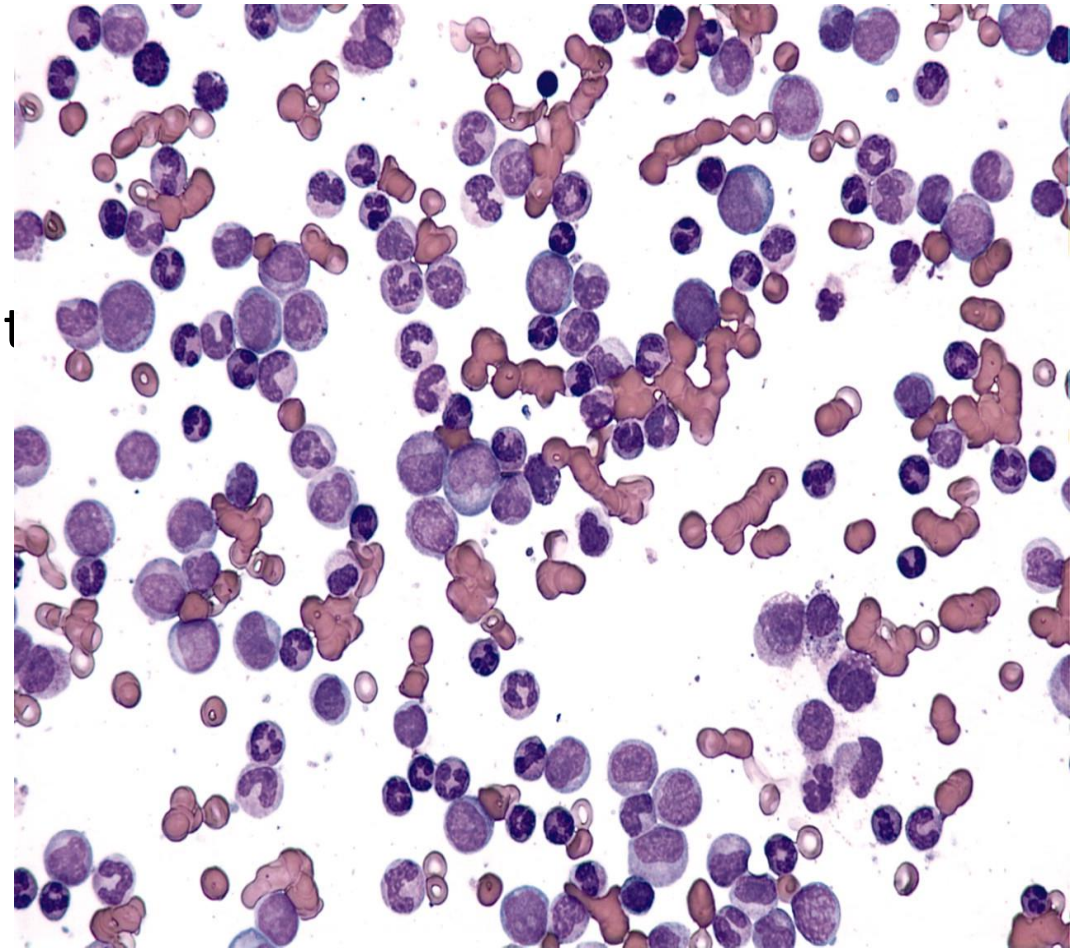
CML: Signs and Symptoms

- Chronic Phase
  - Median survival 5-6 years
  - Asymptomatic in 15-40% of patients
  - Fatigue, LUQ pain
  - Hepatomegaly (10-50%)
  - Splenomegaly (30-70%)
  - No increased risk of infections



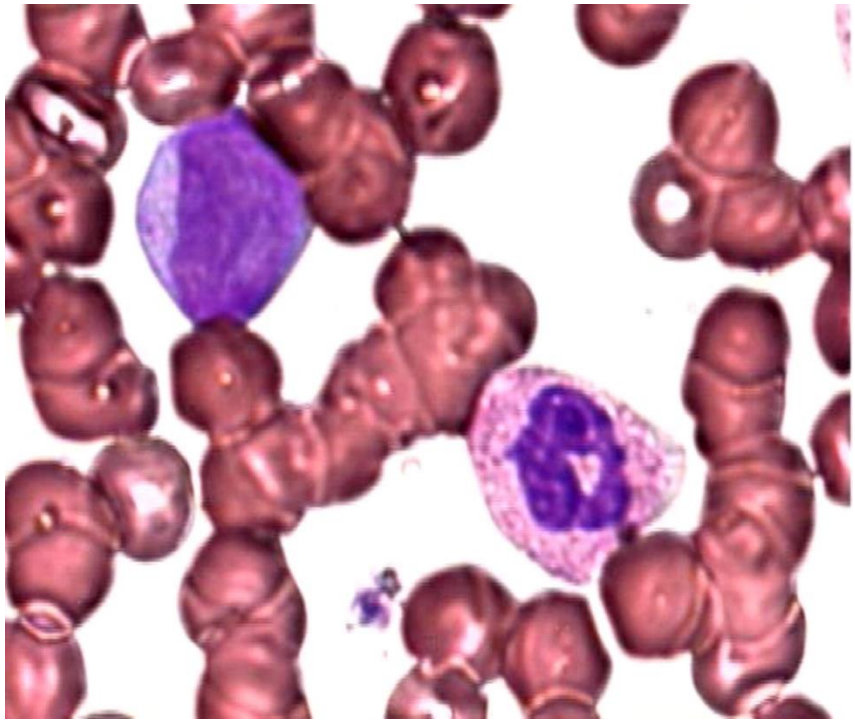
CML: Signs and Symptoms

- Accelerated Phase
  - Median survival < 18 months
  - Fever, night sweats, weight loss, progressive splenomegaly
  - >15% blasts or
  - >30% blasts and promyelocytes
  - >20% basophils



CML: Signs and Symptoms

- Blastic Phase
  - Resembles acute leukemia with >30% blasts
  - Survival 3-6 months
  - Extramedullary deposits of leukemic cells (CNS, lymph nodes, skin)



Treatment

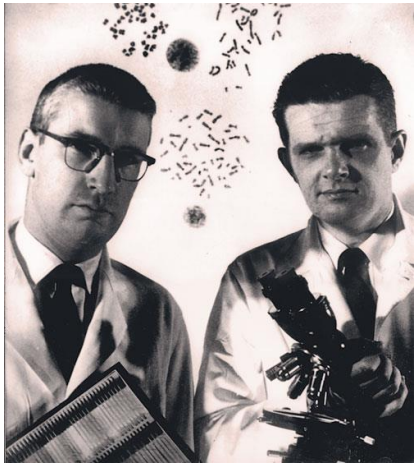
- Busulfan
  - Hematologic control in 50-80% of patients
  - Lung, bone marrow and heart fibrosis
  - Addison-like disease
  - Prolongued myelosupression
- Hydroxyurea
  - Hematologic control in 50-80% of patients
  - No reduction in the cells bearing the Ph Chromosome

Treatment

- Interferon
  - Induces hematologic response in 70-80% of patients
  - Cytogenetic response seen in 40-60% of patients
  - Side effects
    - Flu-like syndrome, fatigue and insomnia
    - Depression
    - Weight loss
    - Alopecia
    - Reduced libido and impotence

