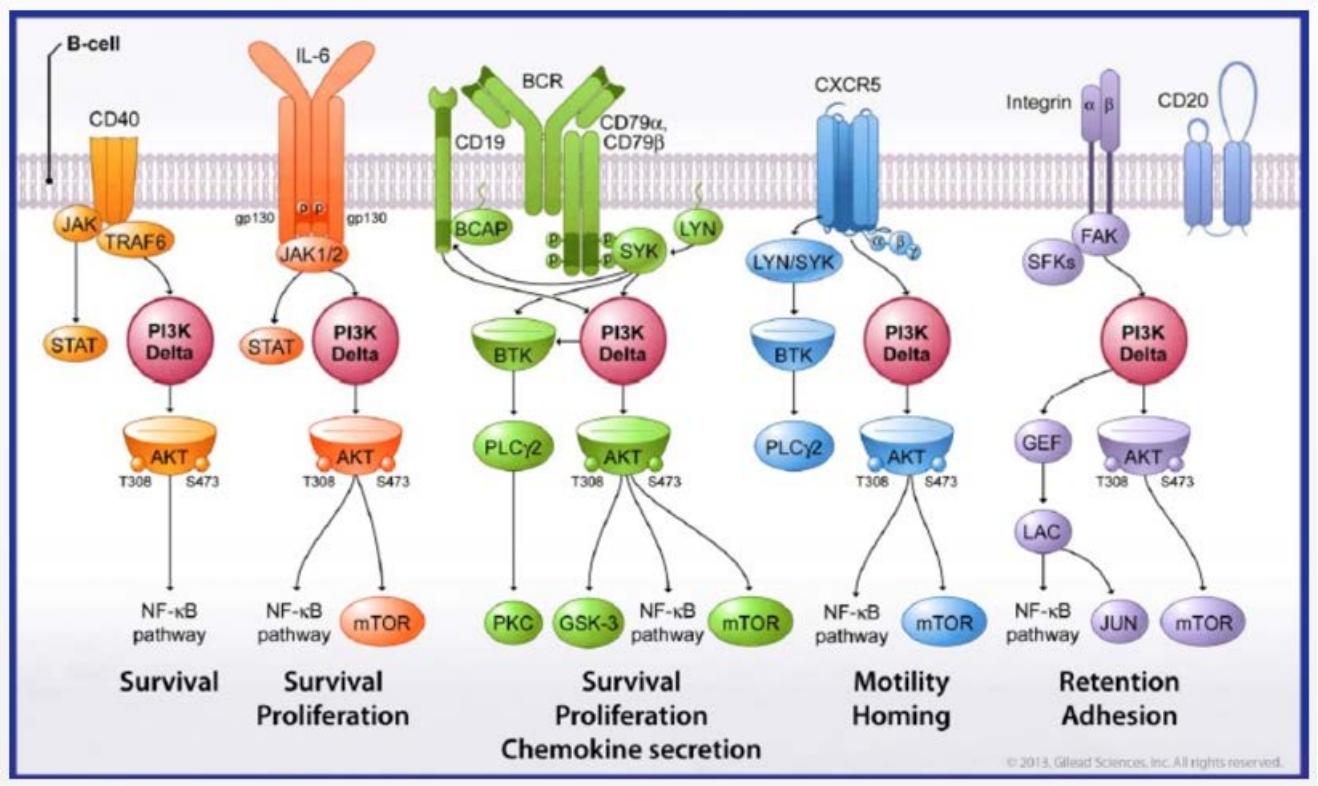
~~Lymphoma~~ Update



Javier Munoz, MD, MS, FACP

Banner MD Anderson ~~Cancer~~ Center
Making Cancer History®

Lymphoma / SLL / CLL

No conflicts of interest

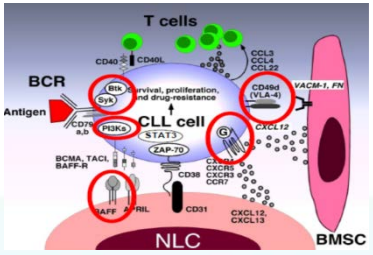
We will discuss some agents that have <u>not yet been approved</u> by the FDA

Topics

1. Overview: Lymphoma.
2. CLL: Definition.
3. CLL: Presentation/Staging.
3. CLL: Prognosis.
4. CLL: Treatment.
5. Novel Agents
6. Clinical Trials

A. Chemotherapy

B. Novel agents



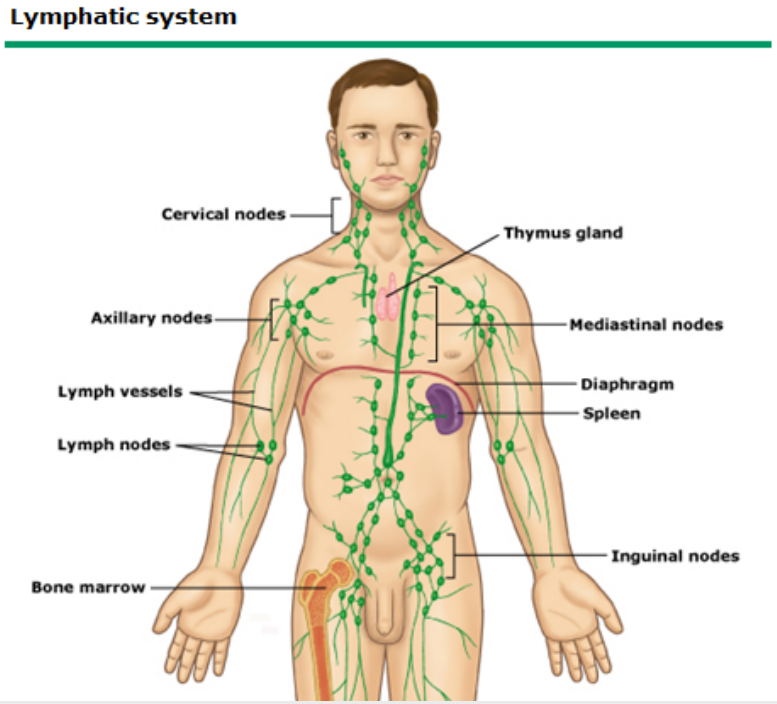
What Is Lymphoma?

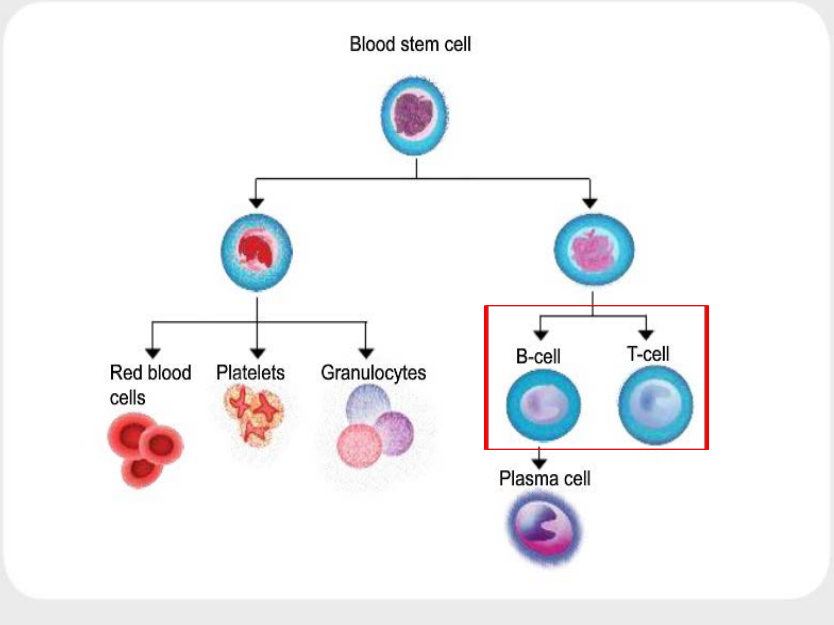
Lymphoma

"Lymphoma" is a general term for many blood cancers that originate in the lymphatic system. Lymphoma results when a lymphocyte (a type of white cell) undergoes a malignant change and multiplies out of control. Eventually, healthy cells are crowded out and malignant lymphocytes amass in the lymph nodes, liver, spleen and/or other sites in the body.

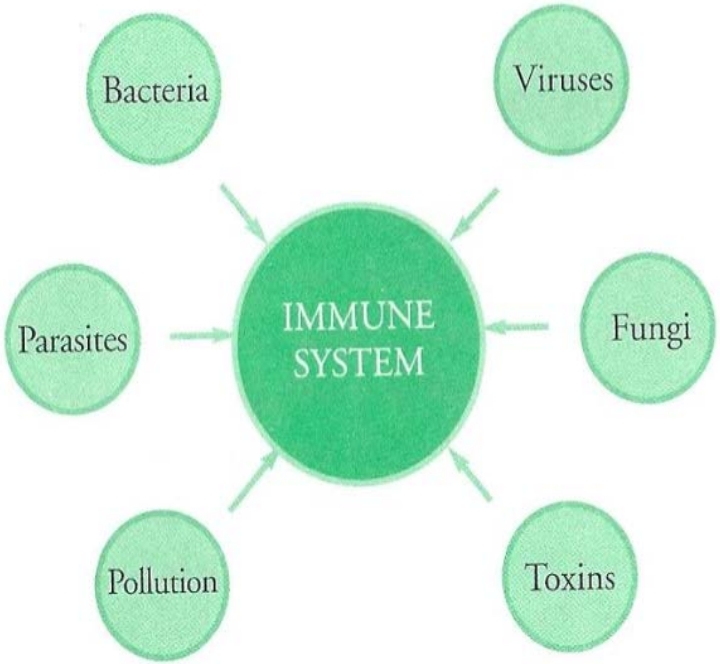
Lymph-oma
Lymph-ocytes
Lymph-nodes

- White Blood Cells (WBC's)
  - Responsible for immune protection
- Areas of generation
  - Bone marrow (B-Cells) and thymus (T-Cells)
- Areas of population
  - Lymph nodes and spleen
- T-cells: cell mediated immunity
- B-cells: humoral immunity (antibodies)

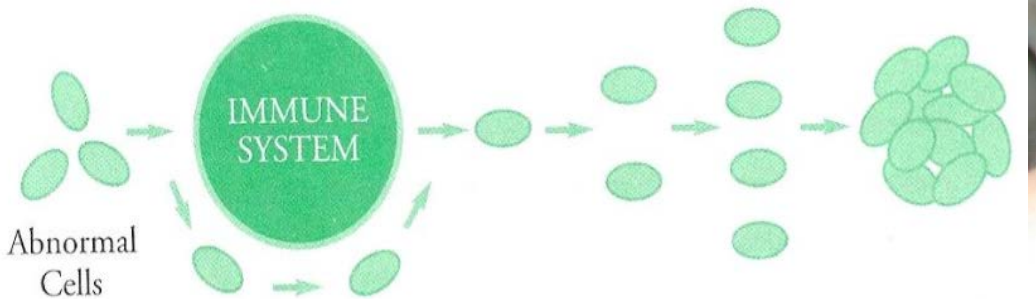




Lymph-node as a filter



It acts like a shield to defeat these invaders



Lymph nodes are like oil filters, filtering out bacteria and other things that don't belong in the body.

Question

A 58 year-old woman is evaluated for a 6 month history of progressive lymphadenopathy. She is otherwise asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Cervical and axillary lymphadenopathy is palpated. Abdominal examination reveals splenomegaly; the liver is not enlarged. The remainder of the examination is unremarkable.

Laboratory studies indicate a leukocyte count of 12,000/ul, with 65% lymphocytes.

CT scans show diffuse cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following diagnostic studies should be performed next?

A. Bone marrow biopsy
B. Excisional biopsy of an enlarged node
C. Fine-needle lymph node biopsy
D. Lumbar puncture
E. PET/CT scan

Lymphoma: A group as any other…

- Helpful to divide into:
  - Indolent
    - B-cell (follicular lymphoma)
    - T-cell (mycosis fungoides)
  - Aggressive
    - B-cell (diffuse large B-cell lymphoma)
    - T-cell (Sezary syndrome)

Isn't just one disease–it's actually a diverse group of blood cancers that share a single characteristic in how they develop

Lymphoma: A family as any other…

LEUKEMIA & LYMPHOMA SOCIETY®
fighting blood cancers

someday is today®

Non-Hodgkin lymphoma (NHL) has about 60 subtypes classified by the World Health Organization (WHO). It's important to know your subtype since it plays a large part in determining the type of treatment you'll receive.

How many types of Lymphoma are there?

Hodgkin and Non-Hodgkin Lymphoma

Hodgkin Lymphoma. Hodgkin lymphoma (HL) represents 11.5 percent of all types of lymphoma diagnosed in 2014. This disease has characteristics that distinguish it from other diseases classified as lymphoma, including the presence of the Reed-Sternberg cell, a large, malignant cell found in HL lymphoma tissues.

Non-Hodgkin Lymphoma. Non-Hodgkin lymphoma (NHL) represents a diverse group of diseases that are distinguished by the characteristics of the cancer cells associated with each disease type. The designations "indolent" and "aggressive" are often applied

Lymphoma Subtypes

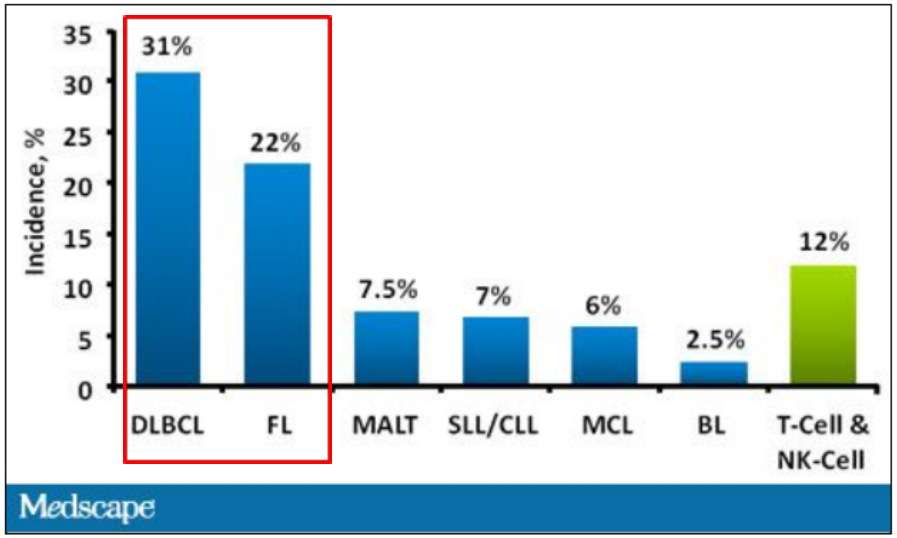
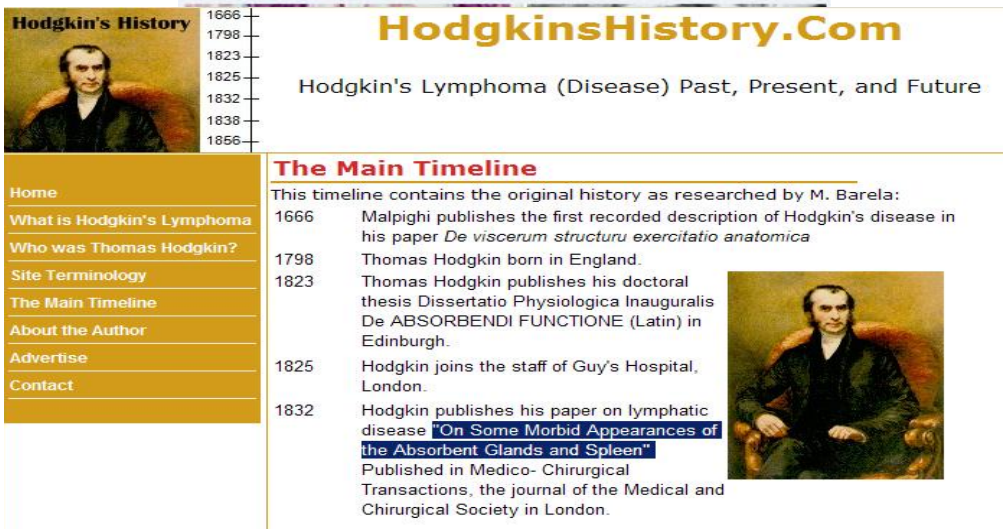
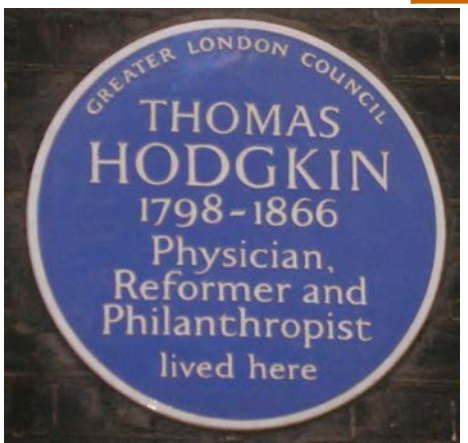
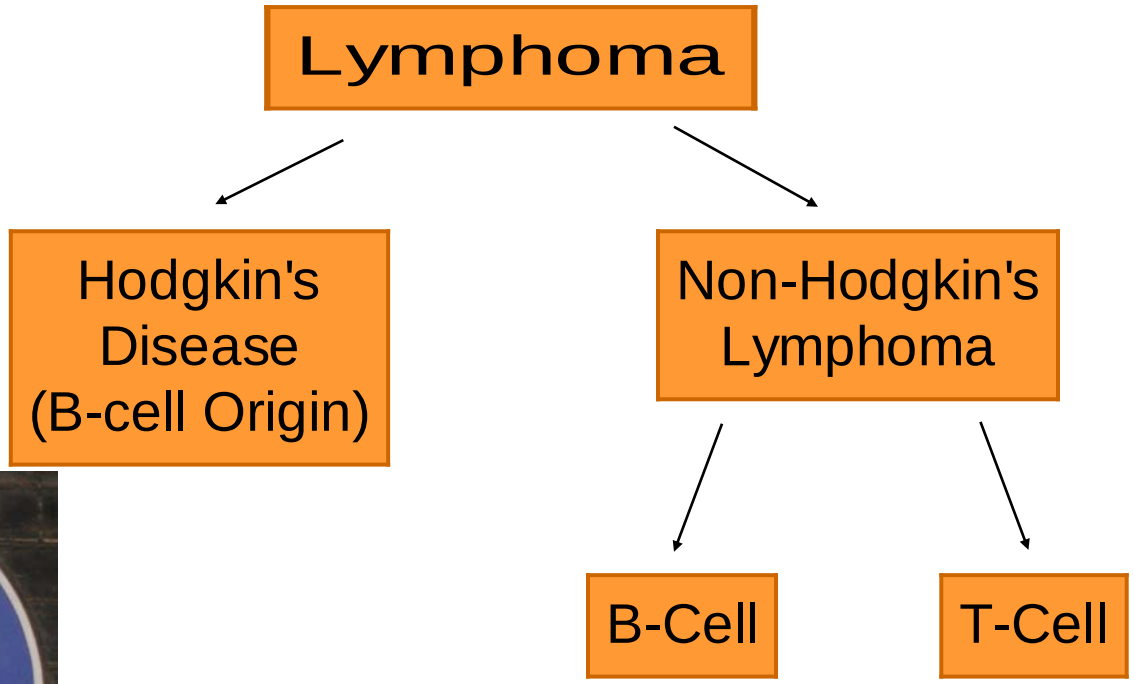


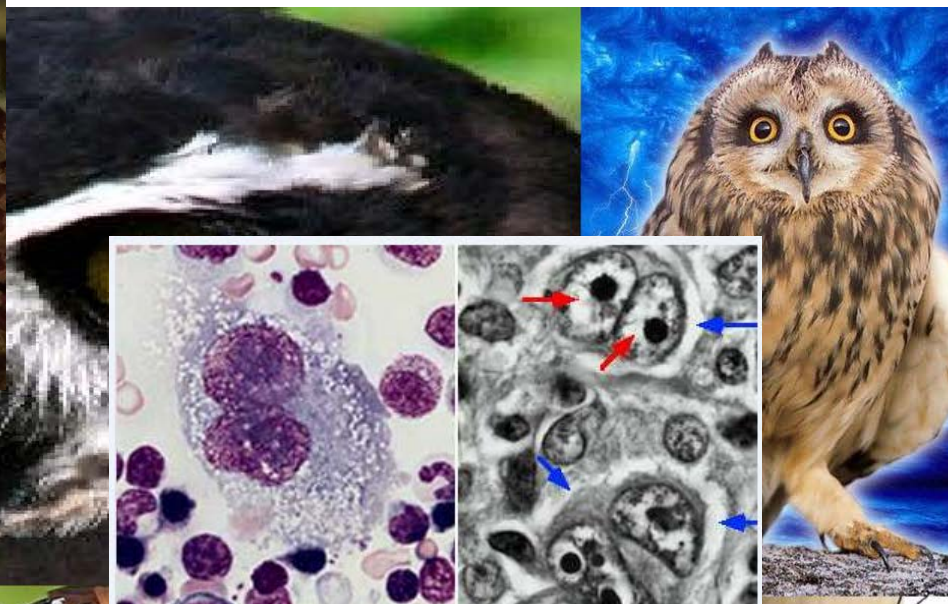
Figure 1. Non-Hodgkin's lymphoma types and prevalence. *BL = Burkitt's lymphoma; CLL = chronic lymphocytic leukemia; DLBCL = diffuse large B-cell lymphoma; FL = follicular lymphoma; MALT = mucosa-associated lymphoid tissue; MCL = mantle cell lymphoma; NK = natural killer; SLL = small lymphocytic lymphoma*


Hodgkin's History
1666
1798
1823
1825
1832
1838
1856
HodgkinsHistory.Com
Hodgkin's Lymphoma (Disease) Past, Present, and Future
Home
What is Hodgkin's Lymphoma
Who was Thomas Hodgkin?
Site Terminology
The Main Timeline
About the Author
Advertise
Contact
The Main Timeline
This timeline contains the original history as researched by M. Barela:
1666 Malpighi publishes the first recorded description of Hodgkin's disease in his paper De viscerum structuru exercitatio anatomica
1798 Thomas Hodgkin born in England.
1823 Thomas Hodgkin publishes his doctoral thesis Dissertatio Physiologica Inauguralis De ABSORBENDI FUNCTIONE (Latin) in Edinburgh.
1825 Hodgkin joins the staff of Guy's Hospital, London.
1832 Hodgkin publishes his paper on lymphatic disease "On Some Morbid Appearances of the Absorbent Glands and Spleen" Published in Medico- Chirurgical Transactions, the journal of the Medical and Chirurgical Society in London.