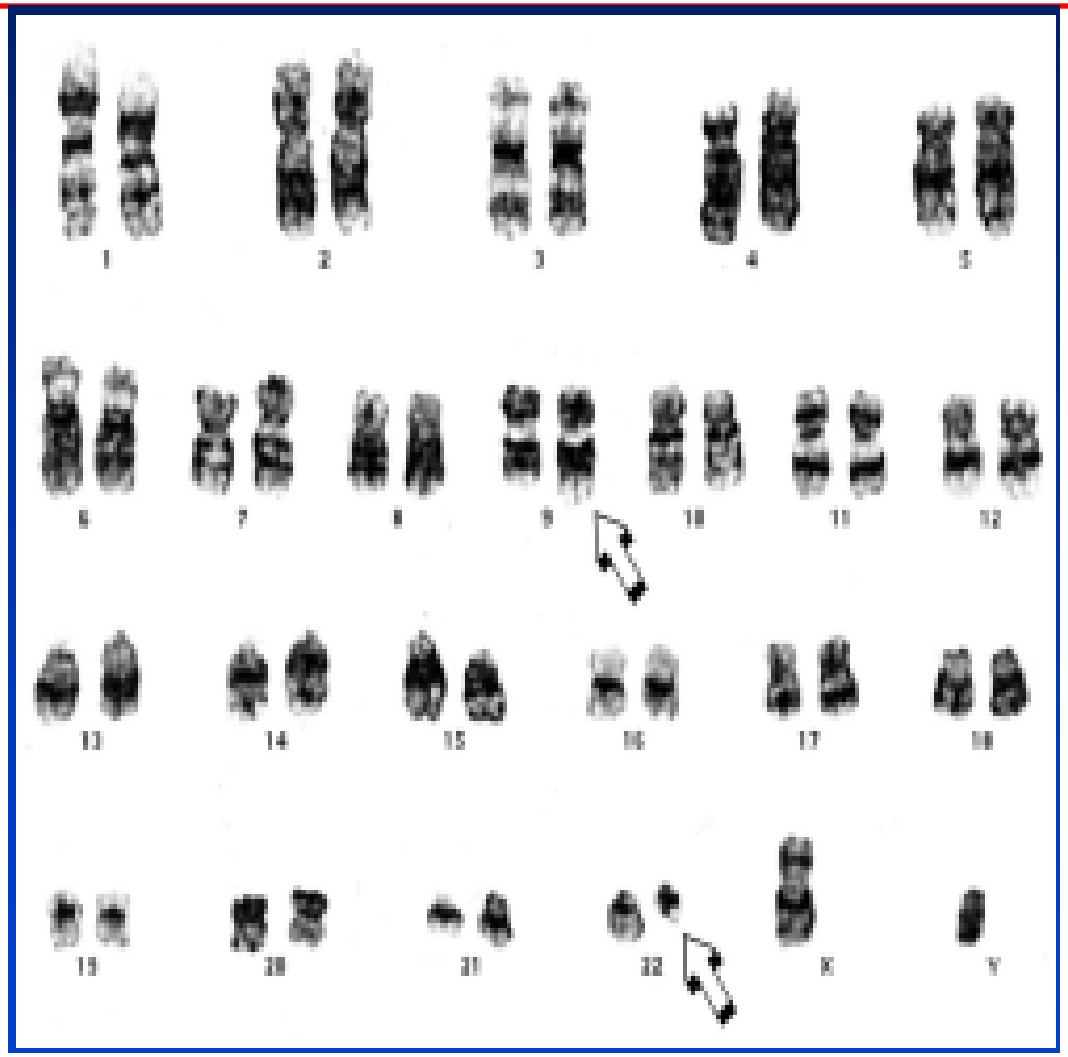
CML Pathogenesis

- 1960: Philadelphia Chromosome (shortened version of chromosome 22, Peter Nowell and David Hungerford)



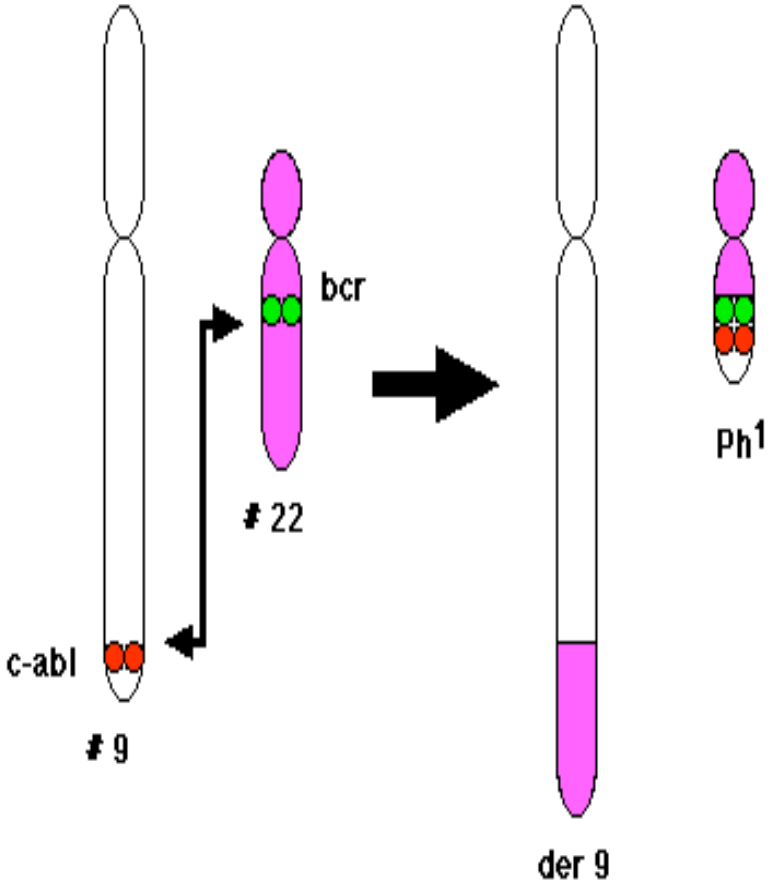
- 1973: translocation between chromosomes 9 and 22 is described (Janet Rowley)

CML Pathogenesis

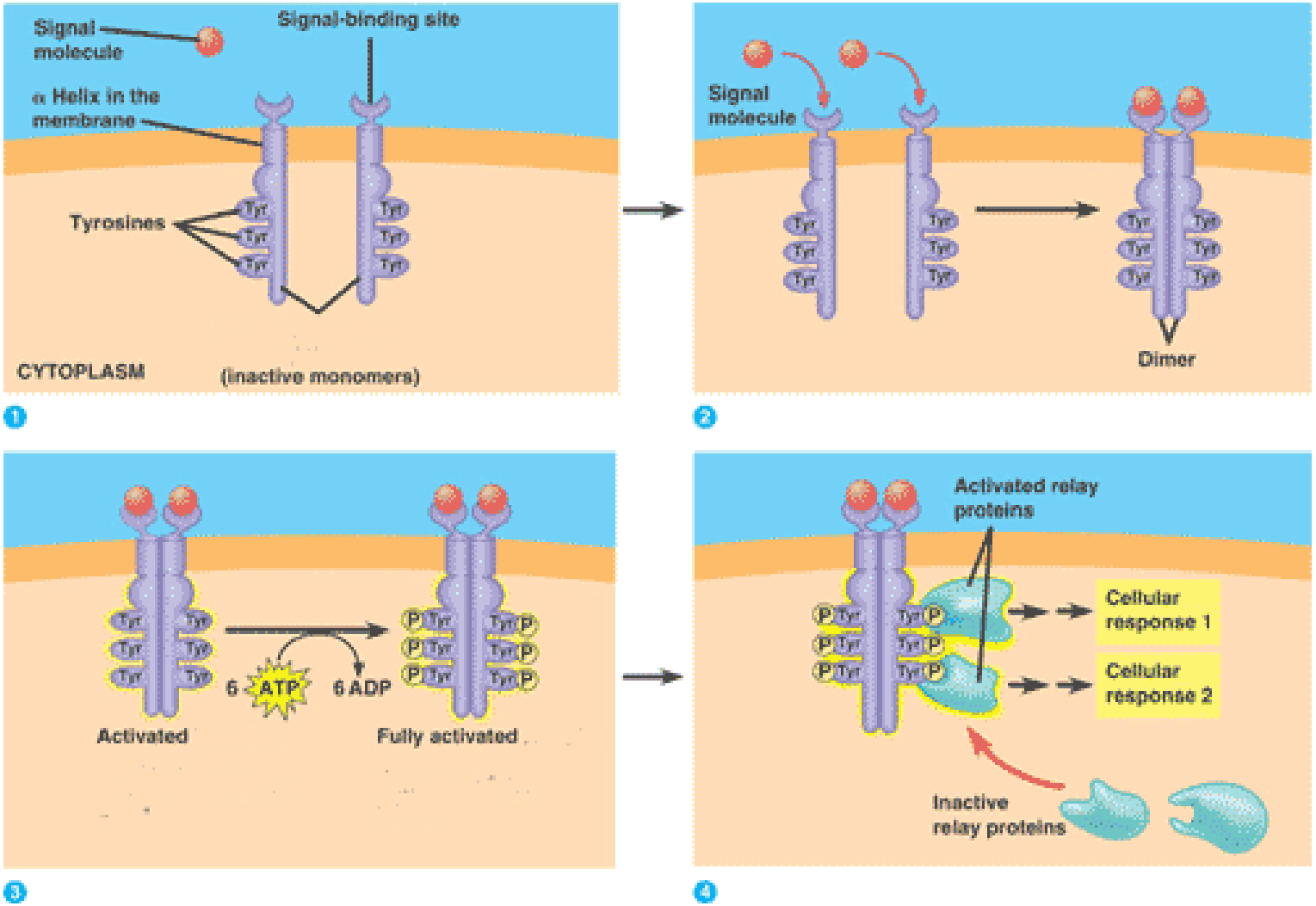


CML: Pathogenesis

- BCR-ABL is the protein produced by the fusion of BCR gene (chromosome 22) and ABL (chromosome 9)
  - Tyrosine kinase
  - Upon phosphorylation it can activate several intracellular pathways which leads to activation of mitogenic signals and inhibition of apoptosis



How does a Tyrosine Kinase works?

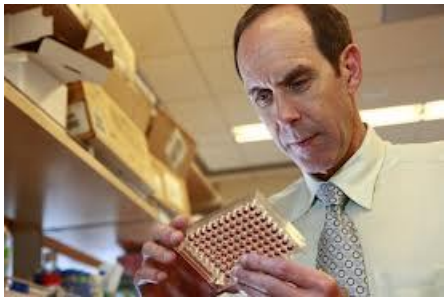


BCR-ABL Pre-Clinical Data

- In vitro studies demonstrate that Bcr-Abl has anti-apoptotic activity and renders leukemic cells resistant to chemotherapy.
- Inhibition of Bcr-Abl expression by antisense oligonucleotides reverses the suppression of apoptosis and makes CML cells susceptible to apoptosis by antileukemic drugs

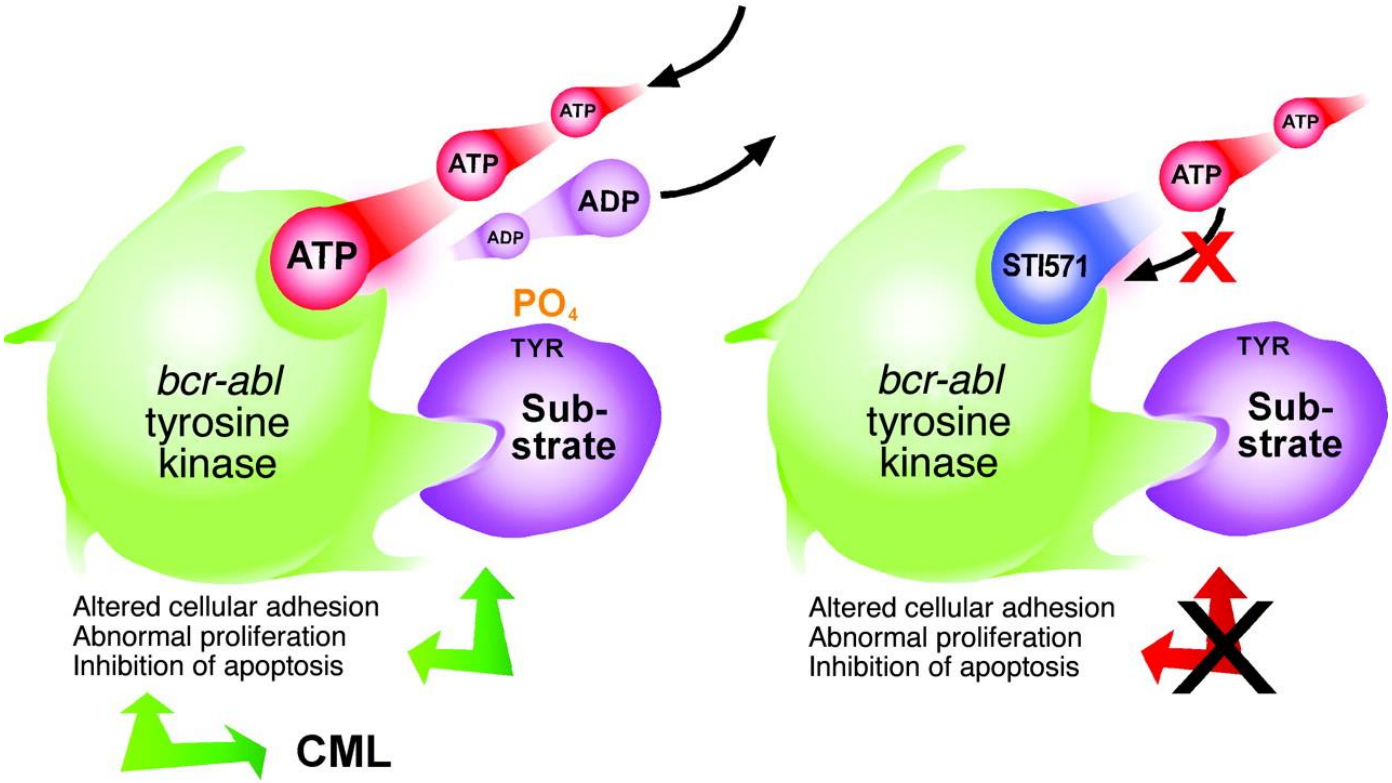
BCR-ABL Pre-Clinical Data

- In the late 1990s a biochemist Nicholas Lydon, (Ciba-Geygi) and oncologist Brian Druker (Oregon Health and Science University), screened chemical libraries to find a drug that would inhibit BCR-ABL
- They identified 2-phenylaminopyrimidine
- This lead compound was then tested and chemically modified to give it enhanced binding properties, resulting in imatinib (STI-571).



Imatinib Mesylate

- Inhibitor of tyrosine kinases



Phase I Study: Gleevec® Achieves Hematologic and Cytogenetic Responses

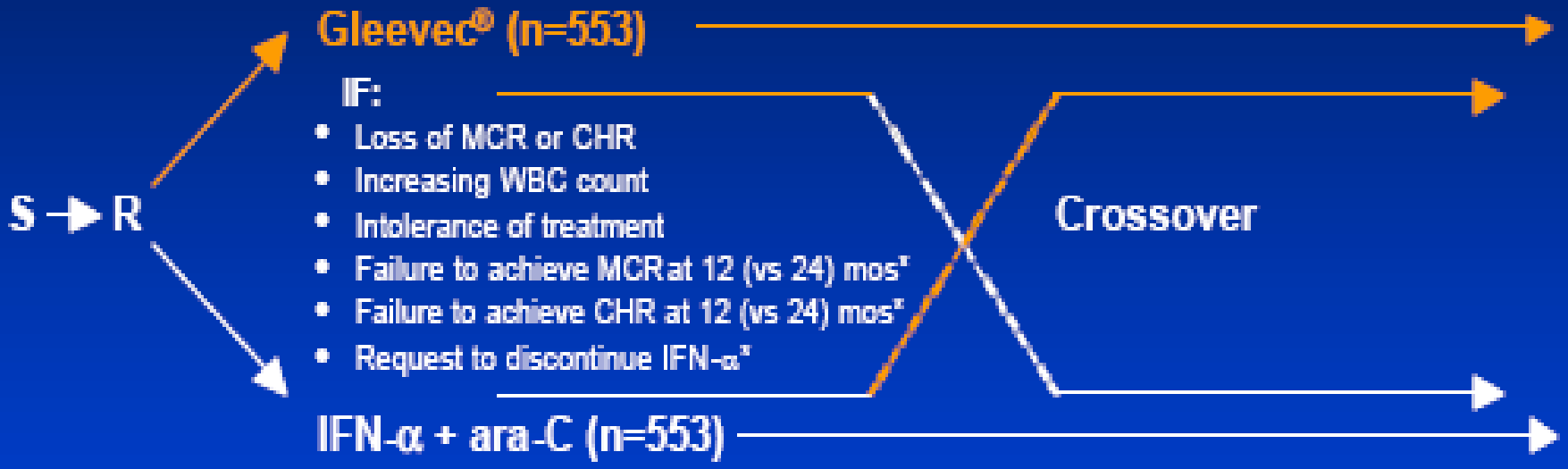
	Chronic Phase IFN-α Failure 300–1000mg/day (n=54)	Blast Crisis, Myeloid 300–1000mg/day (n=38)	Blast Crisis, Lymphoid 300–1000mg/day (n=20)
Hematologic response	100%	55%	70%
Complete	98%	11%	20%
Cytogenetic response			
Major	31%	11%	15%
Complete	13%	8%	10%

- Typically 4 weeks to achieve CHR, 2 to 10 months to achieve MCR
- A maximal tolerated dose (MTD) was not reached (up to 1000mg/day)

Druker BJ et al. *N Engl J Med.* 2001;344:1031-1037.
Druker BJ et al. *N Engl J Med.* 2001;344:1038-1042.

IRIS: The Largest Phase III CML Study to Date

1106 patients enrolled from June 2000 to January 2001

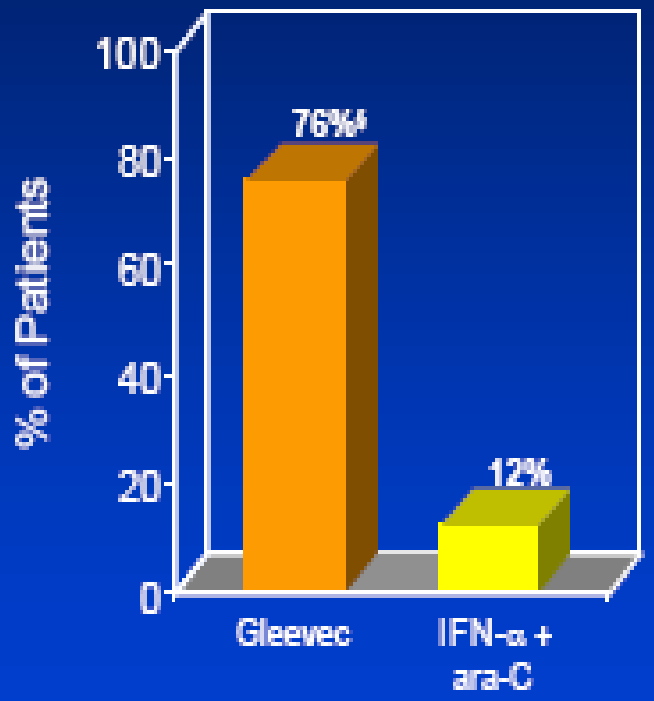


S = screening.
R = randomization.