GREATER LONDON COUNCIL
THOMAS
HODGKIN
1798-1866
Physician,
Reformer and
Philanthropist
lived here

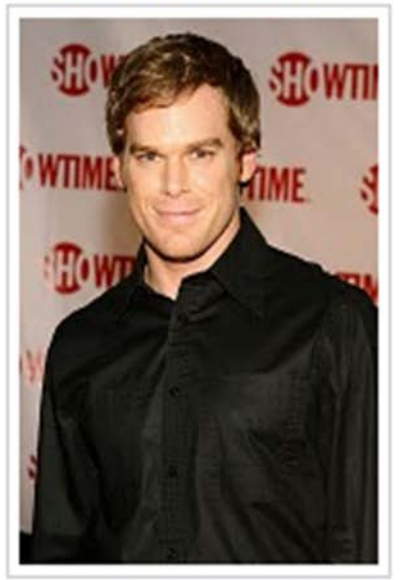

Lymphoma
Hodgkin's Disease (B-cell Origin)
Non-Hodgkin's Lymphoma
B-Cell
T-Cell

HL: “Owl’s eyes”



Reed-Sternberg cells in Hodgkin's lymphoma characteristic clear area surrounding the nucleoli in the right panel (red arrows), giving an "owl's eyes" appearance to the nuclei. Shrinkage artifact clear area surrounding these cells (ie, lacunar cells, blue arrows).

Michael C. Hall



Ethan Zohn

How old of are patients with Lymphoma?

Hodgkin Lymphoma

Age-Specific Incidence Rates for Hodgkin Lymphoma, 2007-2011

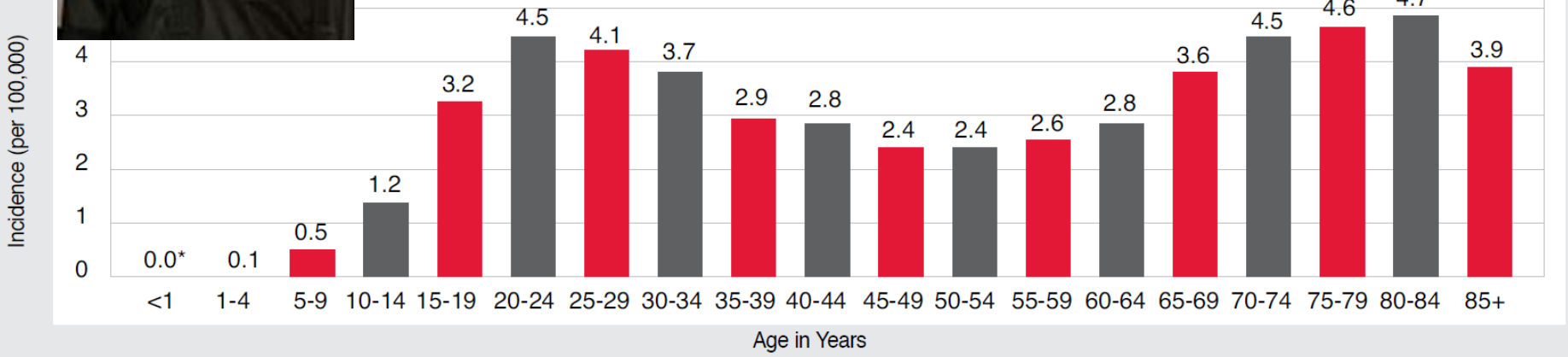


Figure 7. Source: *SEER (Surveillance, Epidemiology and End Results) Cancer Statistics Review, 1975-2011.* National Cancer Institute; 2014.
*<16 cases for each age and time interval, SEER 18 areas.

How old of are patients with Lymphoma?

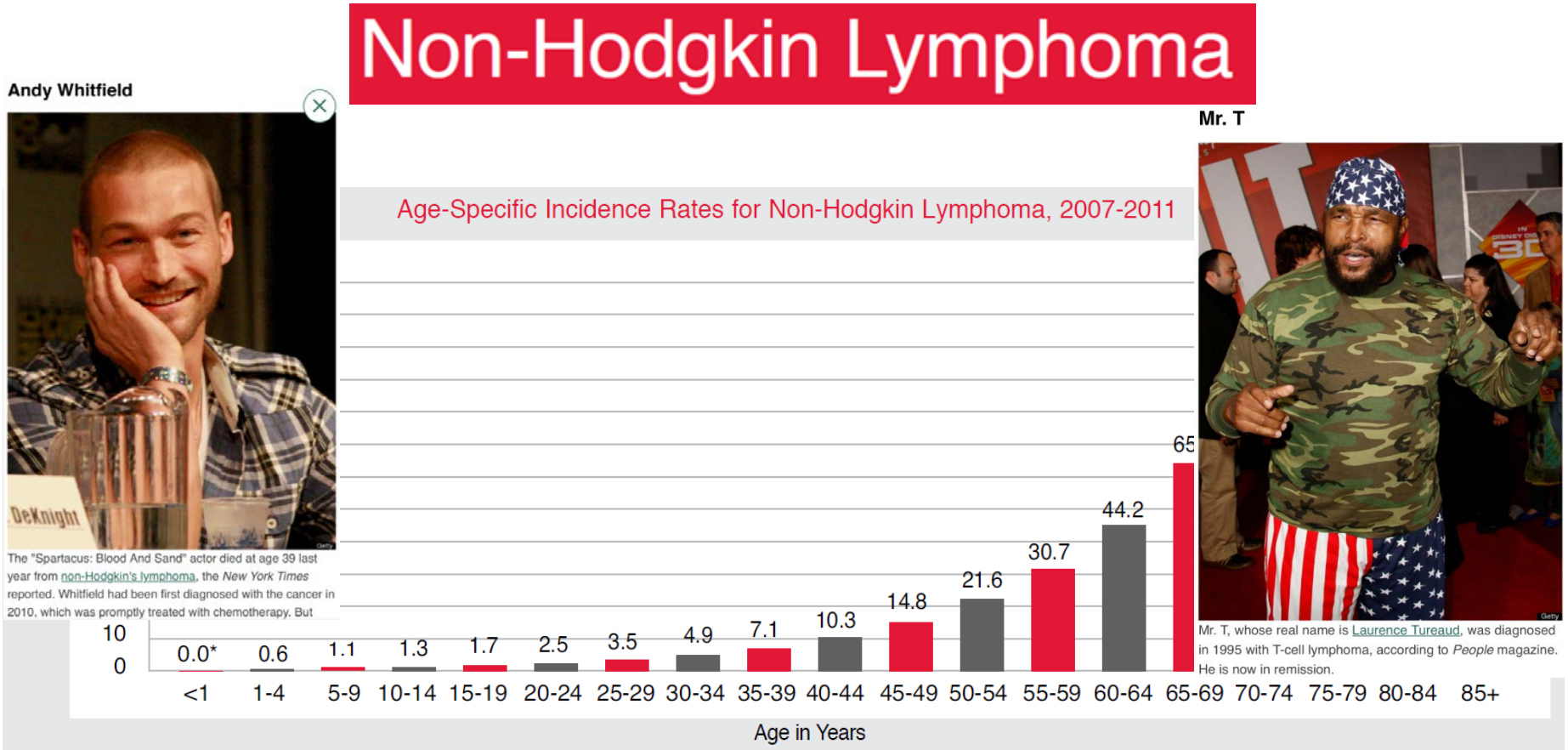
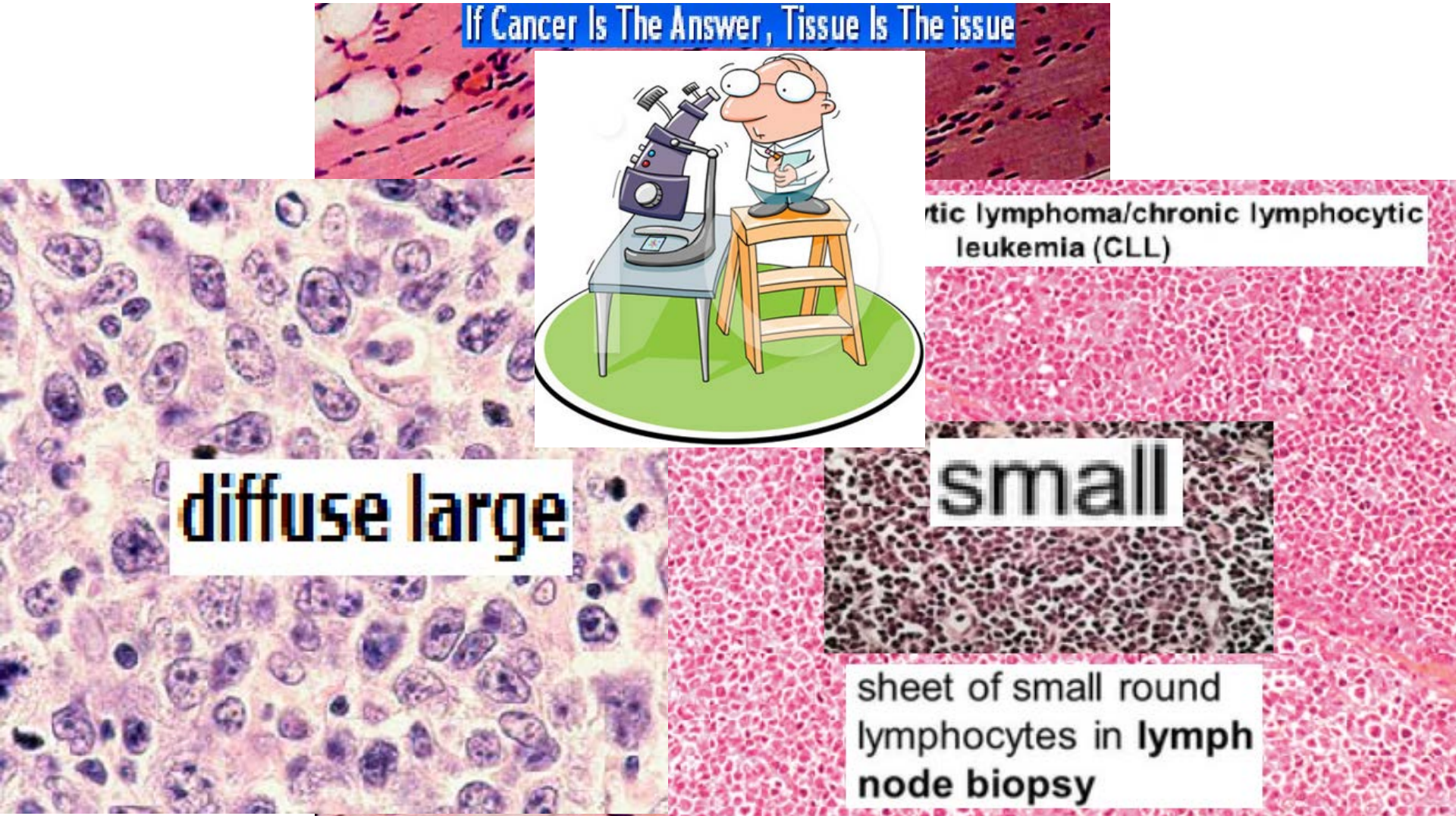


Figure 8. Source: *SEER (Surveillance, Epidemiology and End Results) Cancer Statistics Review, 1975-2011.* National Cancer Institute; 2014.
*<16 cases for each age and time interval, SEER 18 areas.

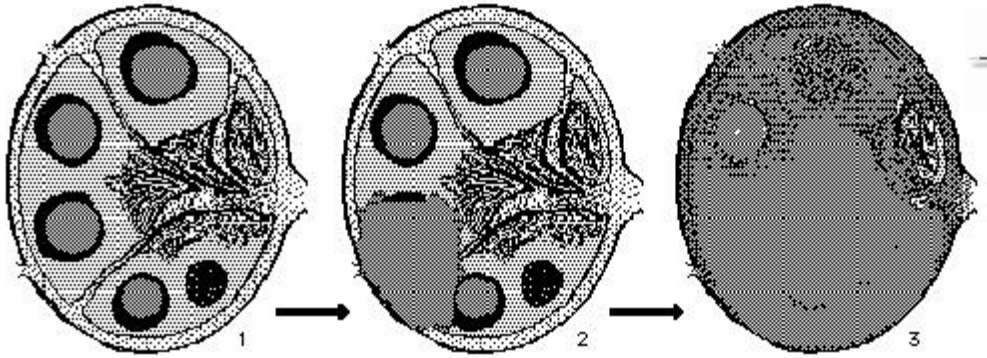
How do we <u>diagnose</u> it?



How do we diagnose it?

Excisional lymph node biopsy

In lymphoma, normal lymph node architecture is distorted or effaced by the proliferating malignant lymphoid cells.

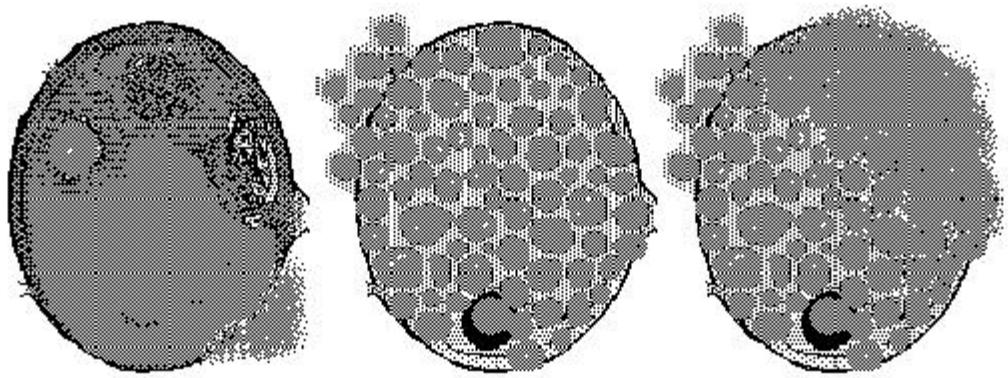


Normal Lymph Node

Partial Involvement by Lymphoma

Extensive Lymphoma with nearly complete effacement of normal architecture

The effacement of nodal architecture may be either diffuse (left) or follicular (center). The follicular pattern may evolve into a diffuse pattern (right). The growth pattern is observed at low magnification while high magnification is used for assessment of cell type (next card). Note the growth or extension of lymphoma outside of the capsule. This is typical of lymphoma.

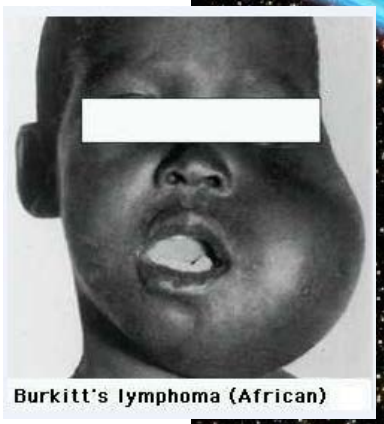


Diffuse

Follicular (nodular)

Follicular (nodular) and Diffuse

The biopsy gives us the diagnosis: "Starry sky"



Why EBV?

WIKIPEDIA
The Free Encyclopedia

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Epstein–Barr virus

From Wikipedia, the free encyclopedia

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Contents
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Help
About Wikipedia
Community portal
Recent changes

The **Epstein–Barr virus** (**EBV**), also called **human herpesvirus 4** (HHV-4), is a virus of the herpes family, and is one of the most common viruses in humans.

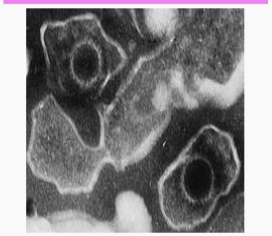
It is best known as the cause of infectious mononucleosis (glandular fever). It is also associated with particular forms of cancer, such as Hodgkin's lymphoma, Burkitt's lymphoma, nasopharyngeal carcinoma, and conditions associated with human immunodeficiency virus (HIV) such as hairy leukoplakia and central nervous system lymphomas.[1][2] There is evidence that infection with the virus is associated with a higher risk of certain autoimmune diseases,[3] especially dermatomyositis, systemic lupus erythematosus, rheumatoid arthritis, Sjögren's syndrome,[4][5] and multiple sclerosis.[6]

Infection with EBV occurs by the oral transfer of saliva[7] and genital secretions.

Most people become infected with EBV and gain adaptive immunity. In the United States, about half of all five-year-old children and 90 to 95 percent of adults have evidence of previous infection.[8] Infants become susceptible to EBV as soon as maternal antibody protection disappears. Many children become infected with EBV, and these infections usually cause no symptoms or are indistinguishable from the other mild, brief illnesses of childhood. In the United States and other developed countries, many people are not infected with EBV in their childhood years. When infection with EBV occurs during adolescence, it causes infectious mononucleosis 35 to 50 percent of the time.[9]

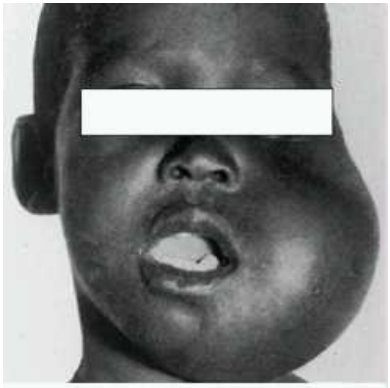
EBV infects B cells of the immune system and epithelial cells. Once the virus's initial lytic infection is brought under control, EBV latently persists in the individual's B cells for the rest of the individual's life.[7]

Epstein–Barr



Two Epstein–Barr virions

Virus classification



Burkitt's lymphoma (African)

History [edit]

The Epstein–Barr virus is named after Michael Anthony Epstein, a professor emeritus at the University of Bristol, and Yvonne Barr (born 1932 in London), a 1966 Ph.D graduate from the University of London, who together discovered and documented the virus.[25] In 1961, Epstein, a pathologist and expert electron microscopist, attended a lecture on "The Commonest Children's Cancer in Tropical Africa—A Hitherto Unrecognised Syndrome." This lecture, by Denis Parsons Burkitt, a surgeon practicing in Uganda, was the description of the "endemic variant" (pediatric form) of the disease that bears his name. In 1963, a specimen was sent from Uganda to Middlesex Hospital to be cultured. Virus particles were identified in the cultured cells, and the results were published in *The Lancet* in 1964 by Epstein, Bert Achong, and Barr. Cell lines were sent to Werner and Gertrude Henle at the Children's Hospital of Philadelphia who developed serological markers. In 1967, a technician in their laboratory developed mononucleosis and they were able to compare a stored serum sample, showing that antibodies to the virus developed.[26][27][28] In 1968, they discovered that EBV can directly immortalize B cells after infection, mimicking some forms of EBV-related infections,[29] and confirmed the link between the virus and infectious mononucleosis.[30]

What Is Leukemia?