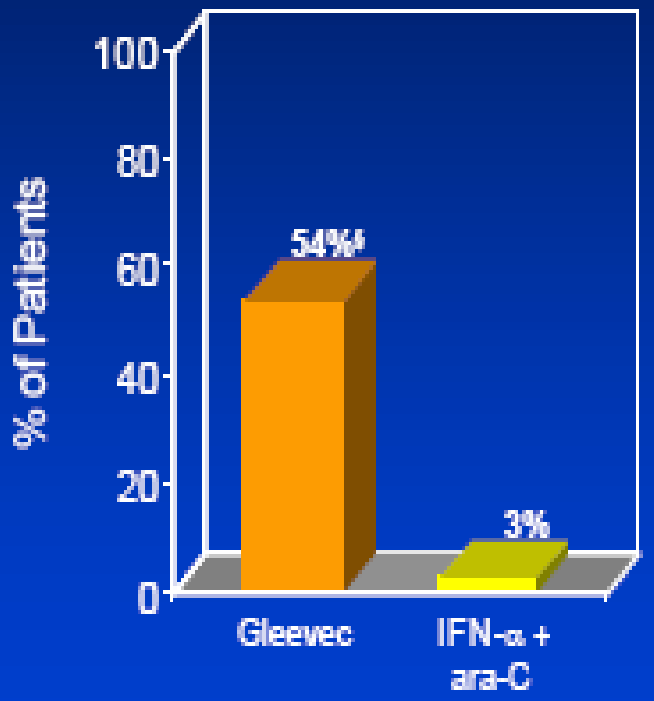
*Independent Data Monitoring Board recommended protocol amendment.

Higher Cytogenetic Response Rates With Gleevec®*

Major Cytogenetic Response†



Complete Cytogenetic Response‡



*IRIS Study; n=553 in each arm.

†≤35% Ph+ cells.

‡0% Ph+ cells.

For important safety information, please see slide 3 or full Prescribing Information.

§P<0.001. Confirmed responses shown.

Unconfirmed MCR—Gleevec: 83%; IFN-α + ara-C: 20%.

Unconfirmed CCR—Gleevec: 68%; IFN-α + ara-C: 7%.

More Patients Remain on Gleevec® Therapy

	Gleevec n=553	IFN-α + ara-C n=553
All Crossovers	**1% (n=7)**	**39% (n=218)**
Intolerance	<1%	23%
No CHR at 6 months	0%	7%
Increasing WBC count	<1%	5%
Loss of CHR	0%	4%
Loss of MCR	<1%	<1%
All Discontinuations	**9% (n=51)**	**31% (n=170)**
Withdrawal of consent	2%	13%
Adverse events	2%	6%
Progression to accelerated phase or blast crisis	1.5%	5%
All other causes	3.5%	7%
Remained on originally assigned treatment	**90% (n=495)**	**30% (n=165)**

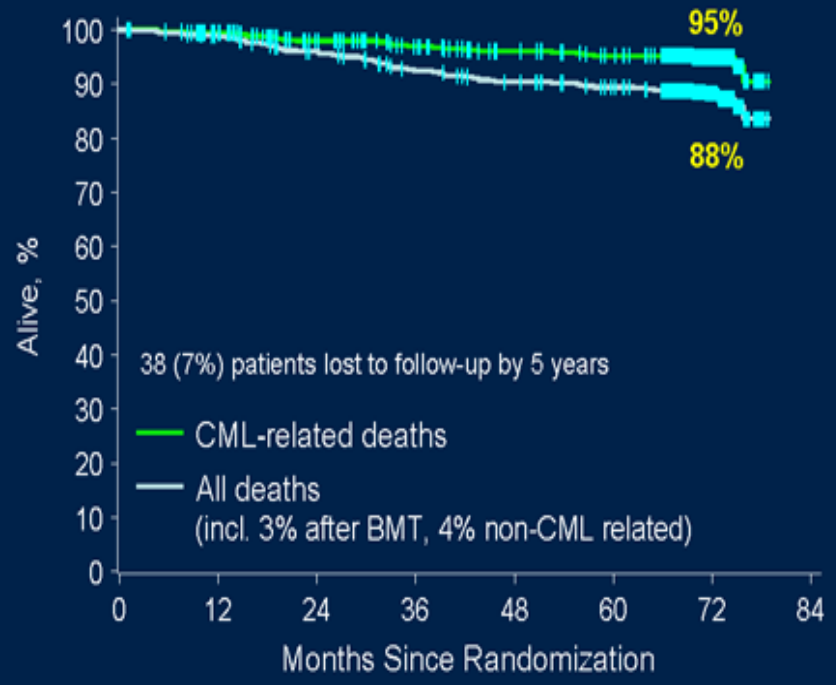
Most Non-Hematologic Adverse Events Less Common With Gleevec®*

Event	All Grades (%)		Grades 3/4 (%)	
	Gleevec n=551†	IFN-α + ara-C n=533†	Gleevec n=551†	IFN-α + ara-C n=533†
Superficial edema	53	9	<1	<1
Nausea	43	61	<1	5
Muscle cramps	35	10	1	<1
Musculoskeletal pain	34	41	3	8
Rash	32	25	2	2
Fatigue	31	65	1	24
Diarrhea	30	41	1	3
Headache	29	42	<1	3
Joint pain	27	38	2	7

*IRIS study; most common adverse events, listed by incidence with Gleevec (≥25%, regardless of causality).
†All patients who received at least 1 dose of study drug.

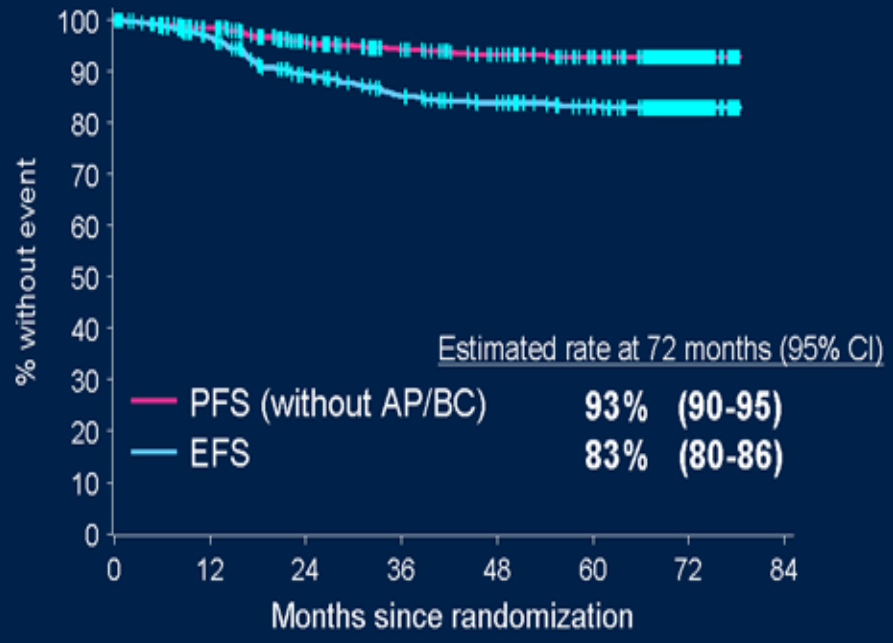
Frontline Therapy in Chronic Phase CML

IRIS 6-Year Update: Overall Survival (ITT Principle)



Hochhaus A, Druker B, Larson R, et al. Blood (ASH Annual Meeting Abstracts), Nov 2007; 110: 25.

IRIS 6-Year Update: Event-Free and Progression-Free Survival



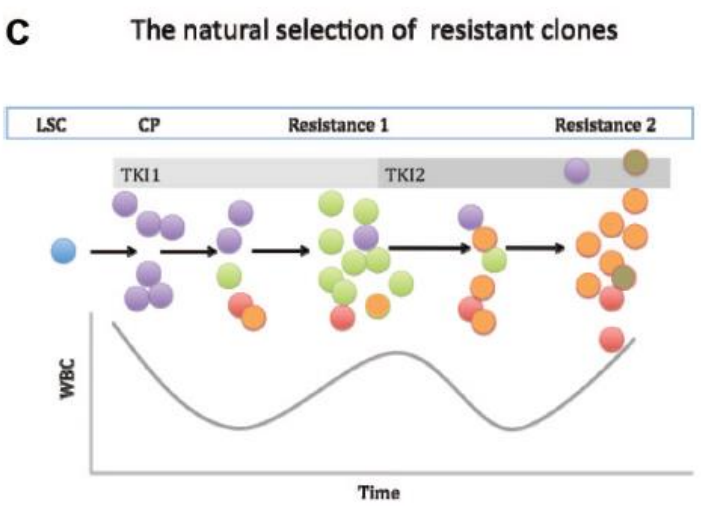
Hochhaus A, O'Brien S, Guilhot F, et al., Leukemia (2009) 23, 1054–1061.