Leukemia

Leukemia is a cancer of the marrow and blood. The four major types of leukemia are chronic lymphocytic leukemia (CLL), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), and acute myeloid leukemia (AML).

Leukemia is called "lymphocytic" (or "lymphoblastic") if the cancerous change takes place in a type of marrow cell that forms lymphocytes (a type of white blood cell). Leukemia is called "myelogenous" (or "myeloid") if the cell change takes place in a type of marrow cell that would normally go on to form red blood cells, some kinds of white blood cells and platelets.

Acute leukemia is a more quickly growing disease that affects unformed cells or cells that are not yet fully developed. These immature cells cannot carry out their normal functions. Chronic leukemia is a slow-growing blood cancer that permits the growth of greater numbers of more developed cells. In general, these more mature cells can carry out some of their normal functions.

What Is CLL/SLL?

Chronic lymphocytic leukemia (CLL) and small cell lymphocytic lymphoma (SLL)

Chronic lymphocytic leukemia (CLL) results from an acquired (not present at birth) mutation (change) to the DNA of a single marrow cell that develops into a lymphocyte.

In 95 percent of people with CLL, the change occurs in a B lymphocyte. In the other 5 percent of people with CLL, the cell that transforms from normal to leukemic has the features of a T lymphocyte or a natural killer (NK) cell. Thus, any of the three major types of lymphocytes (T cells, B cells or NK cells) can undergo a malignant transformation that causes diseases related to B-cell CLL

Scientists do not yet understand what causes this change. Once the marrow cell undergoes the leukemic change, it multiplies into many cells. CLL cells grow and survive better than normal cells; over time, they crowd out normal cells.

The result is the uncontrolled growth of CLL cells in the marrow, leading to an increase in the number of CLL cells in the blood. The leukemic cells that accumulate in the marrow in people with CLL do not prevent normal blood cell production as extensively as is the case with acute lymphoblastic leukemia. This is an important distinction: It is the reason for the generally less severe early course of CLL.

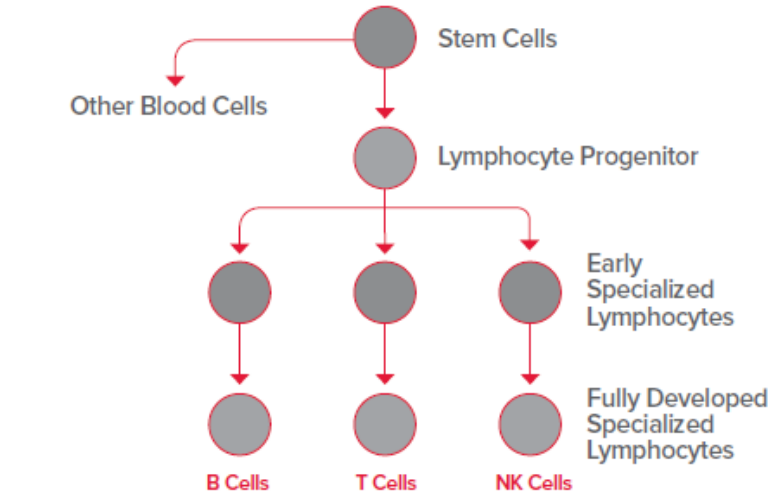


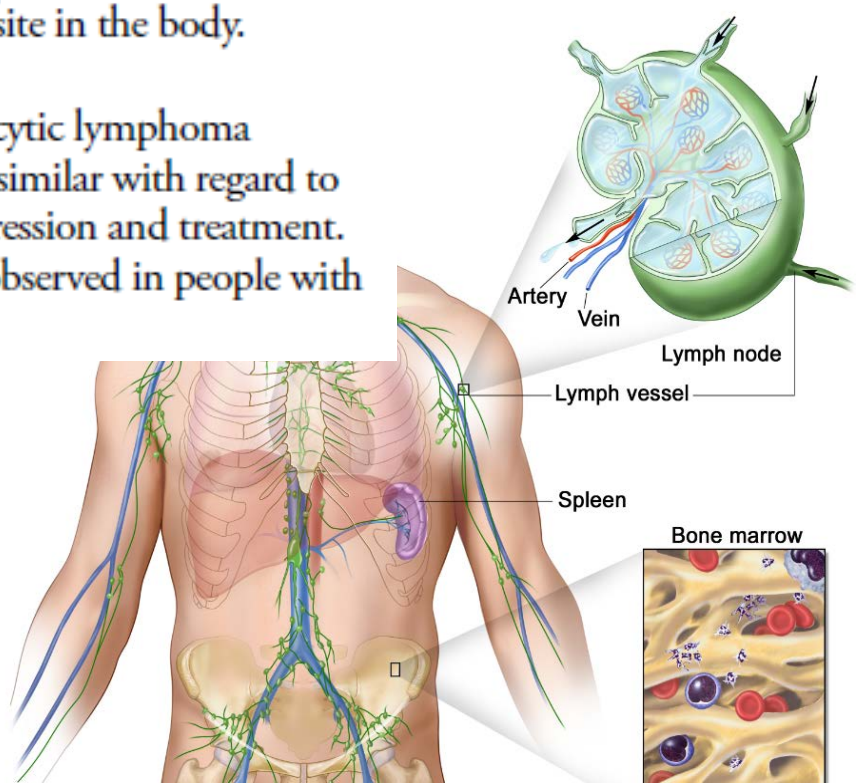
Figure 2. | Mutation of DNA can occur when the early specialized lymphocytes are formed or after the lymphocyte progenitor has differentiated into one of the three specific types of lymphocytes. The leukemic cells may be principally B cells, T cells or natural killer (NK) cells. Most patients have a B-cell type of CLL.

Does Location Matter? (CLL vs SLL)

What Is CLL/SLL?

Lymphocytic Leukemia and Lymphoma. The World Health Organization (WHO) includes "lymphocytic leukemias" and "lymphoma" within one classification. Each of these cancers is the result of a change to a cell that was destined to be a lymphocyte. However, lymphocytic leukemia and lymphoma originate in different parts of the body. Lymphocytic leukemia develops in the lymphatic tissue within the bone marrow. Lymphoma begins in a lymph node, or another lymphatic structure in the skin, the gastrointestinal tract, or some other site in the body.

Chronic lymphocytic leukemia (CLL) and small cell lymphocytic lymphoma (SLL) are often considered to be one disease because they are similar with regard to incidence, signs and symptoms, genetic features, disease progression and treatment. The leukemic lymphocytes and tissue abnormalities that are observed in people with SLL are identical to those observed in patients with CLL.

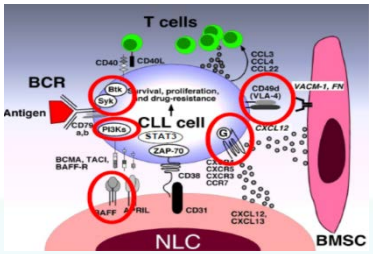


CLL: Why is it important?

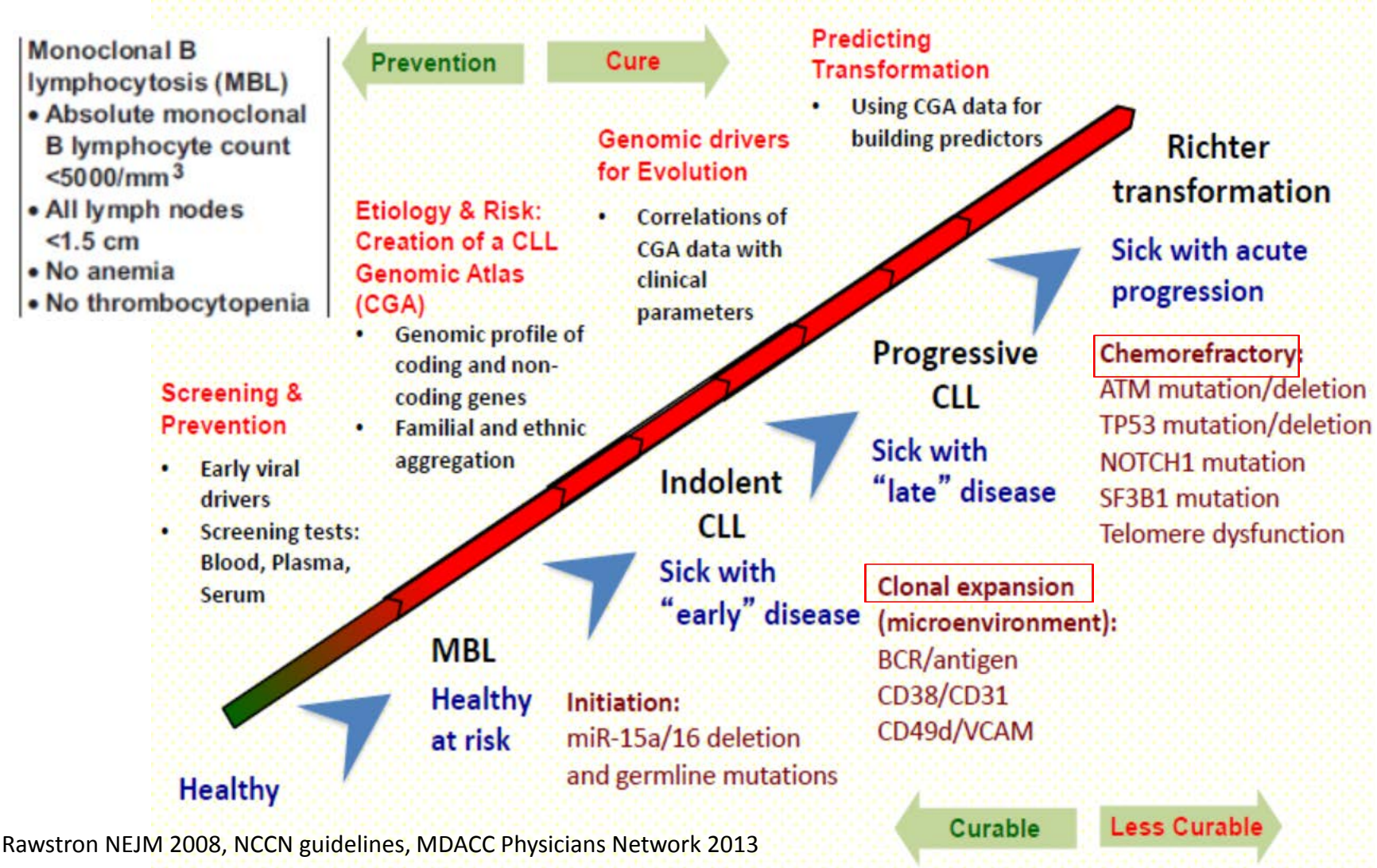
1. The most common leukemia in adults.
2. Incurable.
3. Elderly and Unfit.
4. Good versus Bad actors.
5. Watch & Wait versus Watch & Worry.
6. Unmet Medical Needs (17p, 11q, unmutated)

1. Chemotherapy

2. Novel agents



CLL: Spectrum of disease



Rawstron NEJM 2008, NCCN guidelines, MDACC Physicians Network 2013

CLL: Spectrum of disease

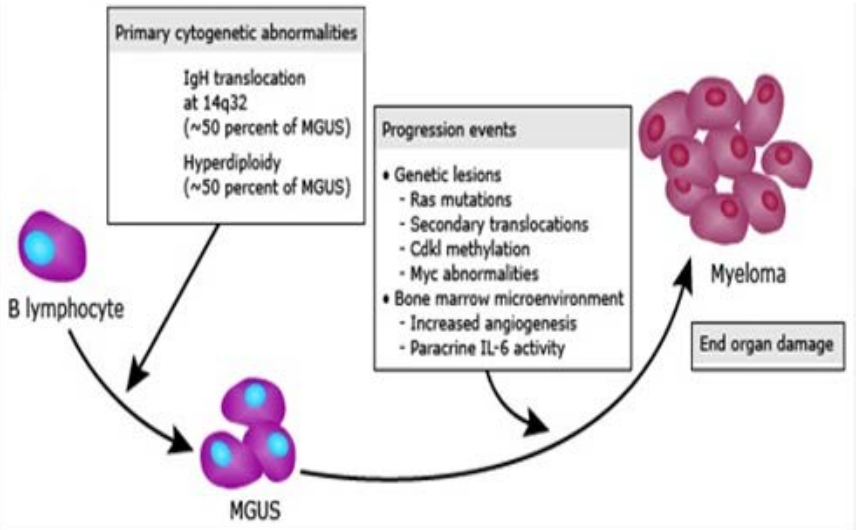
Monoclonal B-cell lymphocytosis (MBL)
- Absolute monoclonal B lymphocyte count <5000/mm^3
- All lymph nodes <1.5 cm
- No anemia
- No thrombocytopenia

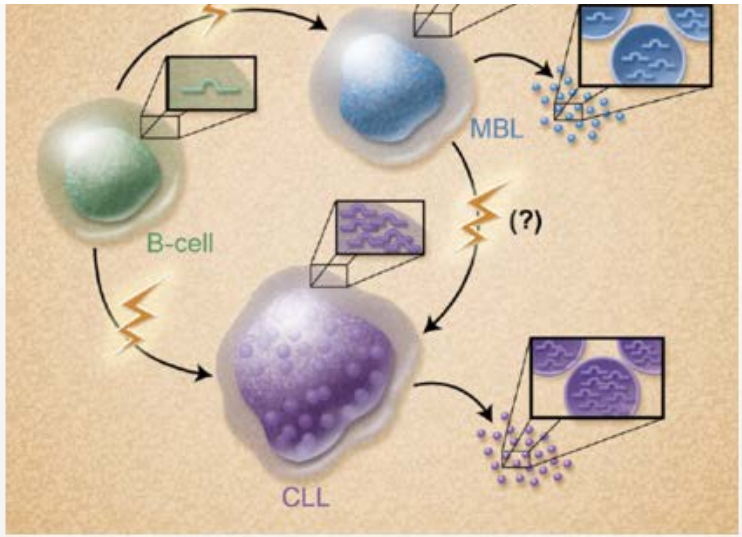
→ Observe

MGUS to MM

TABLE 3. NCI and International Workshop on CLL (IWCLL) diagnostic criteria for CLL

Cells	NCI	IWCLL
Lymphocytes	>5 × 10^9/L + >1 B-cell marker (CD19, CD20, CD23) + CD5, monoclonal	>10 × 10^9/L B-cell phenotype or bone marrow involvement
Atypical cells (eg, prolymphocytes)	<55%	Not stated
Bone marrow lymphocytes	>30%	>30%





National Comprehensive Cancer Network®

NCCN Guidelines Version 2.2013
CLL/SLL

NCCN Guidelines Index
NHL Table of Contents
Discussion

Rajkumar Clin Can Res 2009

Schmittgen, Blood, 2013 122: 1843-1844

CLL: What are the symptoms?

- Asymptomatic: 25%
- Superficial lymph node presentation: 80%
  - Painless, rubbery node in neck
  - Less common in axillae/groin
  - 'Waxing and waning'
- "B" symptoms: 5-10%
  - fever (> 38 degrees), night sweats, weight loss (>10% over 6 months; unintentional)

How do we stage it?

Rai System[a]

Stage	Description
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow
I	Stage 0 with enlarged node(s)
II	Stage 0-I with splenomegaly, hepatomegaly, or both
III[c]	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%
IV[c]	Stage 0-III with platelets <100,000/mcL

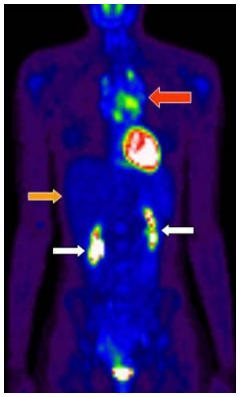


TABLE 2. Rai staging system

Lymphocytosis	Stage		
	Low 0	Intermediate I, II	High III, IV
Lymphocytosis (>5 × 10^9/L)	+	+	+
Lymphadenopathy-splenomegaly	–	–	+ or –
Thrombocytopenia (100 × 10^9/L)	–	–	+
Anemia (HB <10 g/L)	–	–	+
Survival (yr)	>10	6-8	1-2

Table 1. Commonly Used CLL Staging Systems

Rai Staging System Stage and Signs at Diagnosis	Binet Staging System Stage and Signs at Diagnosis
Low Risk—0 Abnormal increase in the number of lymphocytes in the circulating blood and marrow	A Abnormal increase in the number of lymphocytes in the circulating blood and less than 3 areas of palpable enlarged lymphoid tissue
Intermediate Risk—I & II Abnormal increase in the number of lymphocytes in the circulating blood and marrow and enlarged lymph nodes or Abnormal increase in the number of lymphocytes in the circulating blood and marrow and enlarged spleen and/or liver	B Abnormal increase in the number of lymphocytes in the circulating blood and greater than 3 areas of palpable enlarged lymphoid tissue
High Risk—III & IV Abnormal increase in the number of lymphocytes in the circulating blood and marrow and anemia (hemoglobin <11 g/dL) or Abnormal increase in the number of lymphocytes in the circulating blood and marrow and low platelet count (platelets <100,000/μL)	C Same as B with anemia (hemoglobin <11 g/dL in men or hemoglobin <10 g/dL in women) or low platelet count (platelets <100,000/μL)

Bone marrow

Why me?

Causes and Risk Factors. CLL has generally not been associated with any environmental or external factors. However, the Institute of Medicine of the National Academy of Sciences issued a report "Veterans and Agent Orange: Update 2002," which concluded that there was "sufficient evidence of an association" between herbicides used in Vietnam and CLL. For Veterans with Agent Orange exposure, this may provide additional VA benefits. If you fall into this group of patients, it is worth getting a formal evaluation at the VA.

First-degree relatives of patients with CLL are three to four times more likely to develop CLL than people who do not have first-degree relatives with the disease. However, the risk is still small. For example, the 60-year-old sibling or child of someone with CLL would have three to four chances in 10,000 of developing the disease, compared with the one chance in 10,000 for a 60-year-old person without a family history of the disease.

SPORADIC CANCER

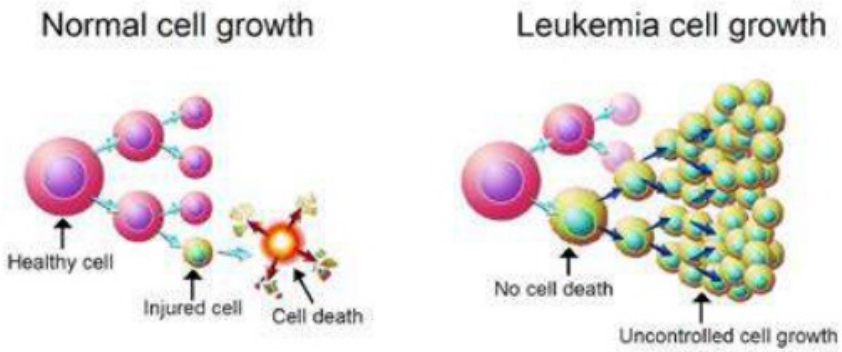
The majority of cancer diagnoses are considered sporadic. These tumors are the result of **environmental exposures** or possible **random events** within a cell.

HEREDITARY CANCER

Hereditary cancers result from an **inherited gene mutation** that is present in every cell. Other cancers that run in a family—labeled **familial**—are not necessarily from an inherited mutation, but may instead result from shared environmental or lifestyle factors.