Chronic Myelogenous Leukemia

May 2001

Mechanisms of Resistance to Imatinib

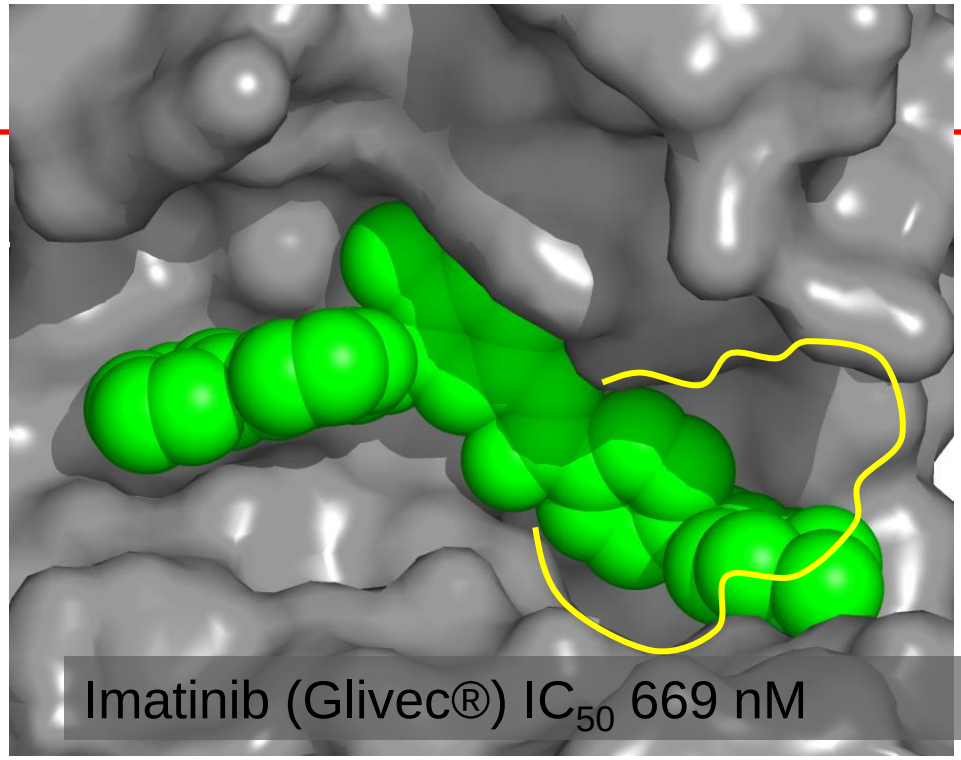
- Bcr-abl gene amplification
- Overexpression of multidrug resistance p-glycoprotein leading to drug efflux
- Mutations in the tyrosine kinase phosphorylation pocket

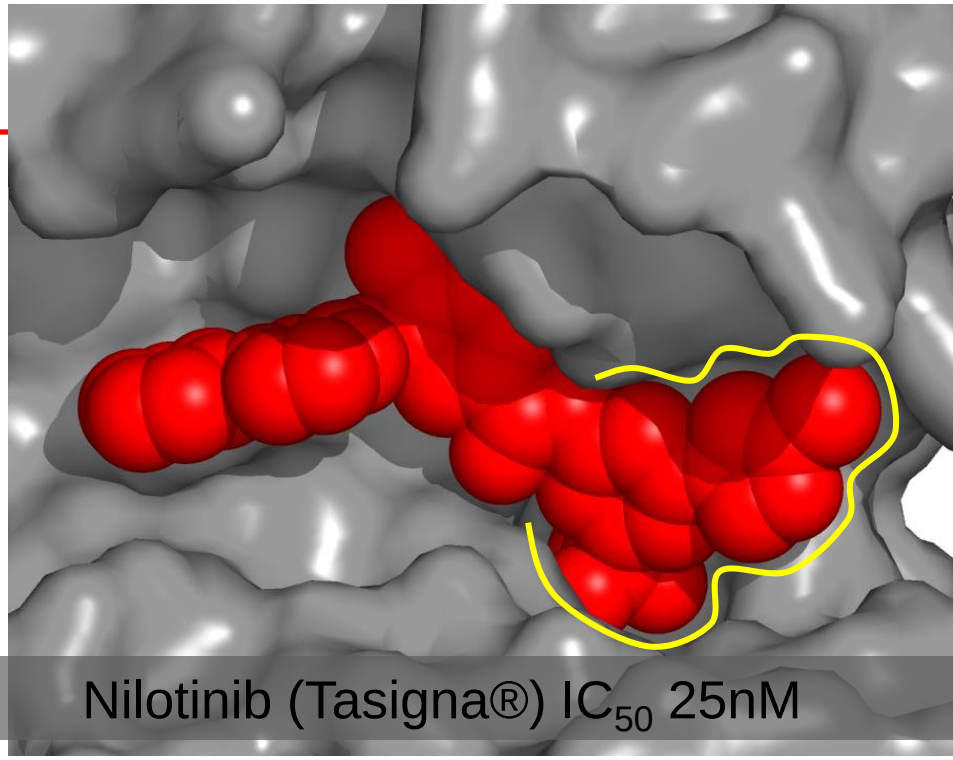


AMN 107

- Researchers at Novartis determined the crystal structure of Bcr-Abl, and then constructed compounds that would lock into the receptor more securely than Gleevec.
- Investigators at Dana-Farber tested the new compounds to measure their effectiveness against CML in laboratory cell cultures and mice with the disease.

Nilotinib has a Better Fit to the Binding Pocket





Rationally designed highly specific inhibitor of BCR-ABL

30x more potent than imatinib; maintains target specificity

No significant effect on other kinases

(Src, FLT3, VEGFR, EGFR, InsR, RET, MET, IGFR, etc)

AMN 107 (Nilotinib)

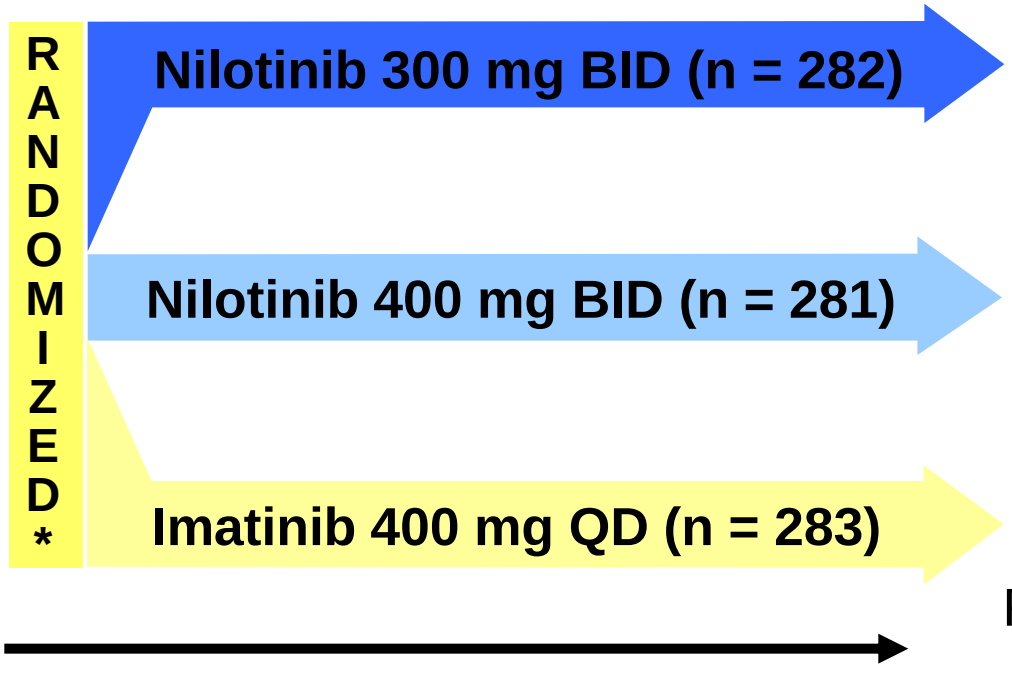
- CML Cell lines
  - Increased cell death
- Mice studies
  - Produced lengthier remissions
  - Triggered remissions in animals in which the disease had become resistant to Gleevec
  - Side effects were minimal
- Synthesized in August 2002
- Early Phase I clinical studies in May 2004 (21 months later)

AMN 107 Phase I trial

Diagnosis	N	Median Days of Treatment	HR	CR
CML-CP	16	127	8/9 (89%)	7/14 (50%)
CML-Clonal Evolution	9	154	5/5 (100%)	9/9 (100%)
CML-AP	49	154	34/49 (69%)	14/49 (29%)
CML-Myeloid BC	23	89	13/23 (57%)	5/23 (22%)
CML-Lymphoid BC	9	43	4/9 (44%)	2/9 (22%)
Ph+ALL	10	38	1/10 (10%)	n/a
Ph+ALL minimal residual disease	3	56	1/3 (33%)	n/a