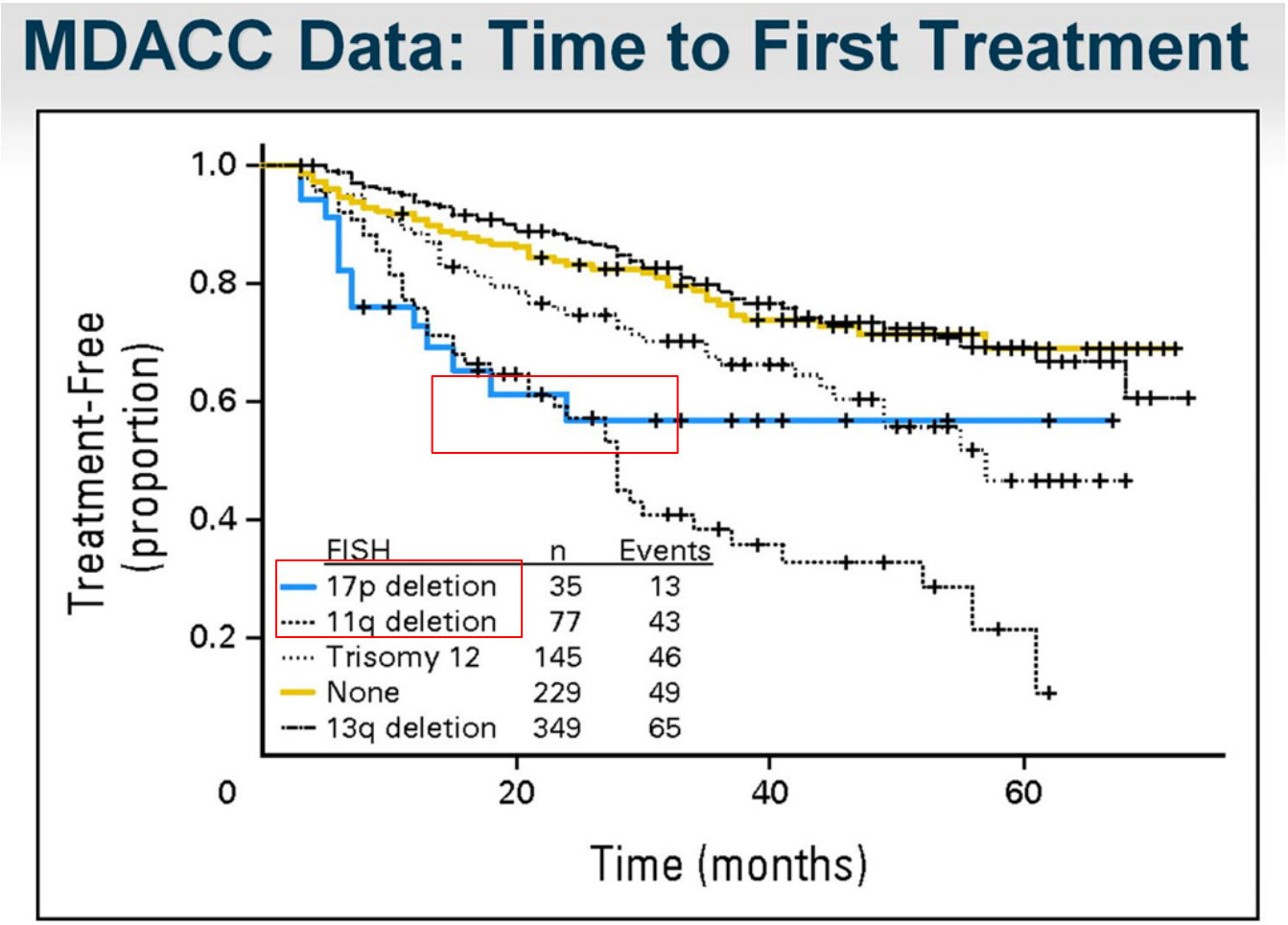
Figure 1.4
Normal cell growth versus leukemia cell growth

Normal cells grow and divide to make new cells as the body needs them. Normal cells die when they are old or damaged. New cells are then made to replace the old. Leukemia cells don't die when they should. Instead, they continue to grow and divide to make more and more copies of themselves.



Patience is well rewarded in CLL

CLL: Spectrum of prognosticators



Wierda WG, et al. *J Clin Oncol*. 2011;29:4088-4095.

CLL: Spectrum of prognosticators

PROGNOSTIC INFORMATION FOR CLL

Immunoglobulin Heavy-Chain Variable (IGHV) Region Gene Mutation and Surrogates by Flow Cytometry

	Outcome Association	
	Favorable	Unfavorable
DNA sequencing[b] IGHV	>2% mutation	≤2% mutation
Flow Cytometry		
CD38	<30%	≥30%
Zap 70	<20%	≥20%

Interphase Cytogenetics (FISH)

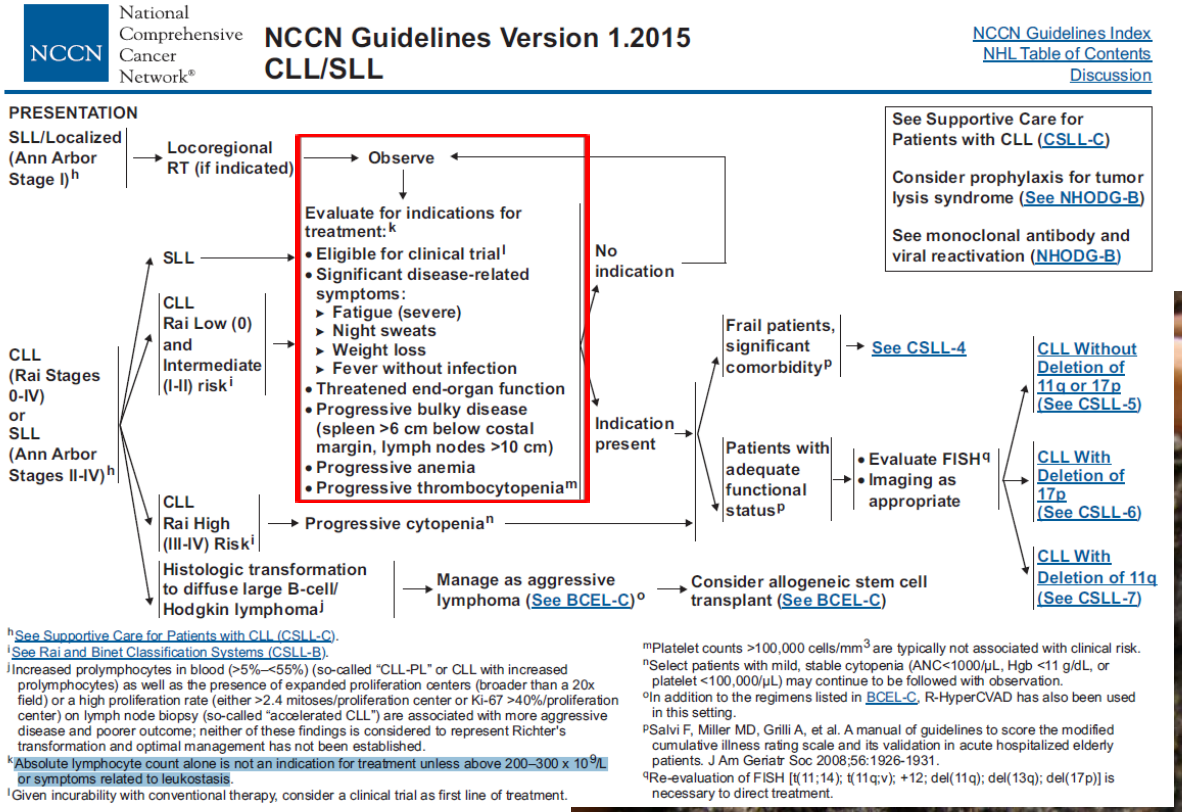
Unfavorable	Neutral	Favorable
del(11q) del(17p)	Normal +12	del(13q) (as a sole abnormality)

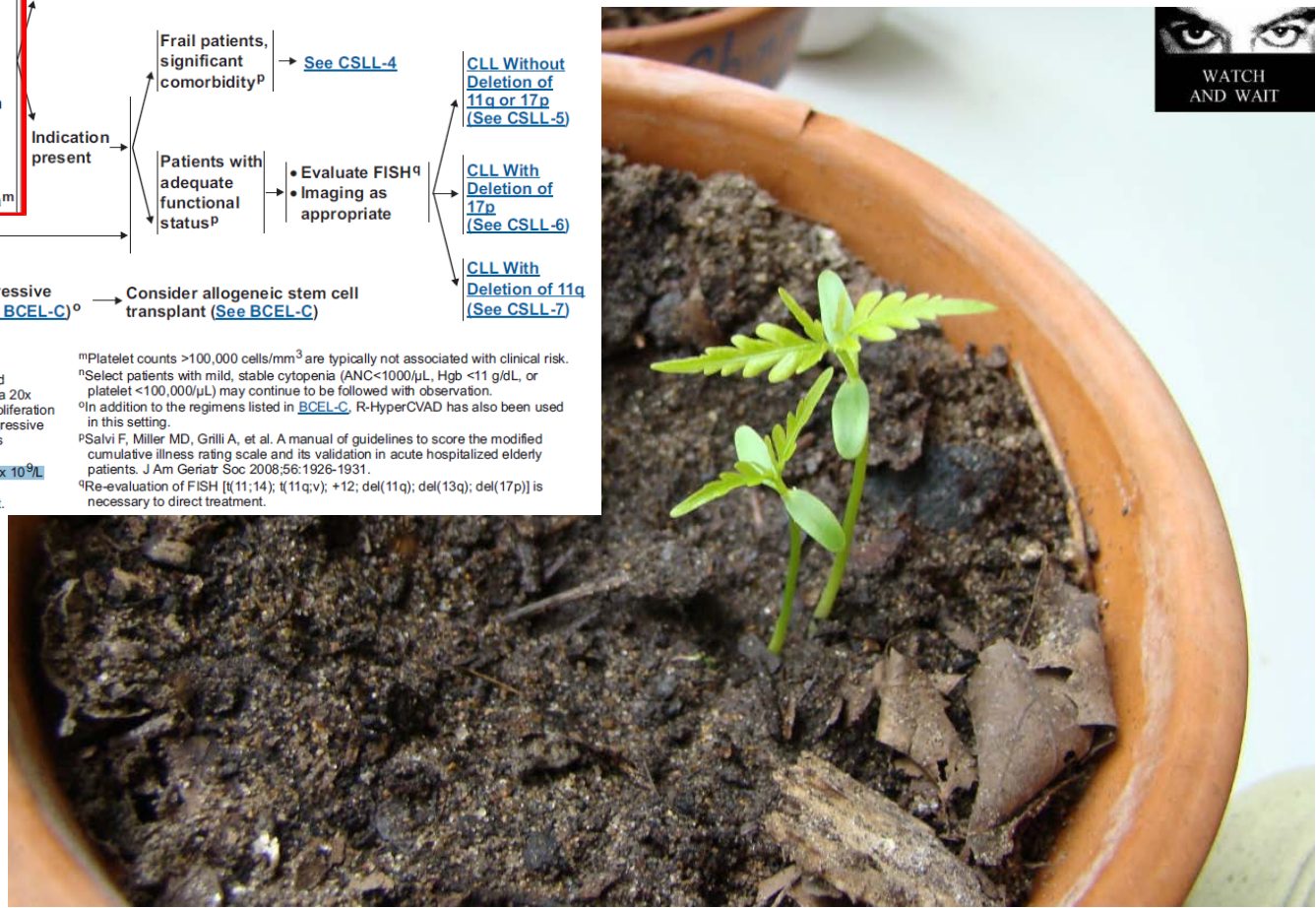
Rai System[a]

Stage	Description
0	Lymphocytosis, lymphocytes in blood >15,000/mcL and >40% lymphocytes in the bone marrow
I	Stage 0 with enlarged node(s)
II	Stage 0-I with splenomegaly, hepatomegaly, or both
III[c]	Stage 0-II with hemoglobin <11.0 g/dL or hematocrit <33%
IV[c]	Stage 0-III with platelets <100,000/mcL

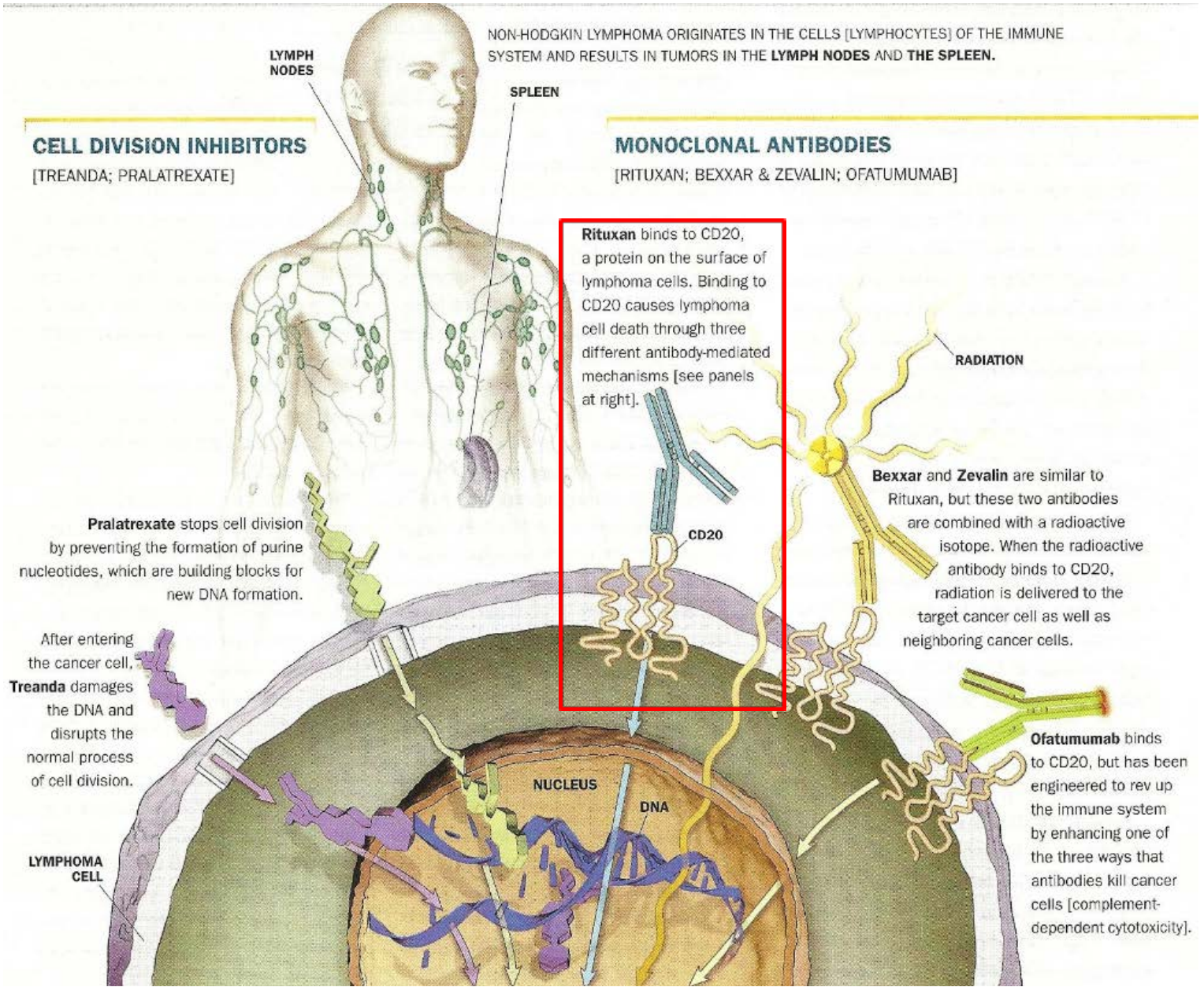
How do we integrate results from multiple markers?

Is treatment needed?

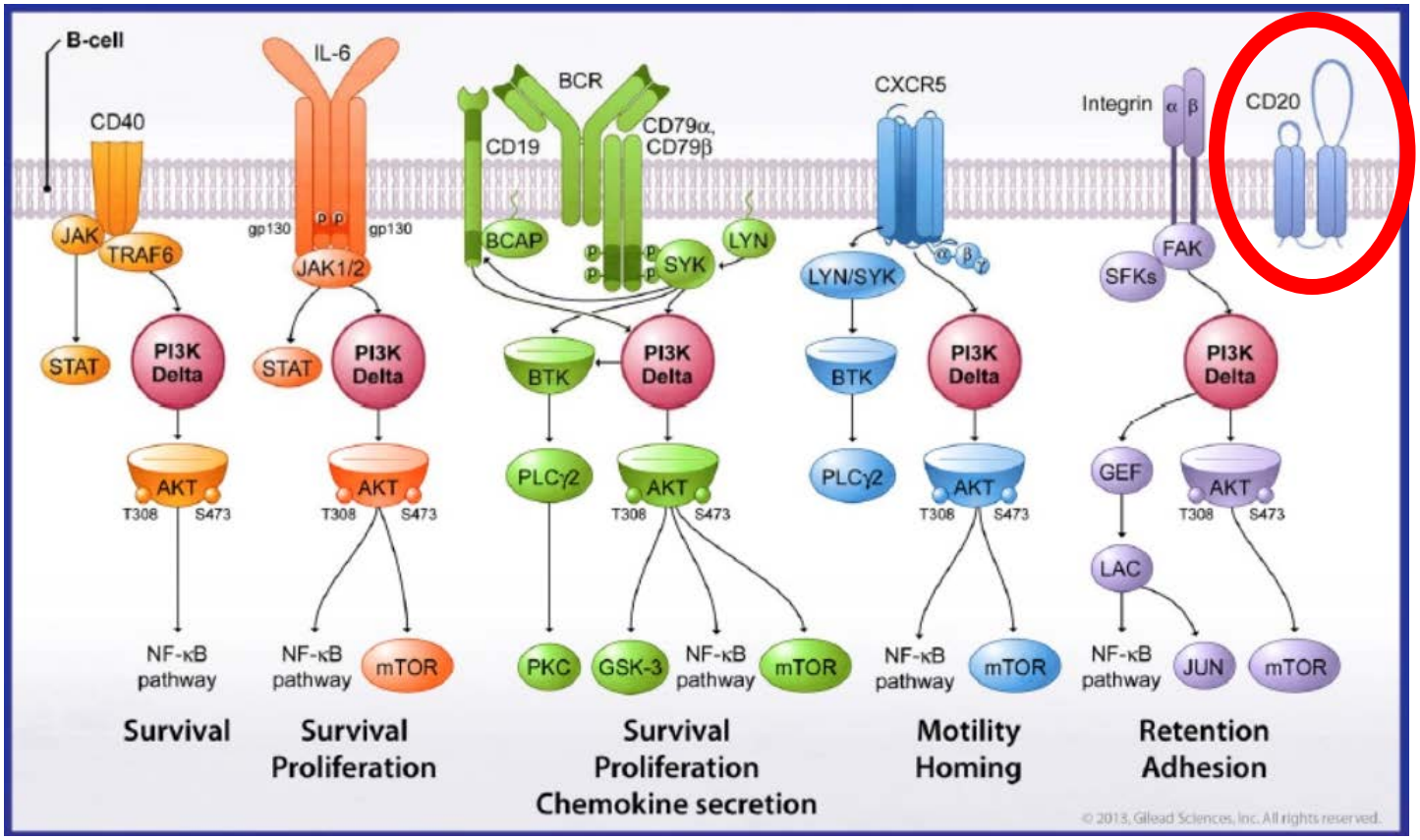




What are the therapies for CLL?

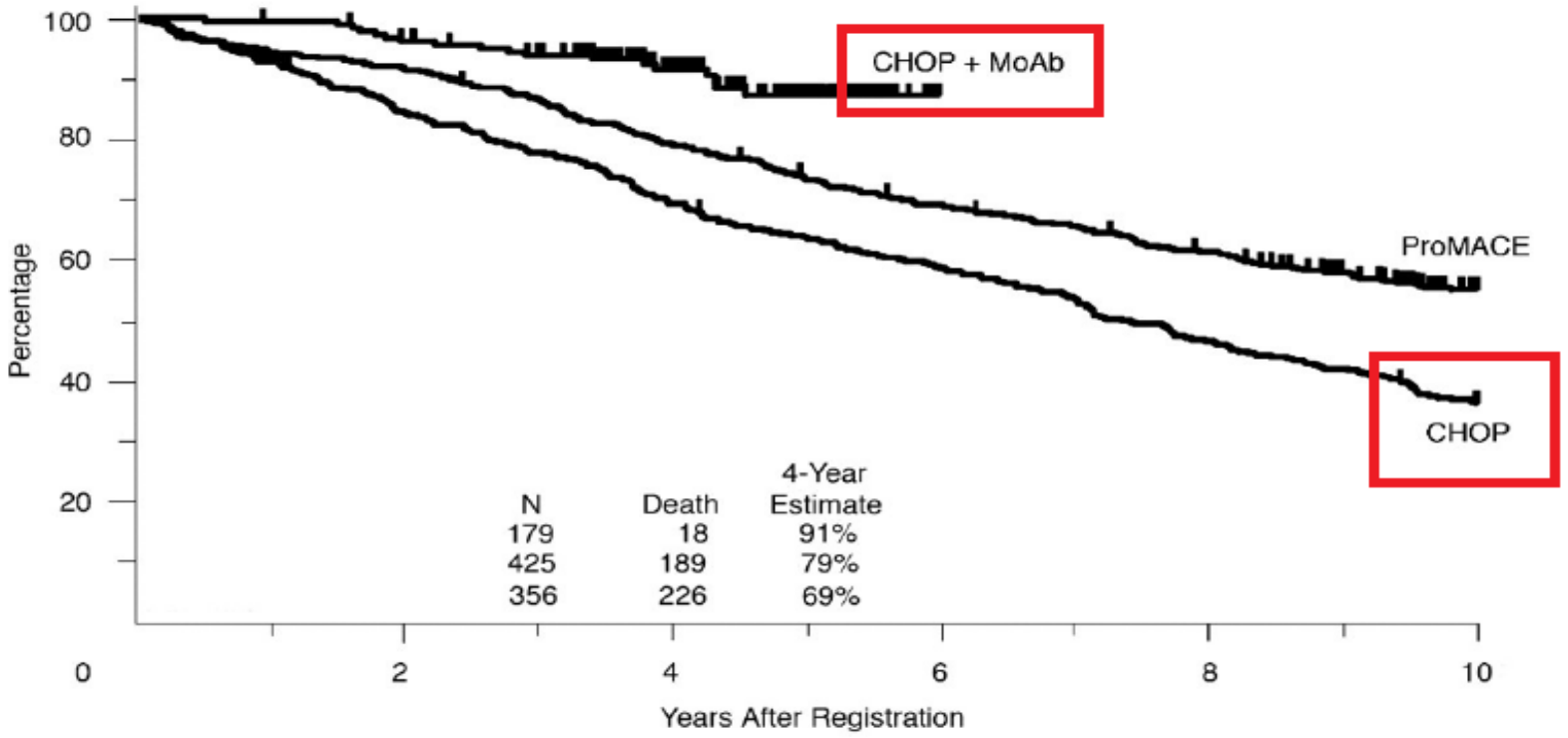


Monoclonal Antibodies



What is Rituximab (Anti-CD20)?

The Addition of Rituximab to chemotherapy has changed the Survival of Patients With Indolent Lymphoma

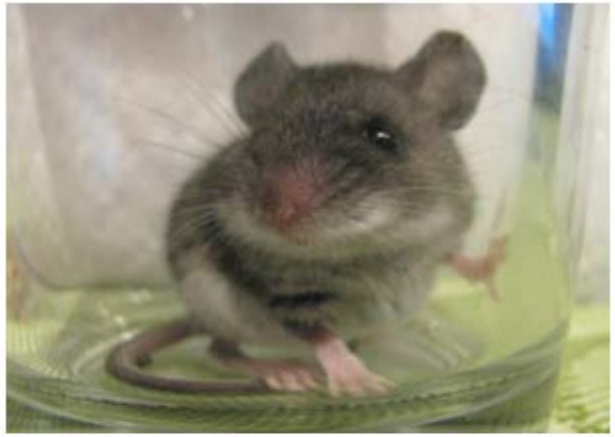


Fisher, R. I. et al. J Clin Oncol; 23:8447-8452 2005

Monoclonal Antibodies

Rituximab
Chimeric Anti-CD20 Monoclonal Antibody

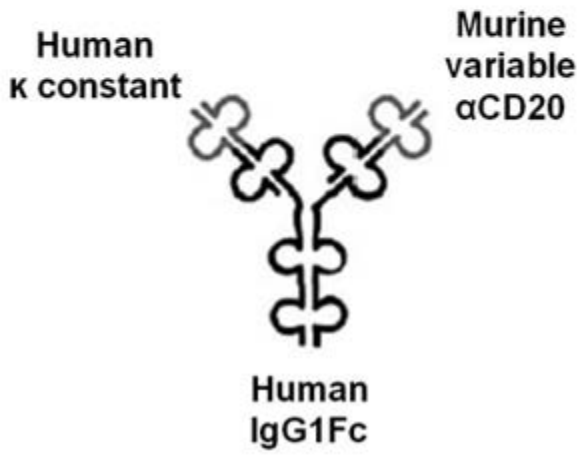
- Binds to CD20 receptor on B cells
- Administered weekly x 4 infusions



Novel anti-CD20 Antibodies
Improving on Rituximab?

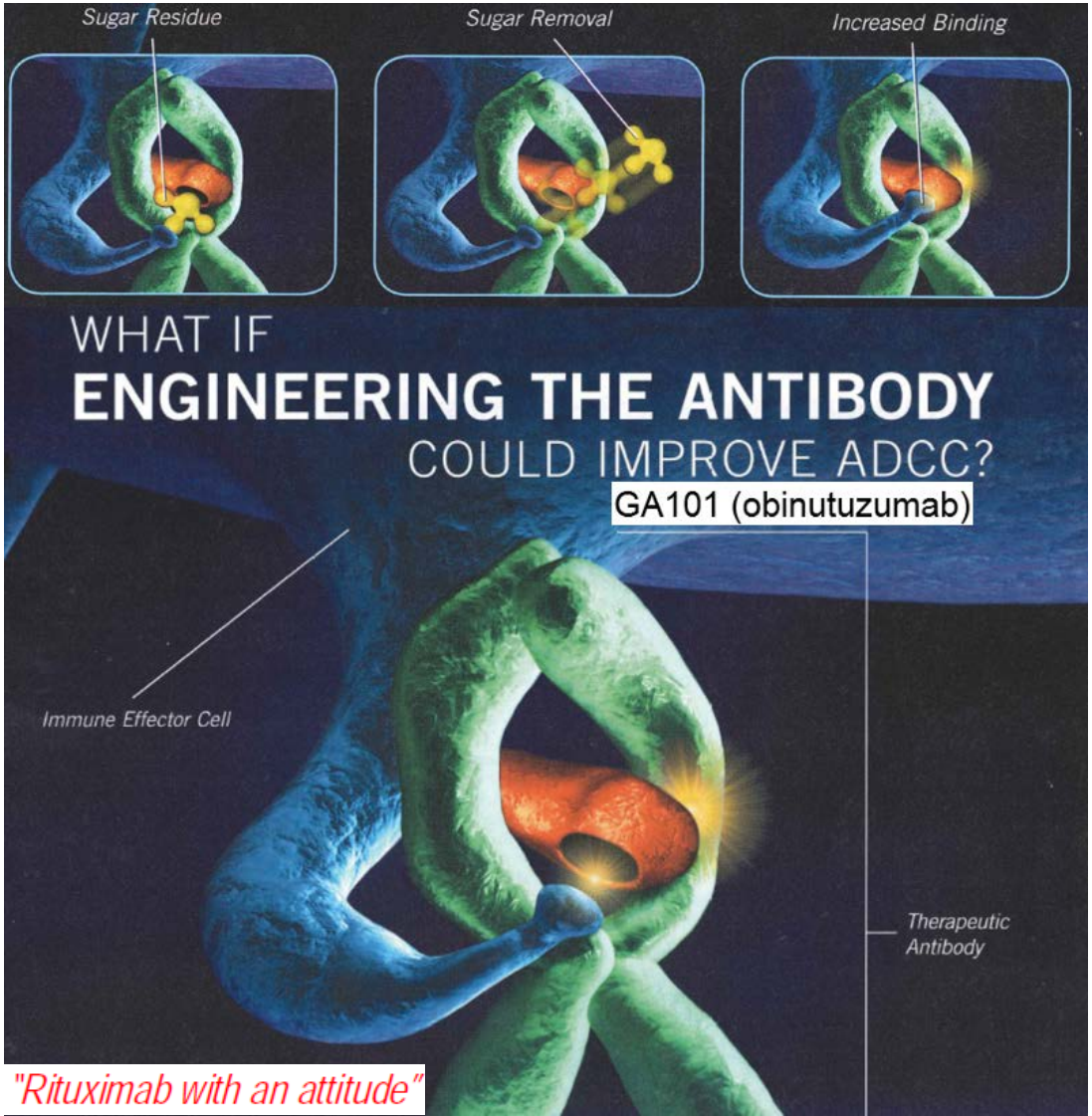
Antibody	Specificity			Activity (vs R)			Additional features
	Type	Isotype	CDR	CDC	ADCC	Apoptosis	
Ofatumumab	I	IgGI	Human	+++	=	=	Binds small extracellular part of CD20; completely human; slower off-rate
PRO131921	I	IgGI	Humanized	=	++	=	Enhanced affinity for FcγRII
Veltuzumab	I	IgGI	Humanized	=/+	=	=	Slower off-rate
AME-133	I	IgGI	Humanized	=	+	=	Enhanced affinity for CD20
Tositumomab	II	IgG2a	Murine	-	=	++	Bound to radioisotopes
GA-101	II	IgGr	Humanized	-	+++	+++	High affinity for FcγRII; strong induction of apoptosis

van Meerten T, Hagenbeek A. *Neth J Med*. 2009;67:251-259.



How to build a "better" rituximab?

Obinutuzumab
a glycoengineered antibody
specific sugar molecules
were modified to
change its interaction



Although it recognizes an overlapping CD20 epitope, obinutuzumab binds to CD20 in a different orientation and at a wider elbow angle than type I anti-CD20mAb

glycoengineered Type II CD20 monoclonal antibody

GA101 – FDA 11/01/13

ASH / FDA Drug Update

In collaboration with the Food and Drug Administration (FDA), and as a service to our members, ASH provides information about newly approved therapies and other important FDA actions (e.g., updated safety information, new prescribing information) for patients. This allows the agency to inform hematologists and professionals in hematology-related fields of recent approvals in a timely manner. Included in the message below is a link to the product label, which provides the relevant clinical information on the indication, contraindications, dosing, and safety. In providing this information, ASH does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the FDA's Office of Hematology and Oncology Products.

On November 1, 2013, the U.S. Food and Drug Administration approved obinutuzumab (GAZYVA™ injection, for intravenous use, Genentech, Inc.; previously known as GA101) for use in combination with chlorambucil for the treatment of patients with previously untreated chronic lymphocytic leukemia (CLL).

Obinutuzumab - Rituximab

German CLL11 trial randomly assigned 589 elderly patients (median age 73 years) - CIRS score > 6:

- Chlorambucil
- Chlorambucil-rituximab
- Chlorambucil-obinutuzumab

	Chlorambucil	Chlorambucil-Rituximab	Chlorambucil-Obinuzumab
ORR	30%	66%	76%
CR	0%	8%	22%
PFS	11 mo	16 mo	23 mo
Grade 3+ AE	41%	46%	67%
Neutropenia	15%	25%	34%
Infection	11%	8%	6%

Goede V, et al. *J Clin Oncol*. 2013;31: Abstract 7004.

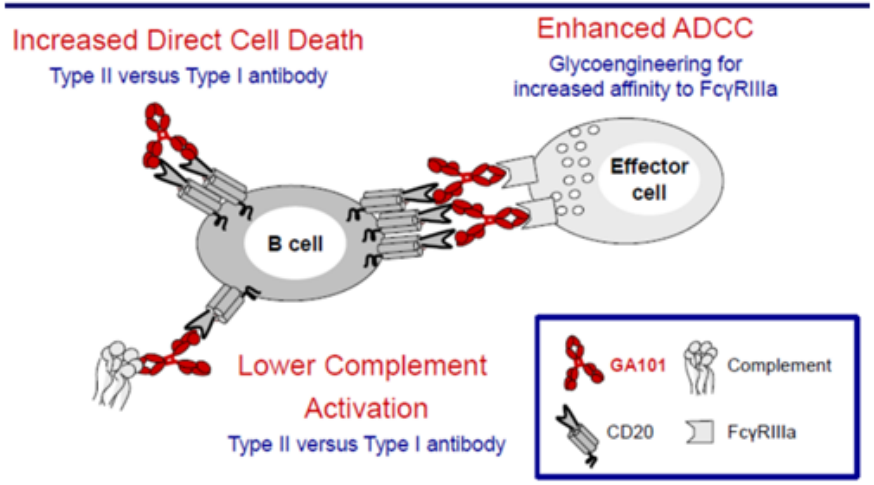
Monoclonal antibodies can induce cell death through a variety of mechanisms:

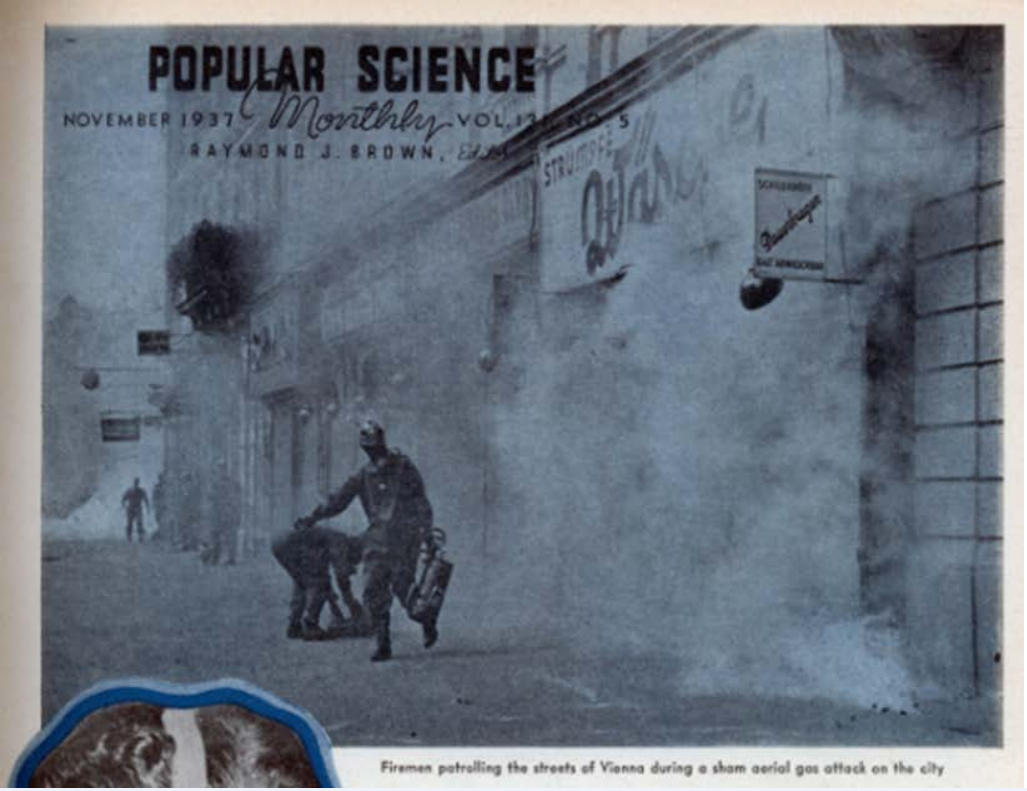
- Antibody-dependent cellular cytotoxicity (ADCC)
- Complement-mediated cell lysis (CDC)
- Direct induction apoptosis

In vitro studies:

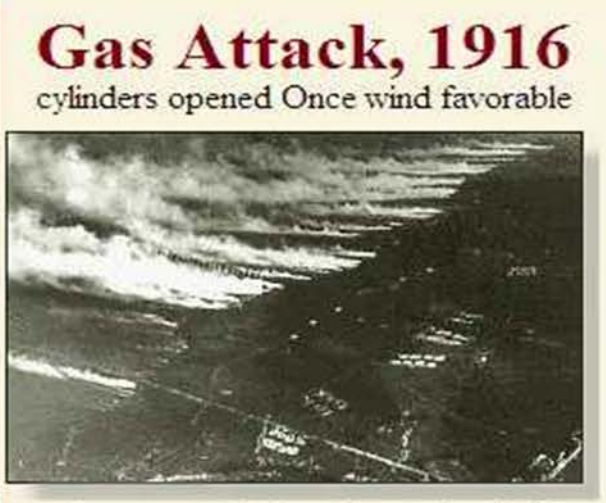
	ADCC	CDC	Direct Apoptosis
Rituximab	++		
Ofatumumab	+++	++	
Obinutuzumab	++		++

Rafiq S, et al. *J Immunol*. 2013;190:2702-2711.





What is chemo therapy?



CLL: How do you treat?

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015
CLL/SLL

NCCN Guidelines Index
NHL Table of Contents
Discussion

SUGGESTED TREATMENT REGIMENS[a]
(in order of preference)

CLL without del (11q) or del (17p)

Frail patient, significant comorbidity
(not able to tolerate purine analogs)

- Obinutuzumab + chlorambucil (category 1)
- Ofatumumab + chlorambucil
- Rituximab + chlorambucil
- Obinutuzumab (category 2B)
- Rituximab (category 2B)
- Chlorambucil (category 2B)
- Pulse corticosteroids (category 3)

First-line therapy[b]

- Age ≥70 y and younger patients with significant comorbidities
  - Obinutuzumab + chlorambucil (category 1)
  - Ofatumumab + chlorambucil
  - Rituximab + chlorambucil
  - Bendamustine (70 mg/m^2 in cycle 1 with escalation to 90 mg/m^2 if tolerated) ± rituximab
  - Obinutuzumab (category 2B)
  - Fludarabine[c,d,e] ± rituximab (category 2B)
  - Chlorambucil (category 2B)
  - Rituximab (category 3)
  - Cladribine (category 3)[f]
- Age <70 y without significant comorbidities
  - Chemoimmunotherapy
    - FCR[c] (fludarabine,[e] cyclophosphamide, rituximab) (category 1)
    - FR[c] (fludarabine,[e] rituximab)
    - PCR (pentostatin, cyclophosphamide, rituximab)
    - Bendamustine ± rituximab

Relapsed/Refractory therapy

See Suggested Regimens for Relapsed/Refractory therapy for CLL without del (11q) or del (17p) (2 of 7)

See Supportive Care for Patients with CLL (CSLL-C)

Consider prophylaxis for tumor lysis syndrome (See NHODG-B)

See monoclonal antibody and viral reactivation (NHODG-B)

See Suggested Regimens for CLL with del (17p) (3 of 7)

See Suggested Regimens for CLL with del (11q) (4 of 7)

[a] See references for regimens CSLL-D 6 of 7 and CSLL-D 7 of 7.
[b] See Supportive Care for Patients with CLL (CSLL-C).
[c] Autoimmune hemolytic anemia (AIHA) should not preclude the use of combination therapy containing fludarabine and patients should be observed carefully.
[d] In patients ≥70 y, fludarabine does not have a benefit for first-line therapy over other therapies including chlorambucil.
[e] See Discussion for further information on oral fludarabine.
[f] In rare circumstances of CNS disease, cladribine is potentially useful.

How do you treat?