Study Design and Endpoints

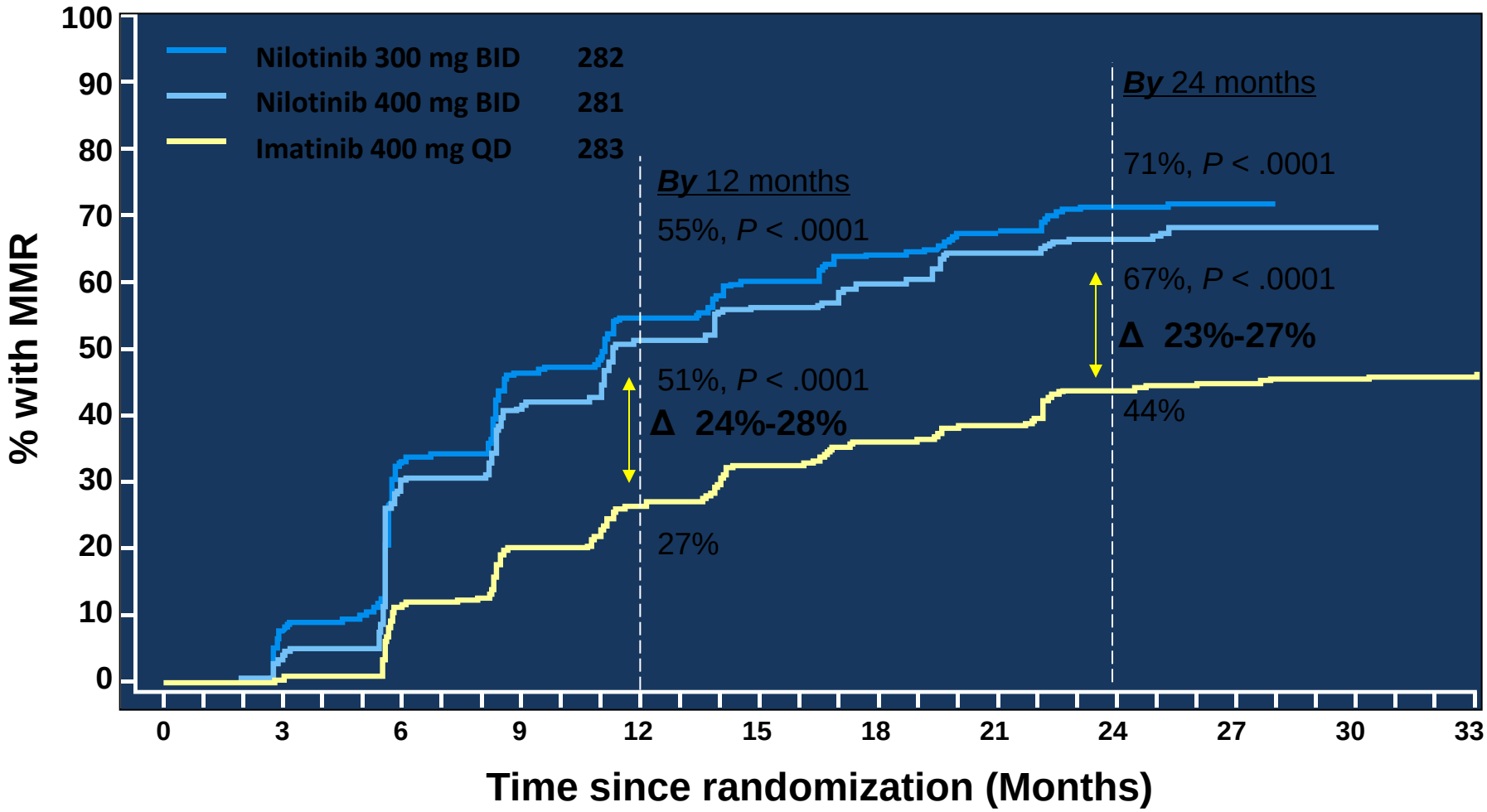
- N = 846
- 217 centers
- 35 countries



- Primary endpoint: MMR at 12 months
- Key secondary endpoint: Durable MMR at 24 months
- Other endpoints: CCyR, time to MMR and CCyR, EFS, PFS, time to AP/BC, OS

Hughes TP, et al. ***Blood. 2010;116(21):94-95 [abstract 207]***

Cumulative Incidence of MMR*



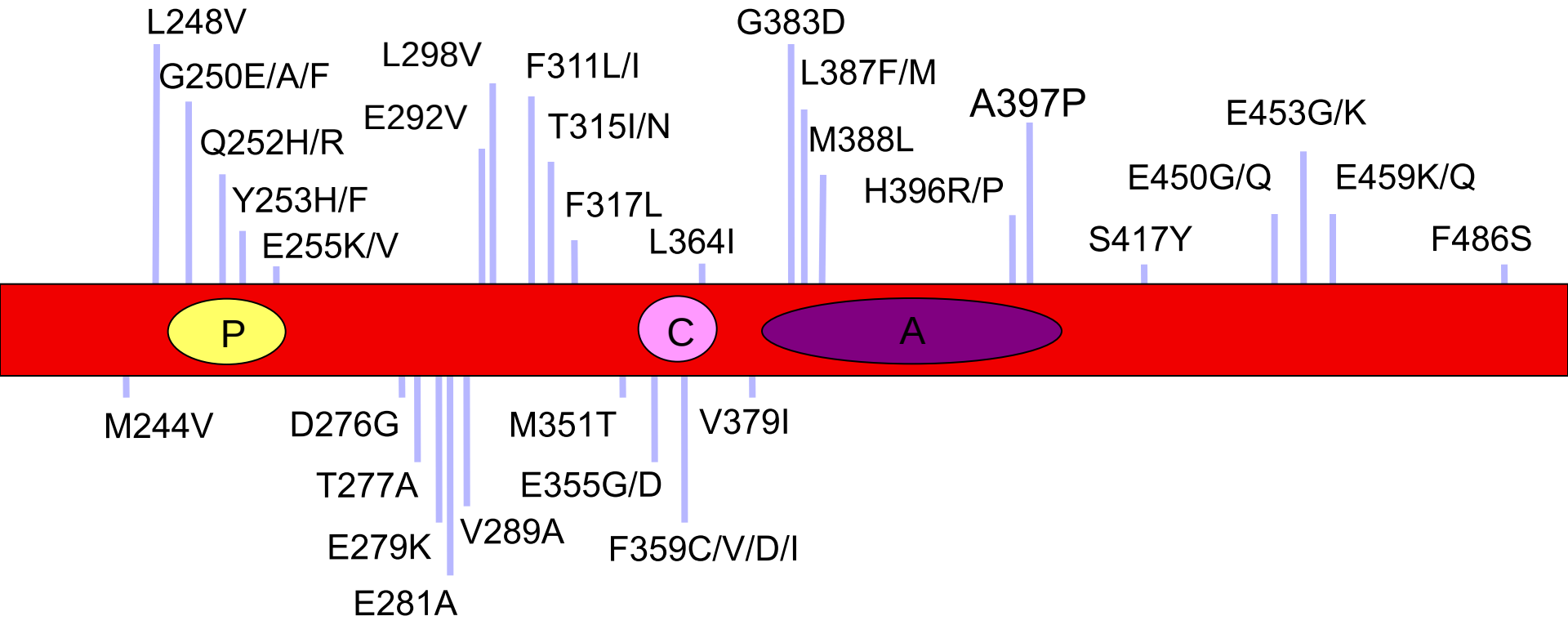
*ITT population

Data cut-off: 20Aug2010

Overall Survival

	Nilotinib 300 mg BID n = 282	Nilotinib 400 mg BID n = 281	Imatinib 400 mg QD n = 283
Total number of deaths	**9**	**6**	**11**
Estimated 24-month rate of OS	**97.4%**	**97.8%**	**96.3%**
***P*-value (OS)**	**0.6485**	**0.2125**	**–**
CML-unrelated	**4**	**3**	**1**
CML-related	**5**	**3**	**10**

BCR-ABL Kinase Domain Mutations Associated with Clinical Resistance to Imatinib (Incomplete Map)