H-E-B®

COLD HEAD CONGESTION

Severe

Pain Reliever / Fever Reducer, Nasal Decongestant, Cough Suppressant, Expectorant

- Headache / Sore Throat.....**Acetaminophen**
- Nasal Congestion.....Phenylephrine HCl
- Coughing.....Dextromethorphan HBr
- Chest Congestion.....Guaifenesin

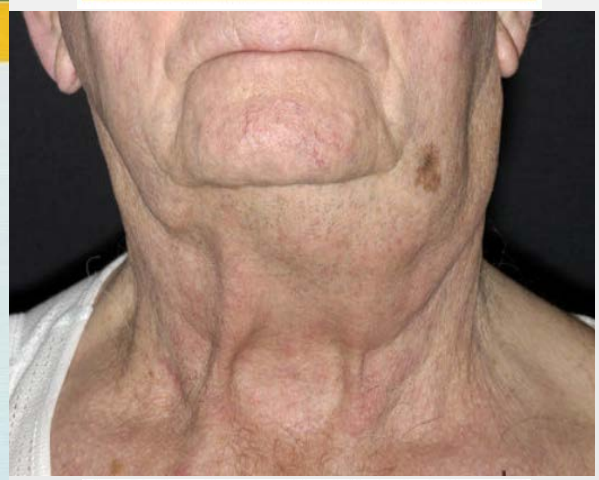
Actual Size

Daytime / Non-Drowsy

See New Warnings Information

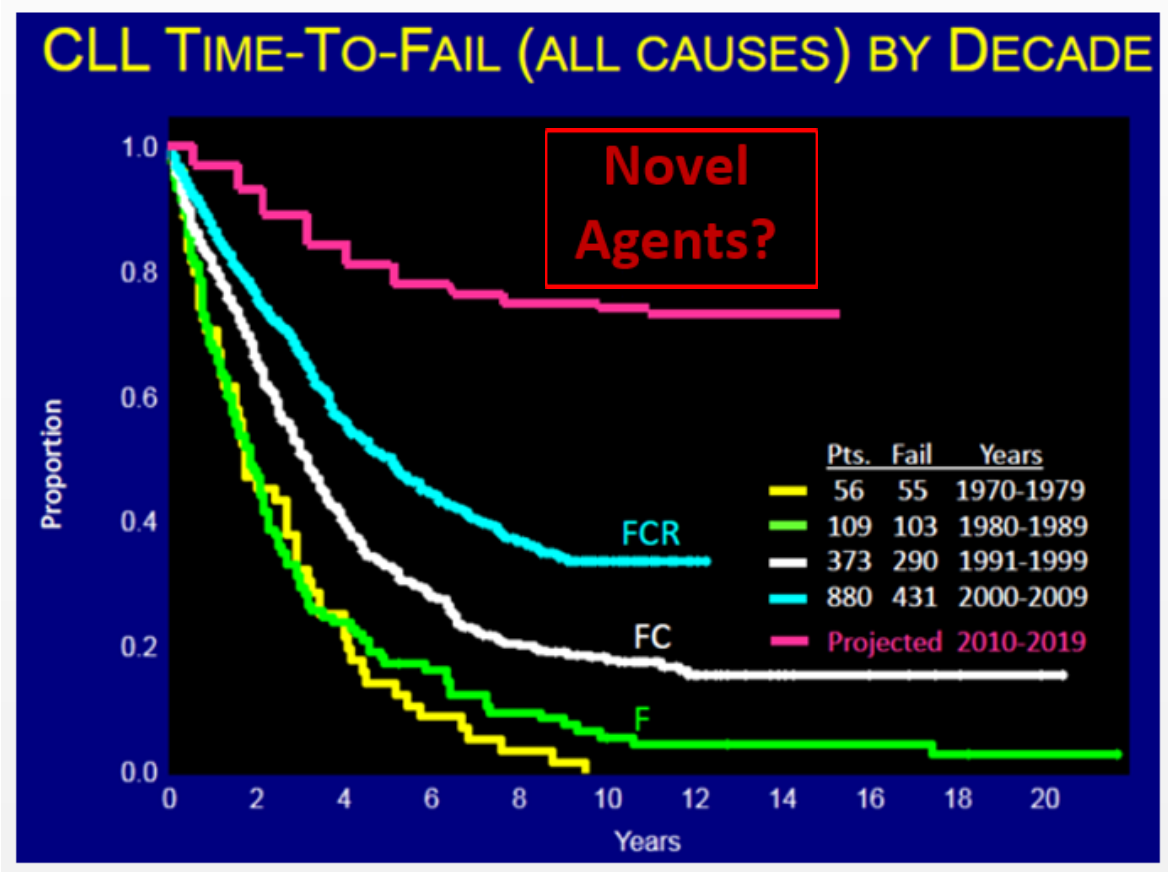
24 Cool Taste Caplets

Cancer



Single?

CLL: A Projection

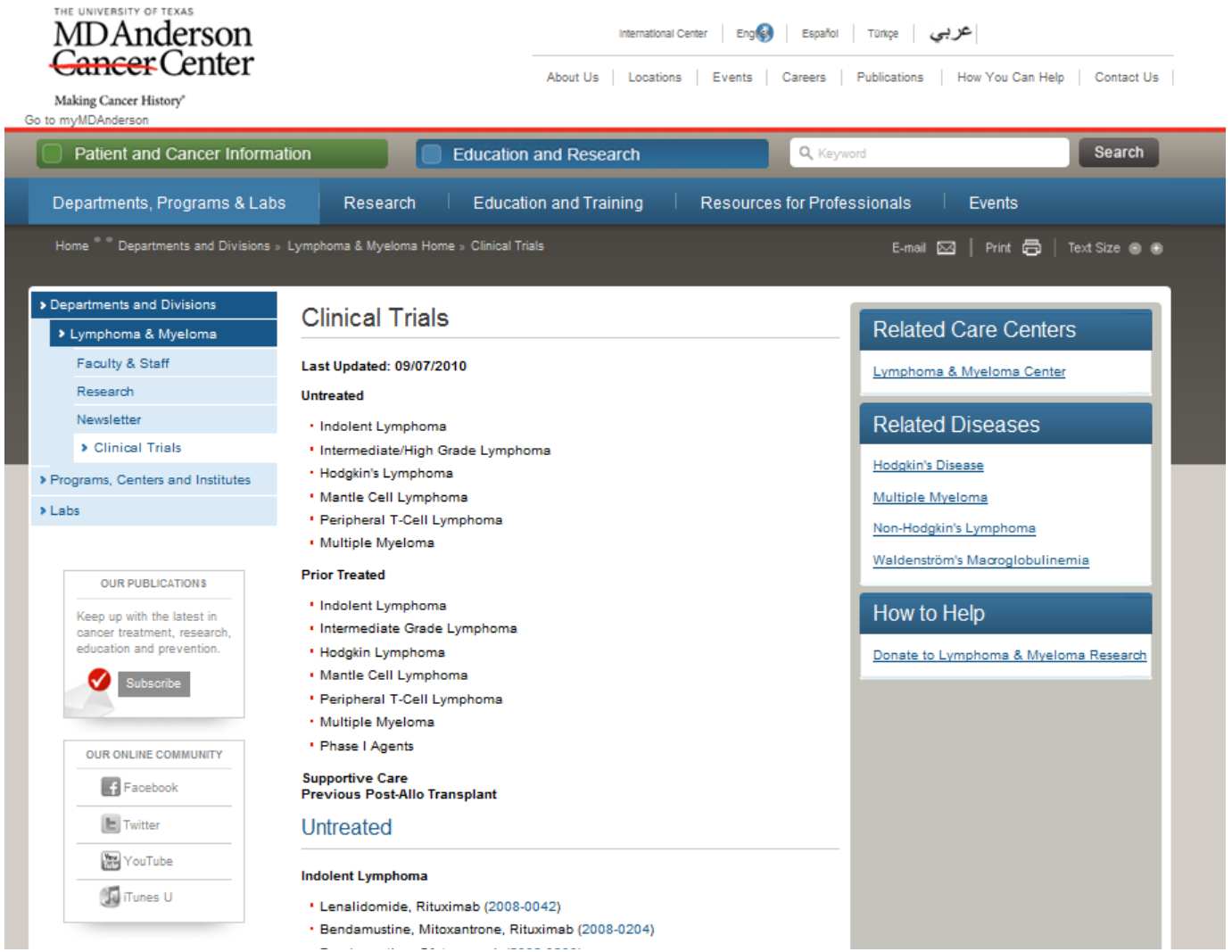


CLL 2013 –a rapidly changing scene
Michael Keating M.B.,B.S.
M.D.Anderson Cancer Center
Houston, Texas

What is new? Clinical trials

www.BannerMDAnderson.com/ClinicalTrials

480-256-6444



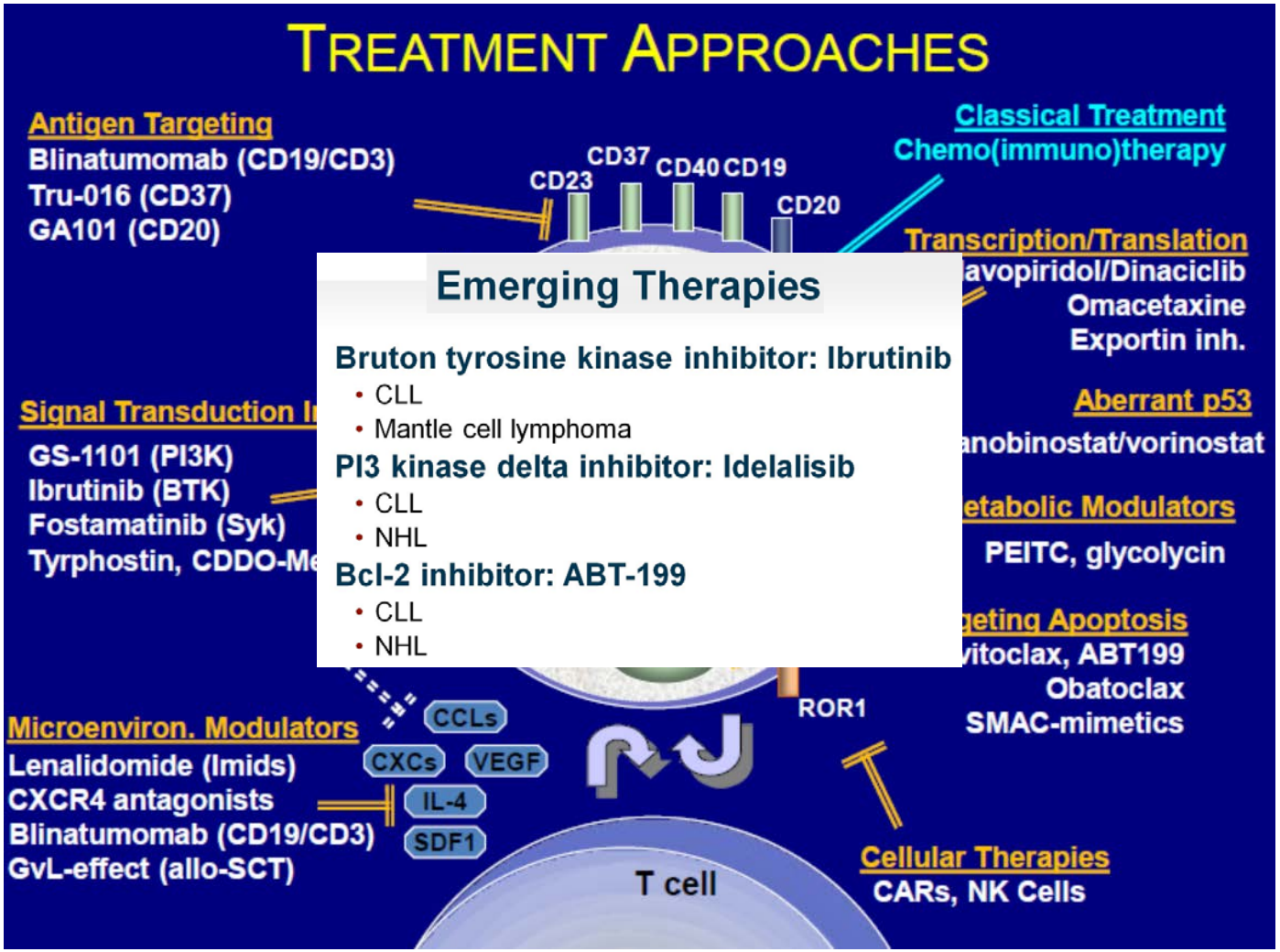
Useful webpages

Clinical trials:
www.BannerMDAnderson.com/ClinicalTrials
480-256-6444

Our facebook page:
www.facebook.com/bannermdanderson

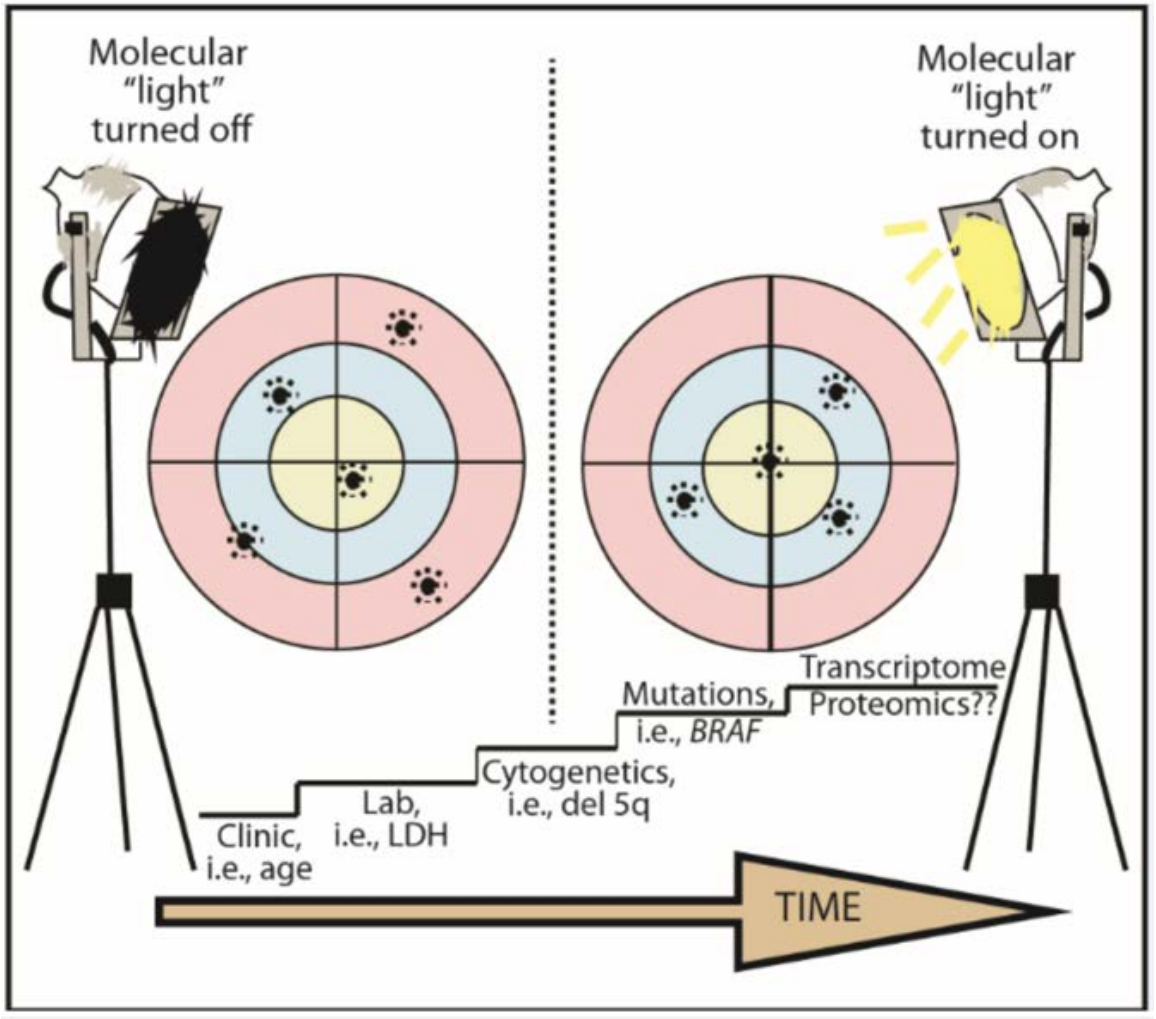
Light The Night Walk:
http://pages.lightthenight.org/az/Phoenix15

Novel Agents



Finding a Target

“Shooting in the dark”

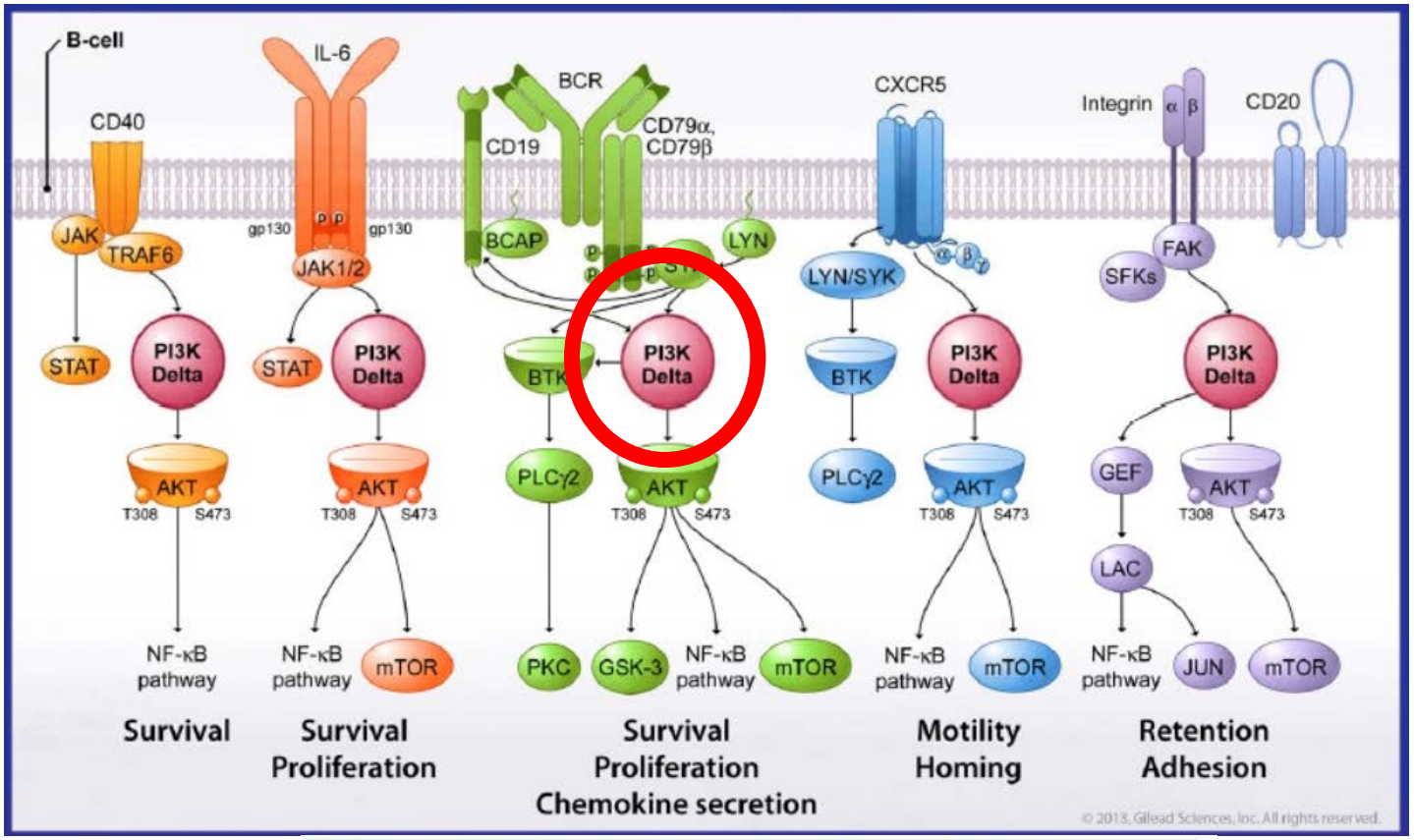


On-Target Versus Off-Target

Munoz et al. ASCO Educational Book 2013

PI3 kinase delta inhibitor

ASCO Calls Transformation Of Treatment For CLL The "Cancer Advance Of The Year."



R Chronic Lymphocytic Leukemia, Follicular B-cell Non-Hodgkin Lymphoma, Small Lymphocytic Lymphoma

Zydelig (idelalisib)*

- Dose: 150 mg PO BID.
- Phosphoinositide 3-kinase (PI3K) delta inhibitor
- *Denotes first approved within a pharmacologic drug class.

PI3 kinase delta inhibitor

There are 4 different isoforms

The δ isoform is is limited to hematopoietic origin

Class I PI3K Isoform	α	β	γ	δ
Cell Type	Mouse embryonic fibroblasts	Mouse embryonic fibroblasts	Human basophils	**Human basophils**
Cell-Based Activity	PDGF-induced pAKT	LPA-induced pAKT	fMLP-induced CD63+	**FcεR1-induced CD63+**
EC_{50} (nM)	>20,000	1,900	3,000	**8**

Lannutti BJ, et al. *Blood*. 2011;117:591-594[13]; O'Brien SM, et al. *J Clin Oncol*. 2013;31. Abstract 7005.[14]

Idelalisib FDA 07/23/14

AMERICAN SOCIETY OF CLINICAL ONCOLOGY
Making a world of difference in cancer care

From the American Society of Clinical Oncology

In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described. The following is a message from the FDA's Office of Hematology and Oncology Products Director, Dr. Richard Pazdur:

On July 23, 2014, the U.S. Food and Drug Administration (FDA) approved idelalisib (Zydelig® tablets, Gilead Sciences, Inc.) for the treatment of patients with relapsed chronic lymphocytic leukemia (CLL), in combination with rituximab, for whom rituximab alone would be considered appropriate therapy due to other co-morbidities.

The approval for CLL was based on the results of an international, multi-center, randomized (1:1), placebo-controlled trial of 220 patients comparing idelalisib 150 mg twice daily in combination with rituximab to placebo in combination with rituximab. Rituximab was administered in 8 doses (first dose at 375 mg/m2, subsequent doses at 500 mg/m2) every 2 weeks for 4 infusions, then every 4 weeks for 4 infusions.

Progression-free survival (PFS) assessed by blinded independent review committee (IRC) was the primary efficacy endpoint. The trial was stopped early based on an interim analysis; median duration of exposure to idelalisib was 5.0 months. Median PFS was not reached [95% CI 10.7, NR) in the idelalisib plus rituximab arm and was 5.5 months (95% CI 3.8, 7.1) in the placebo plus rituximab arm [HR 0.18 (95% CI: 0.10, 0.32); p < 0.0001].

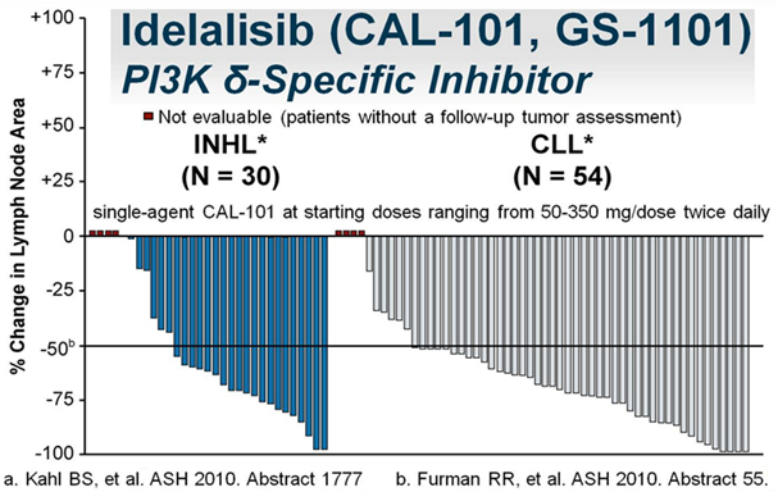
Idelalisib is being approved with a Boxed Warning alerting patients and healthcare professionals of the following fatal and serious adverse reactions: hepatotoxicity, severe diarrhea or colitis, pneumonitis, and intestinal perforation. The most common adverse reactions (incidence greater than or equal to 20%) are diarrhea, pyrexia, fatigue, nausea, cough, pneumonia, abdominal pain, chills, and rash. The most common lab abnormalities (incidence greater than or equal to 30%) are neutropenia, hypertriglyceridemia, hyperglycemia, ALT elevations, and AST elevations.

The recommended dose and schedule for idelalisib is 150 mg orally twice daily for patients with FL and SLL and in combination with rituximab for patients with CLL.

GS1101 >50%

- PI3 kinase (delta isoform) inhibitor
- Phase 2 trial
  - 54 patients with relapsed/refractory CLL
  - Median 4 prior regimens; 80% bulky disease
  - Refractory disease 70%
  - ORR was 30/54 (56%, 2 CR, 28 PR); lymph node response 80%
  - Median time to first response was 1.9 (0.9-12.9) months
  - Median PFS was 17 months
  - Median duration of response was 18 months

Brown JR, et al. *J Clin Oncol*. 2013;31: Abstract 7003.



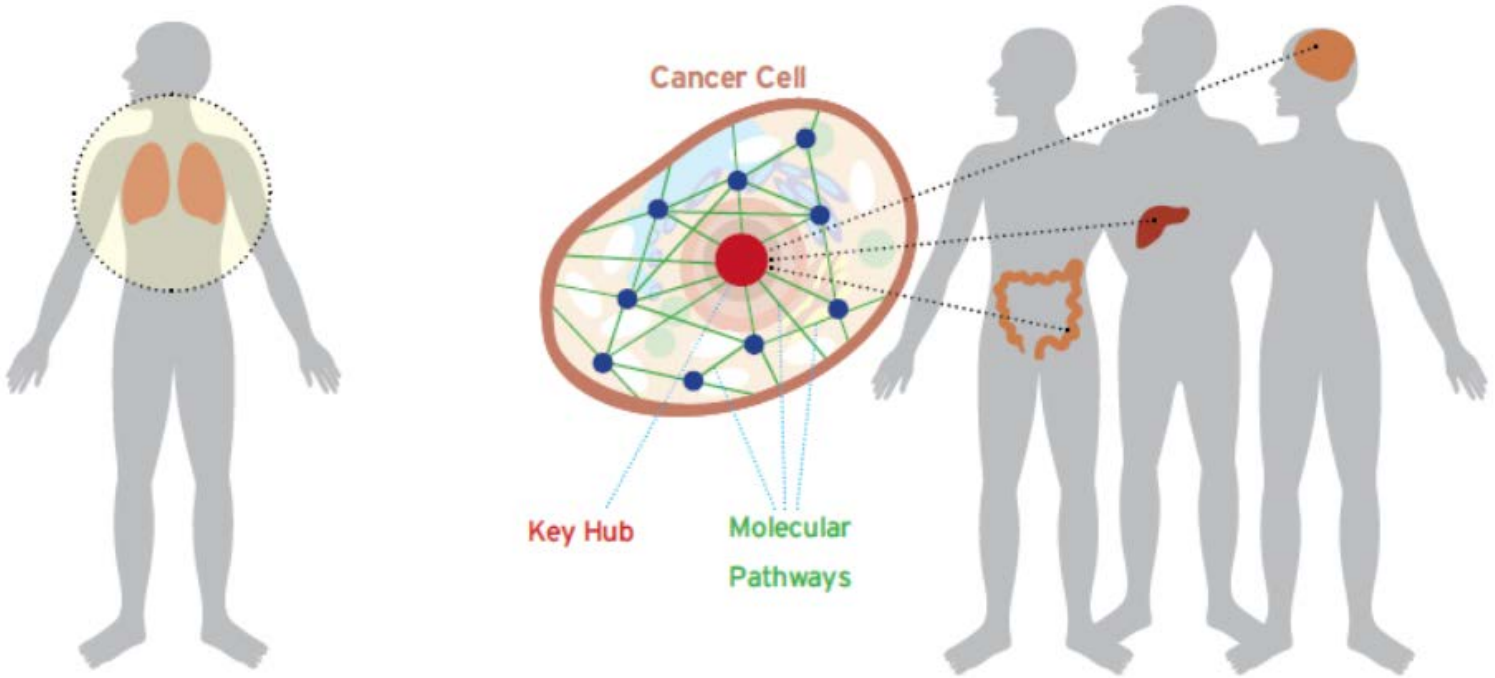
a. Kahl BS, et al. ASH 2010. Abstract 1777 b. Furman RR, et al. ASH 2010. Abstract 55.

Finding a target

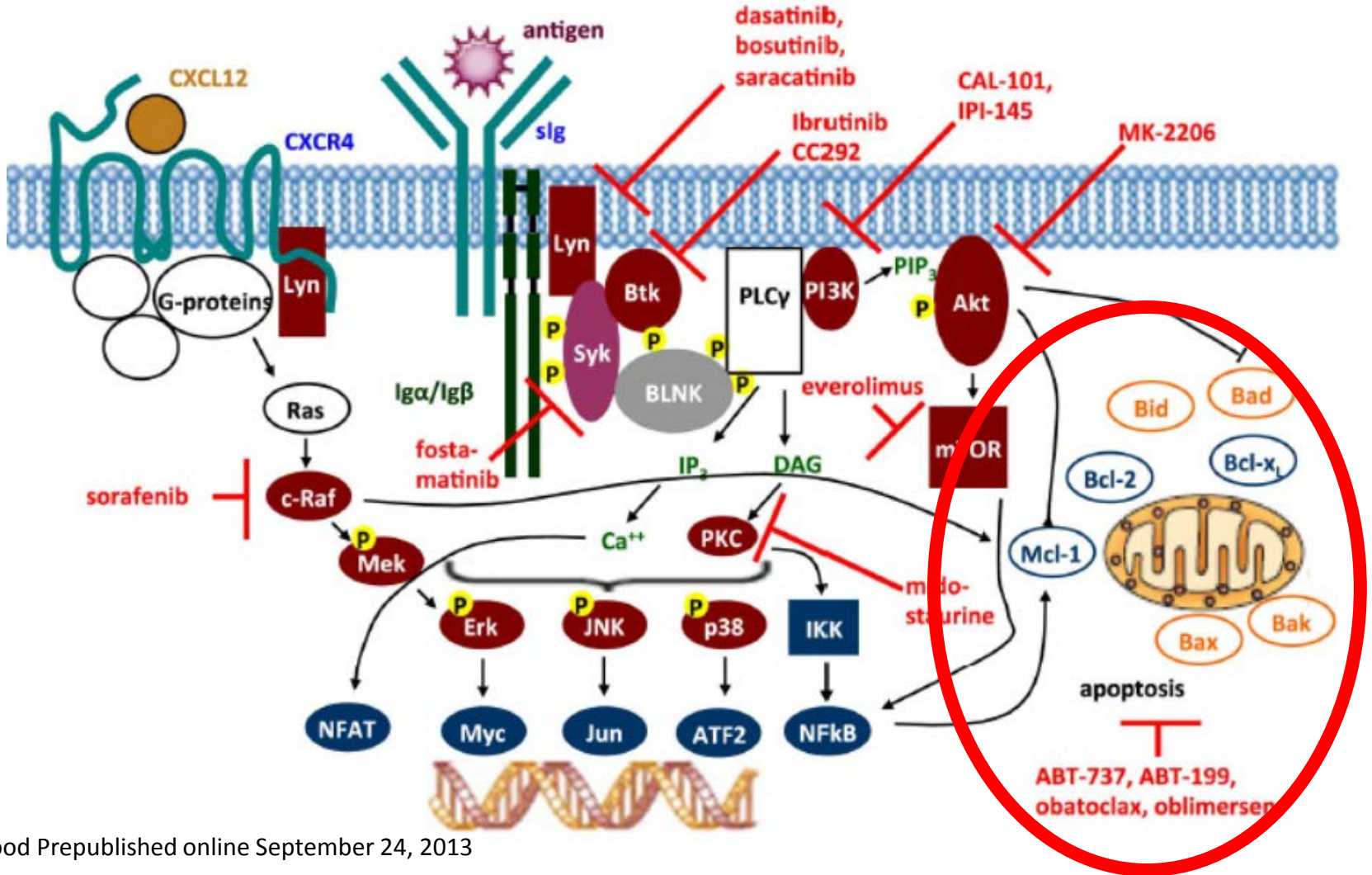
A New Model for Therapeutic Development

OLD MODEL: Treatment is determined by a tumor's location in the body, without regard to the molecular charateristics of the patient or the tumor.

NEW MODEL: Treatment is determined by key molecular "hubs" that must be targeted within the cells, and is only administered to patients whose tumors are found to have those hubs – potentially without regard to the tumor's location in the body.

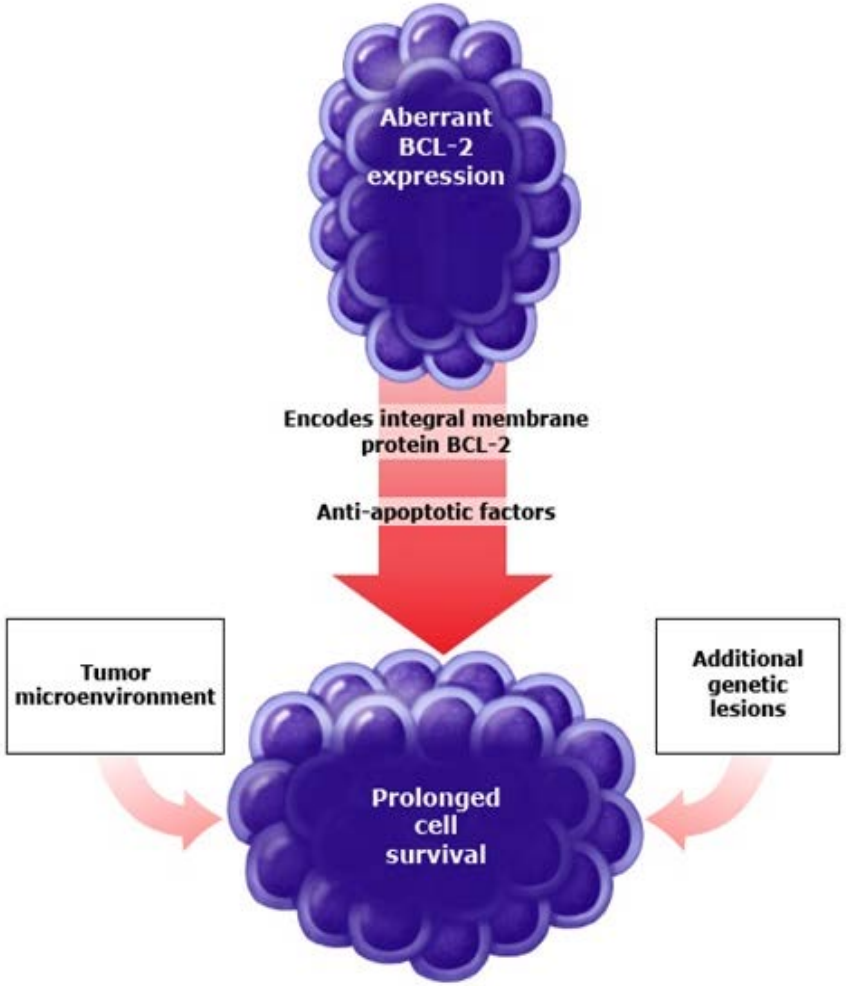


Bcl-2 inhibitor



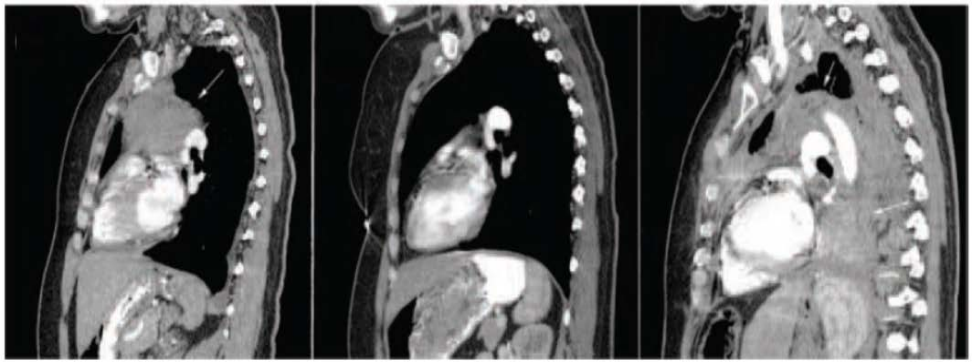
Hallek Blood Prepublished online September 24, 2013

Bcl-2 inhibitor



Bcl-2 (B-cell lymphoma 2) encoded by the **BCL2** gene

Progression of double-hit lymphoma in the midst of R-hyper CVAD



Uptodate, 2013

Munoz, AJH 2012

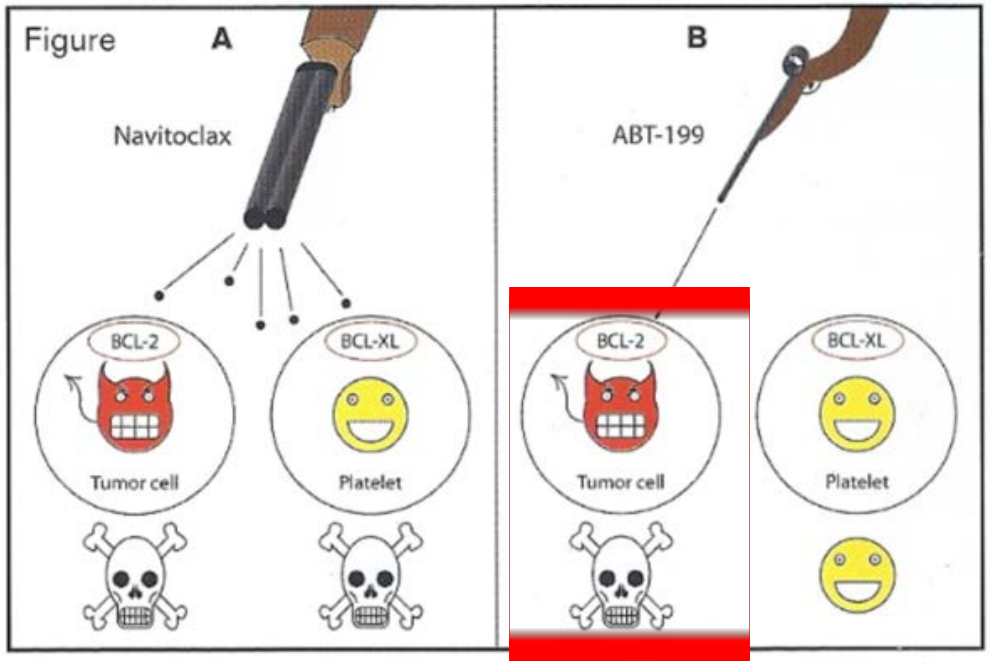
Bcl-2 inhibitor

ABT 199

- Oral inhibitor Bcl-2 (BH3-mimetic)
- Phase 1 trial relapsed/refractory CLL
- N=56
- ORR = 85%; CR=13%
- ORR patients del (17p13) =88%

Seymor JF, et al. *J Clin Oncol.* 2013;31: Abstract 7018.