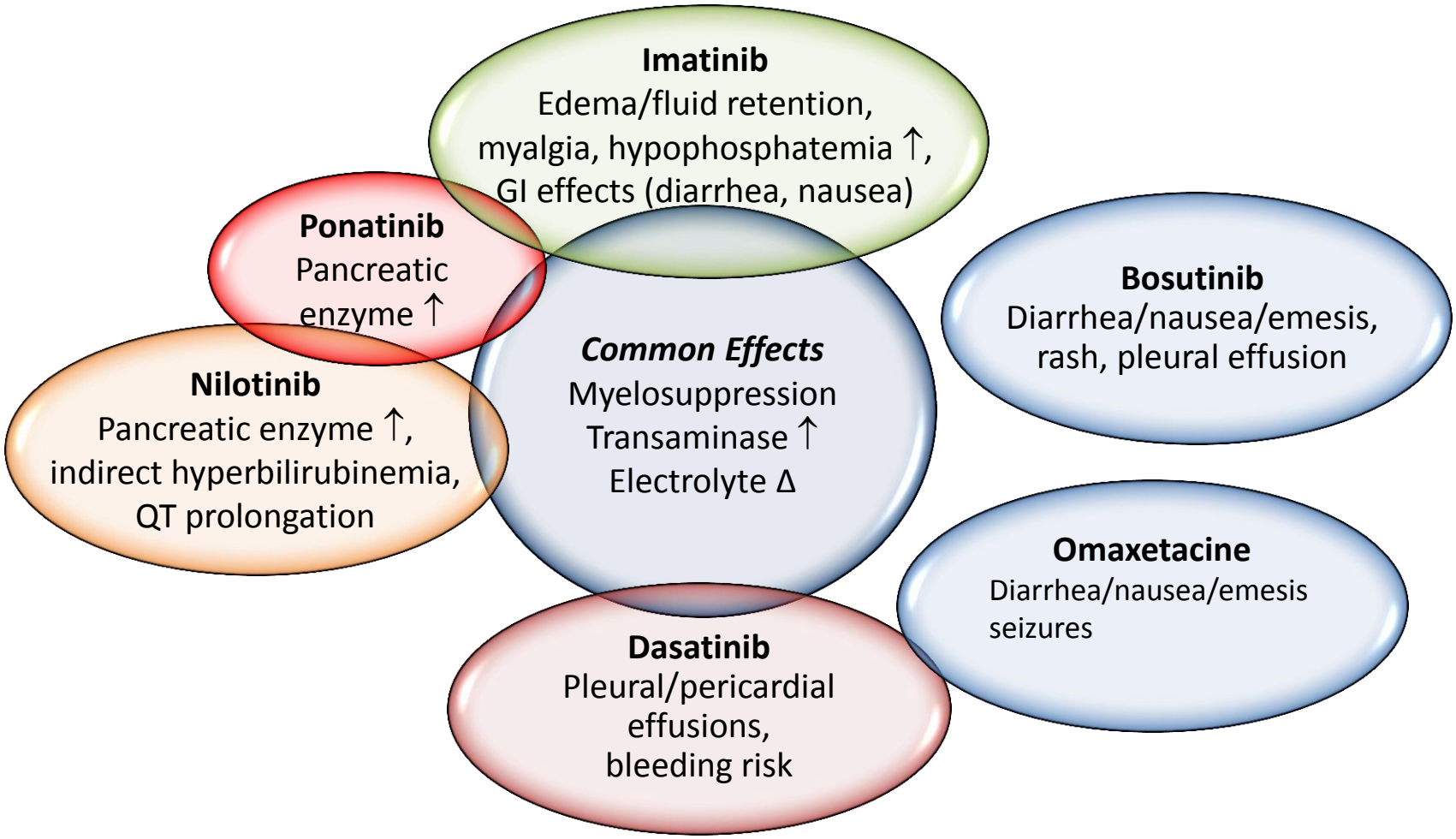
Gorre et al, 2001; von Bubnoff et al, 2002; Branford et al, 2002; Hofmann et al, 2002; Roche-L'Estienne et al, 2002; Shah et al, 2002; Hochhaus et al, 2002; Al-Ali et al, 2004

Courtesy Tim Hughes

Clinical Use of Mutations in CML

- T315I mutation
  - Resistant to all TKIs, except Ponatinib
  - Patient should be evaluated for SCT
- Y253H, E255k/V and F359V/C/I mutations
  - Resistant to Imatinib and Nilotinib but sensitive to Dasatinib
- F317L/V/I/C, V299L and T315A mutations
  - Sensitive to Nilotinib but with intermediate sensitivity to Imatinib and Dasatinib

Current Drugs in CML



Are we changing the natural history of CML with cancer research?

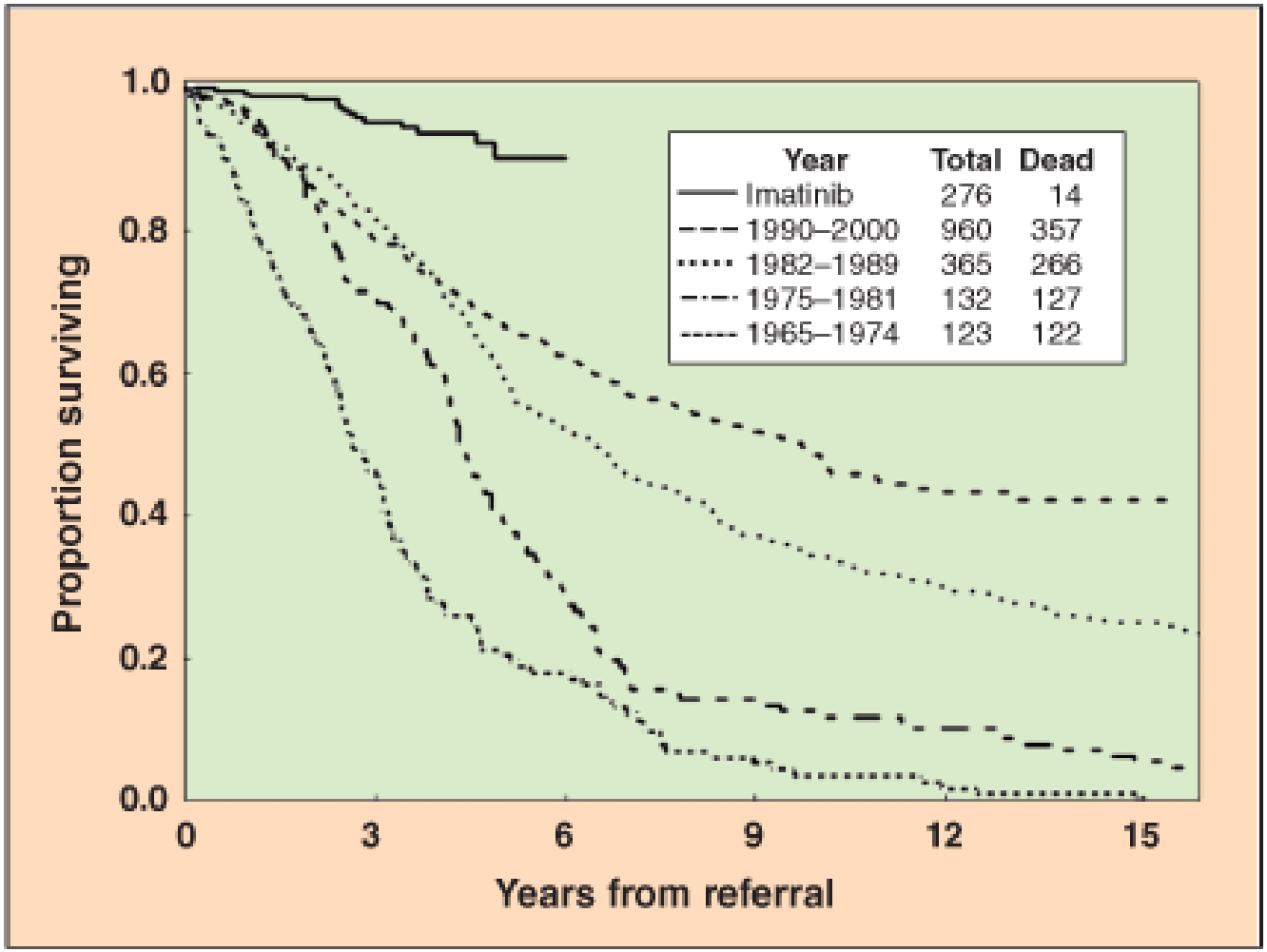
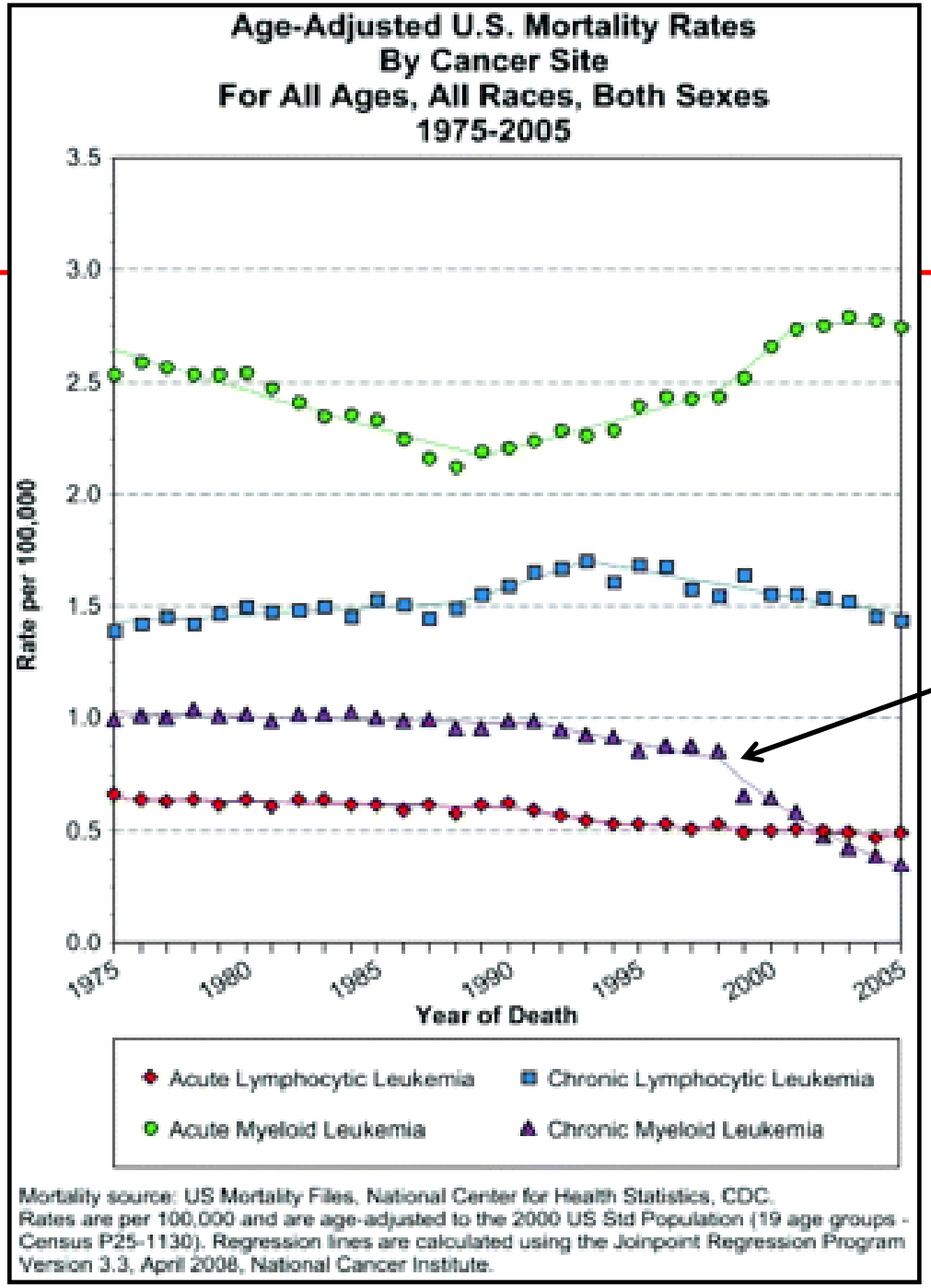


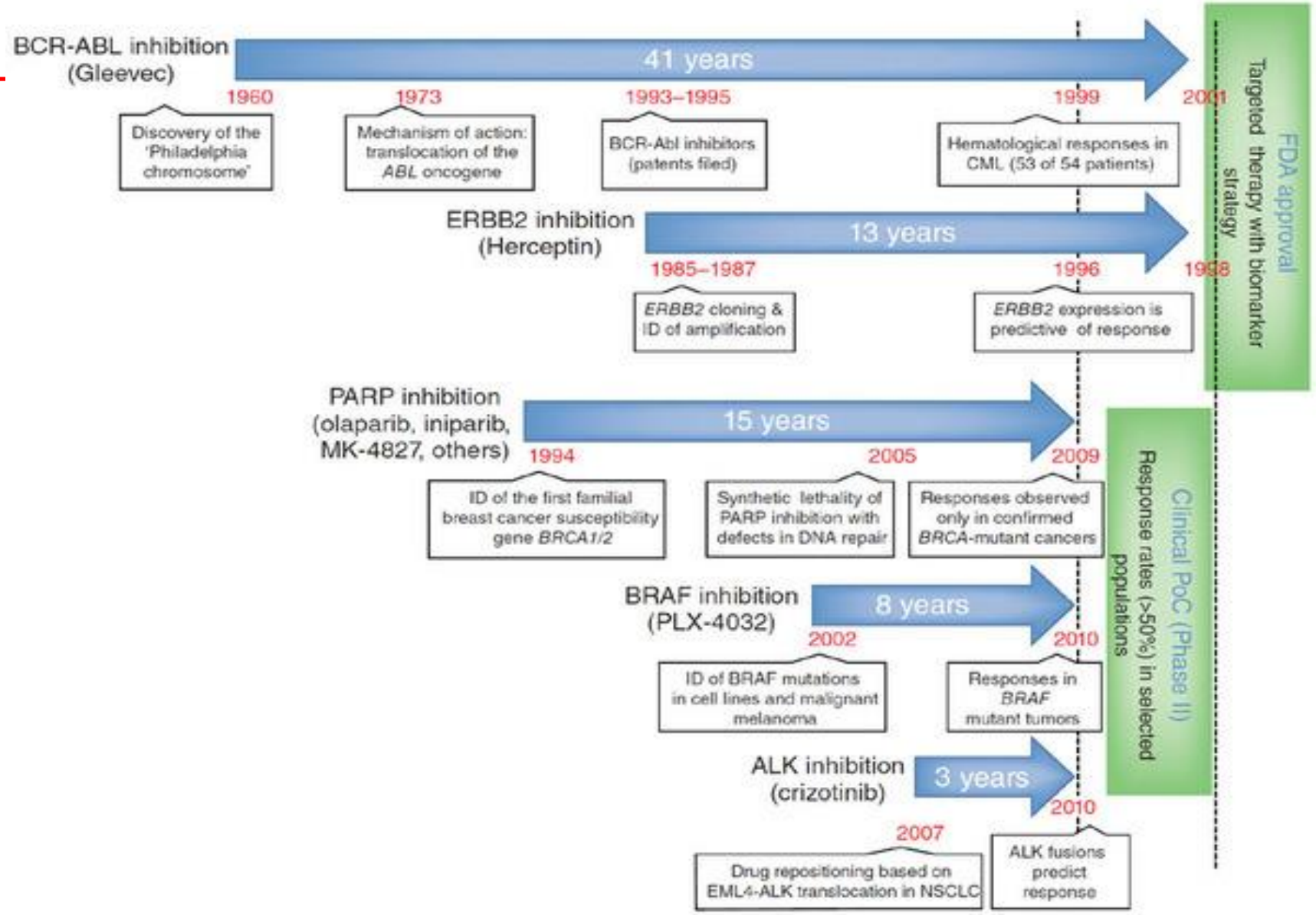
Figure 2: Survival of Chronic Myeloid Leukemia—Survival of patients treated at the University of Texas M.D. Anderson Cancer Center since 1965, by year of therapy and with the advent of imatinib.

Are we changing the natural history of CML with cancer research?



Imatinib

Drug Development in Cancer

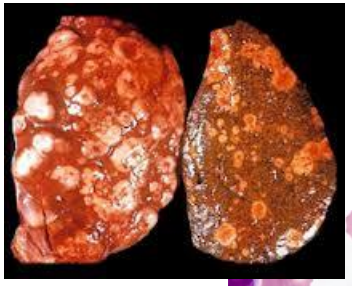


Challenges in Cancer Research

New diagnostics Tools

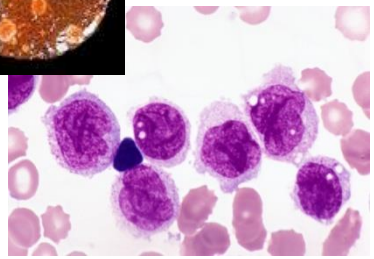
Tissue Banking

PR Cell lines



Survivorship

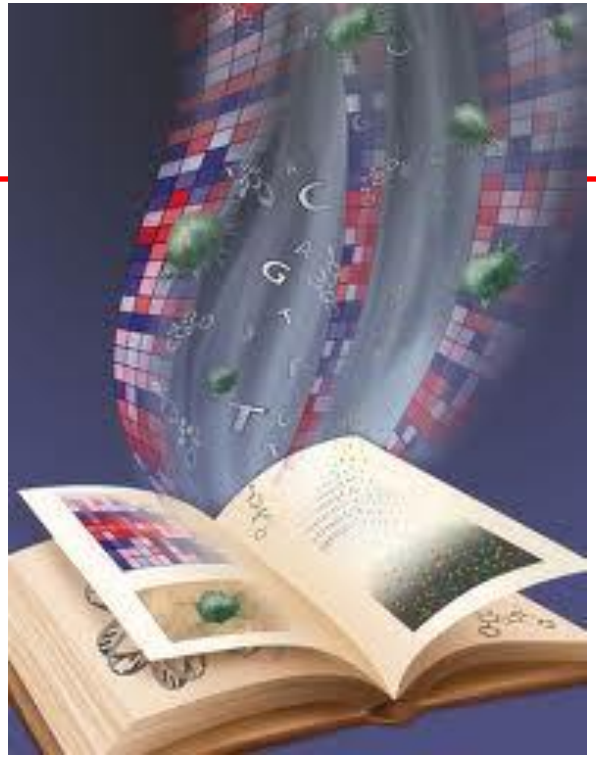
Microenvironment



Animal Models

Drug Development/Target Identification

Risk factors



Contact Information:
Maribel Tirado Gomez, MD
maribel.tirado1@upr.edu
787-772-8300 ext 1108 (office)