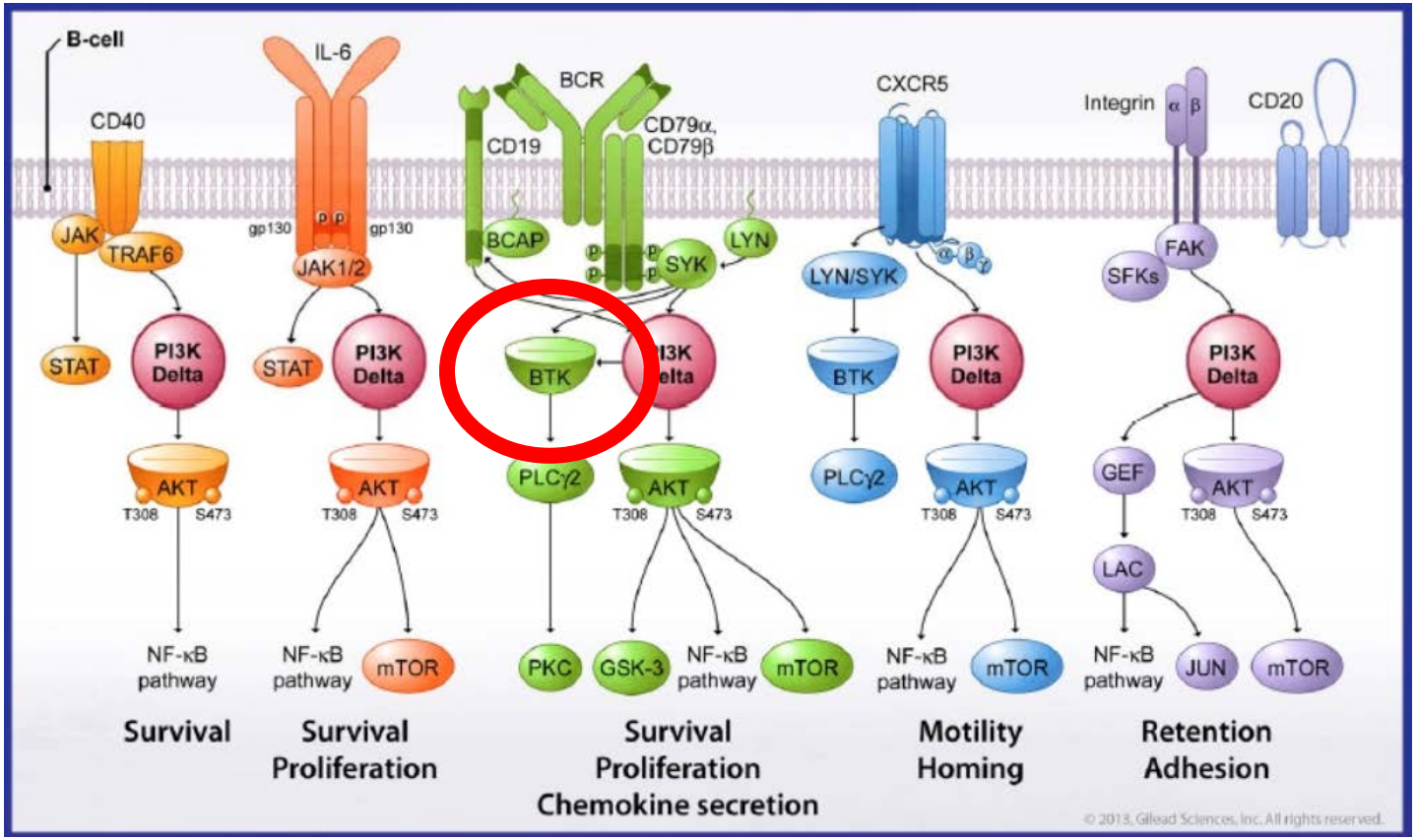
Bcl-2 (B-cell lymphoma 2)
encoded by the **BCL2** gene



ABT-199 Selectively Kills BCL-2-Dependent Tumor Cells While Sparing Platelets. A) Navitoclax (ABT-263) binds to both BCL-2 and BCL-X_L. Platelets are dependent on the anti-apoptotic activity of BCL-X_L for survival. Consequently, thrombocytopenia is a dose-limiting adverse effect of treatment with navitoclax. B) ABT-199 is specific for BCL-2 and induces selective death of BCL-2-dependent tumor cells while sparing platelets.

proteins that regulate cell death (apoptosis)

Ibrutinib: BTK inhibitor

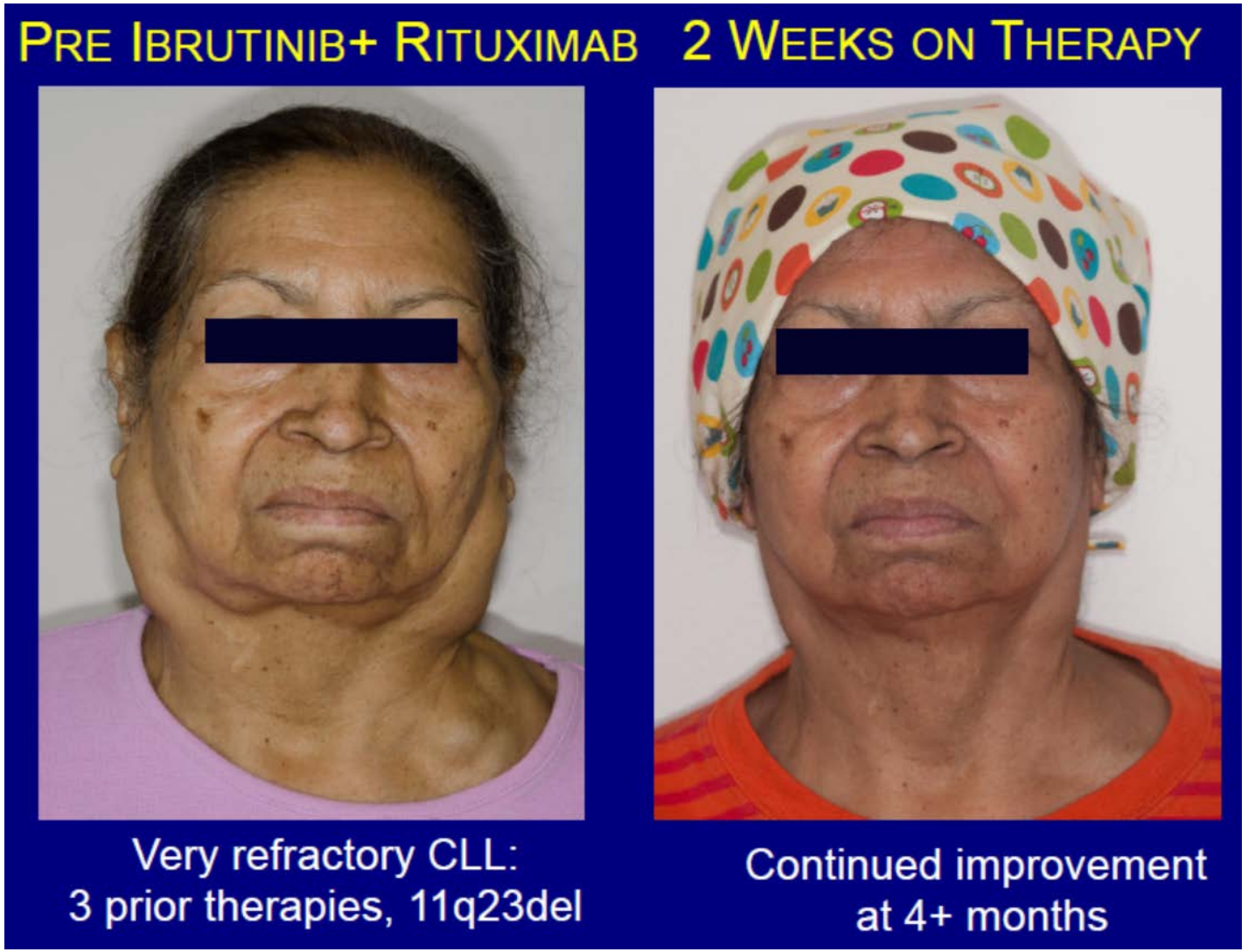


Chronic lymphocytic leukemia (CLL), previously treated: Oral: 420 mg once daily (Byrd, 2014).

CLL with 17p deletion: Oral: 420 mg once daily (Byrd, 2014).

Mantle cell lymphoma (MCL), previously treated: Oral: 560 mg once daily (Wang, 2013).

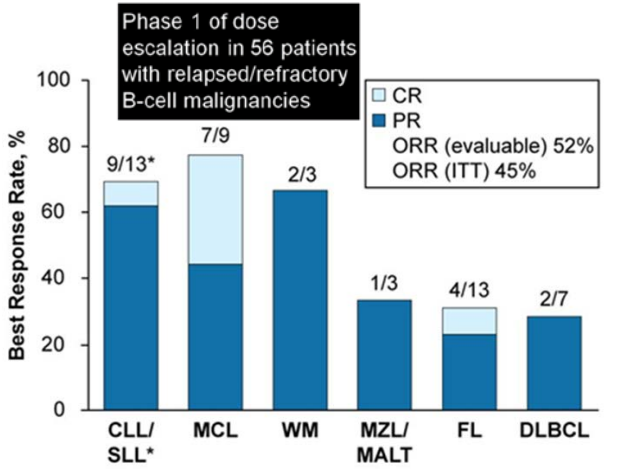
Ibrutinib: Hype vs Hope



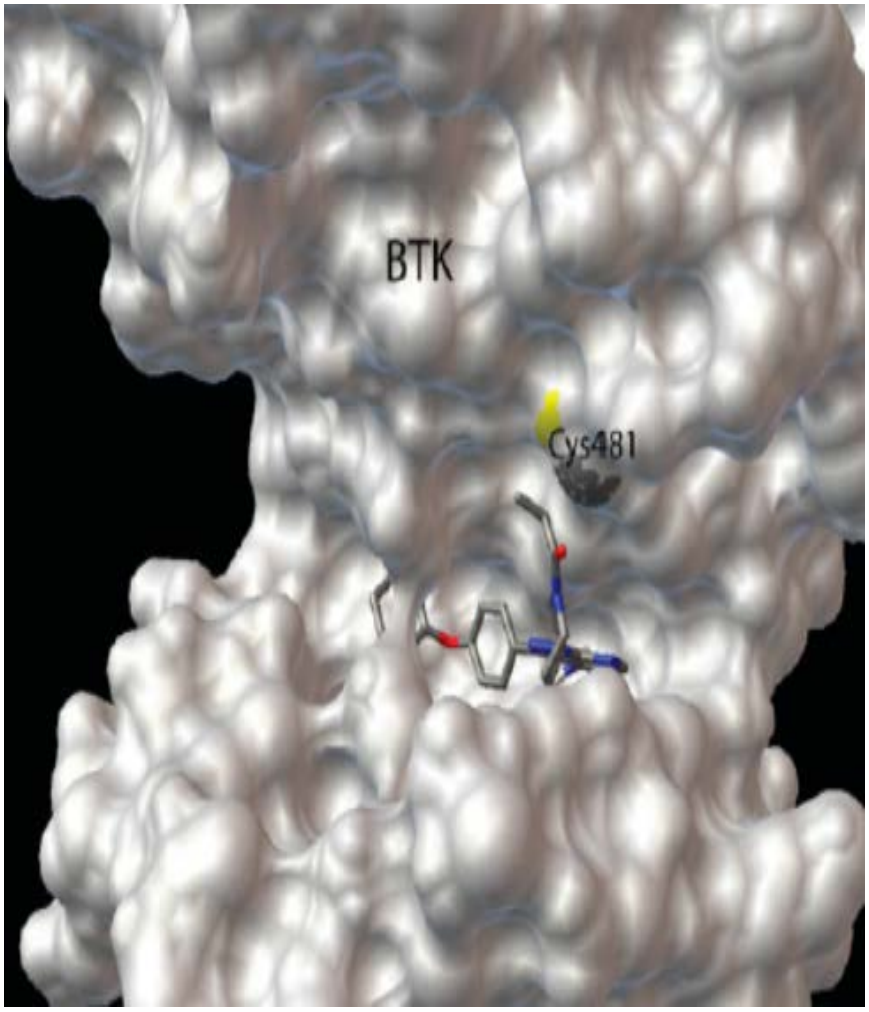
Ibrutinib: Hype vs Hope

(Btk Inhibitor)

- Forms a specific and irreversible bond with cysteine-481 in Btk
- Orally administered with once daily dosing resulting in 24-hour target inhibition
- In CLL cells promotes apoptosis
- Inhibits CLL cell migration and adhesion
- No cytotoxic effect on T-cells or NK-cells

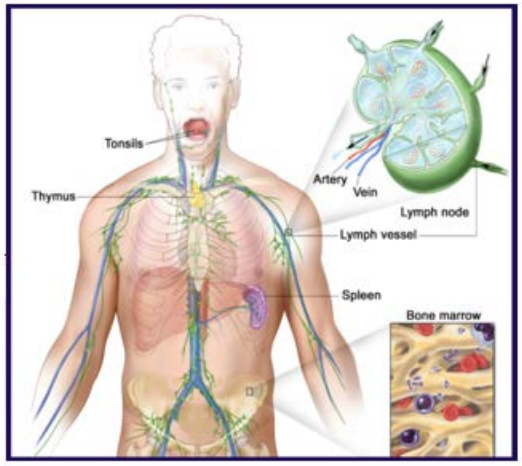


* 2 CLL patients had nodal response with lymphocytosis
Fowler N, et al. ASH 2010. Abstract 964.

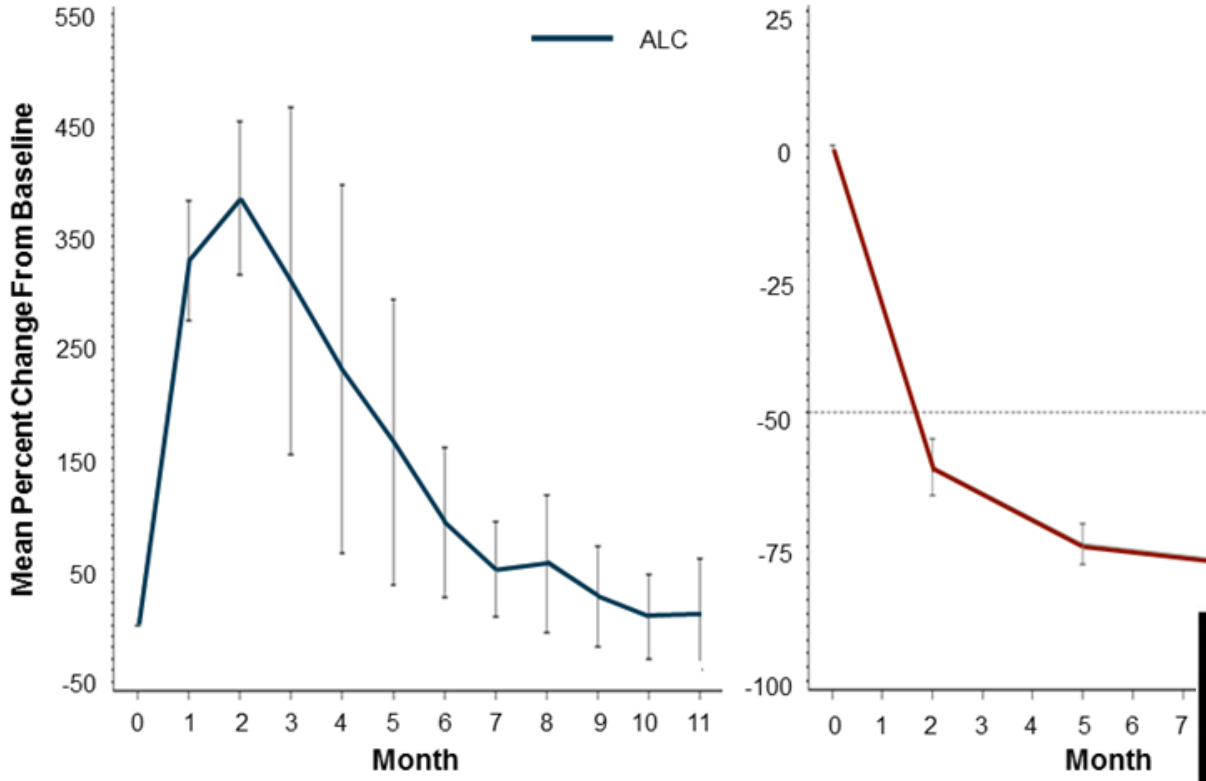


Dubovsky, Blood, online July 25, 2013

Lymphocytosis



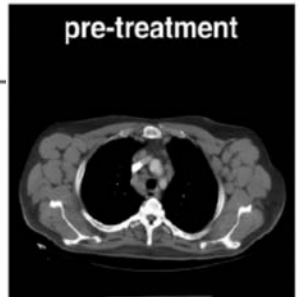
Response Pattern:
Blood Lymphocytes vs Lymph Nodes

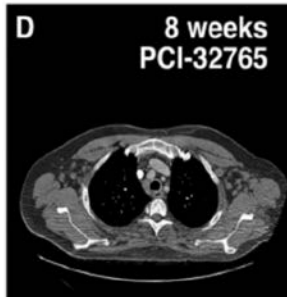


SPD = sum of products of lymph node dimension; ALC = absolute lymphocyte count.
O'Brien S, et al. *Blood*. 2011;118; Abstract 983.

Toxicity

Byrd JC, et al. *N Engl J Med*. 2013;369:32-42.





MCL: Ibrutinib FDA 11/13/13
CLL: Ibrutinib FDA 02/12/14

ASCO® AMERICAN SOCIETY OF CLINICAL ONCOLOGY
Making a world of difference in cancer care

From the American Society of Clinical Oncology
In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ASCO will periodically distribute information about newly approved therapies for cancer patients. This helps FDA to inform oncologists and professionals in oncology-related fields of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical information on the indication, contraindications, dosing, and safety. In sending this information, ASCO d
product or therapy and does not take any po
efficacy of the product or therapy described.
message from the FDA's Office of Hematolog
Director, Dr. Richard Pazdur:

On November 13, 2013, the U. S. Food and Dru
accelerated approval to Ibrutinib (IMBRUVICA,
treatment of patients with mantle cell lymphoma
least one prior therapy.

The approval was based on the results of a mul
single-arm trial enrolling 111 patients with previ
lymphoma. The primary endpoint was overall r

Safety was evaluated in the 111 patients with pr
received ibrutinib 560 mg daily. The most comm
reported in the clinical trial (occurring in greate
patients) were thrombocytopenia, diarrhea, neut
musculoskeletal pain, peripheral edema, upper
bruising, dyspnea, constipation, rash, abdomina
decreased appetite.

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apy described. The following is a message from the FDA's
ology Products Director, Dr. Richard Pazdur:

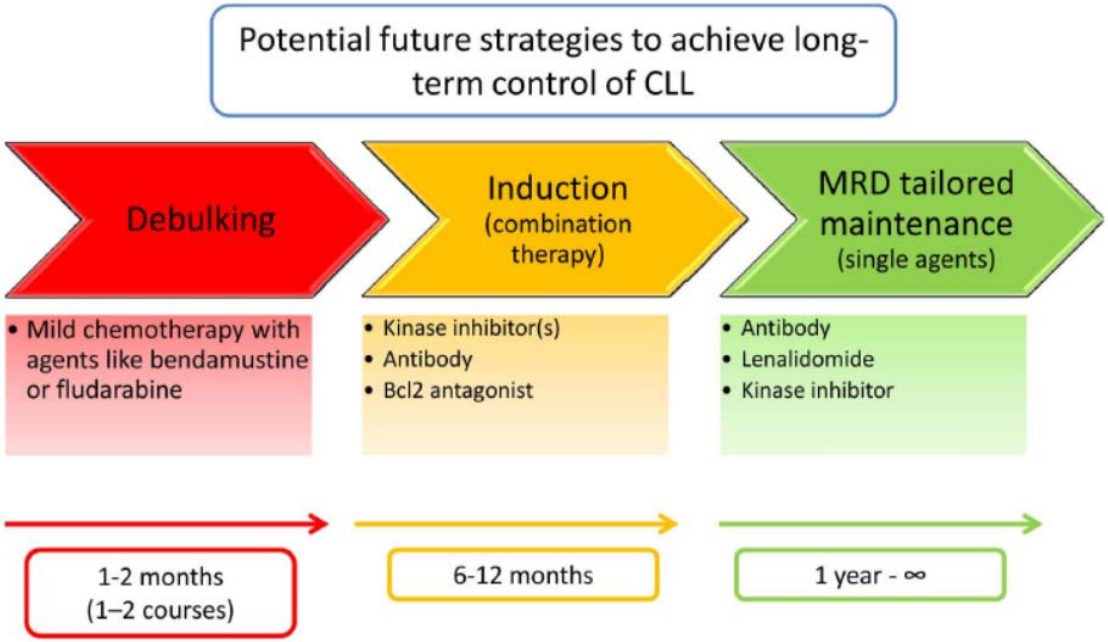
Food and Drug Administration granted accelerated approval to
yclics, Inc.) for the treatment of patients with chronic
have received at least one prior therapy. Ibrutinib previously
November 13, 2013 for the treatment of patients with mantle
d at least one prior therapy.

on the results of a multi-center, single-arm trial of 48 patients
median age was 67 years (range, 37 to 82 years) and 71%
seline ECOG performance status of 0 or 1. The median time
nd the median number of prior treatments was 4 (range, 1 to 12
istered orally at 420 mg once daily until disease progression or

d a 58.3% overall response rate (95% CI: 43.2, 72.4) as
ew committee. No complete responses were observed. The
6 to 24.2+ months, the median was not reached.

pharmacyclics®

The Future



blood

Prepublished online September 24, 2013;
doi:10.1182/blood-2013-05-498287

Signaling the end of chronic lymphocytic leukemia: new frontline treatment strategies

Michael Hallek

Caveats or Downsides

- CLL is a disease with a **long-time horizon**
- New drugs are **expensive**
- Some may have **unacceptable long term toxicity**
- Ibrutinib: Infection, lung toxicity
- Idelalisib: Liver toxicity

Younger; Fit

Deep remission

Older; > Comorbidity

Do no harm

Question

A 58 year-old woman is evaluated for a 6 month history of progressive lymphadenopathy. She is otherwise asymptomatic. Medical history is unremarkable, and she takes no medications.

On physical examination, vital signs are normal. Cervical and axillary lymphadenopathy is palpated. Abdominal examination reveals splenomegaly; the liver is not enlarged. The remainder of the examination is unremarkable.

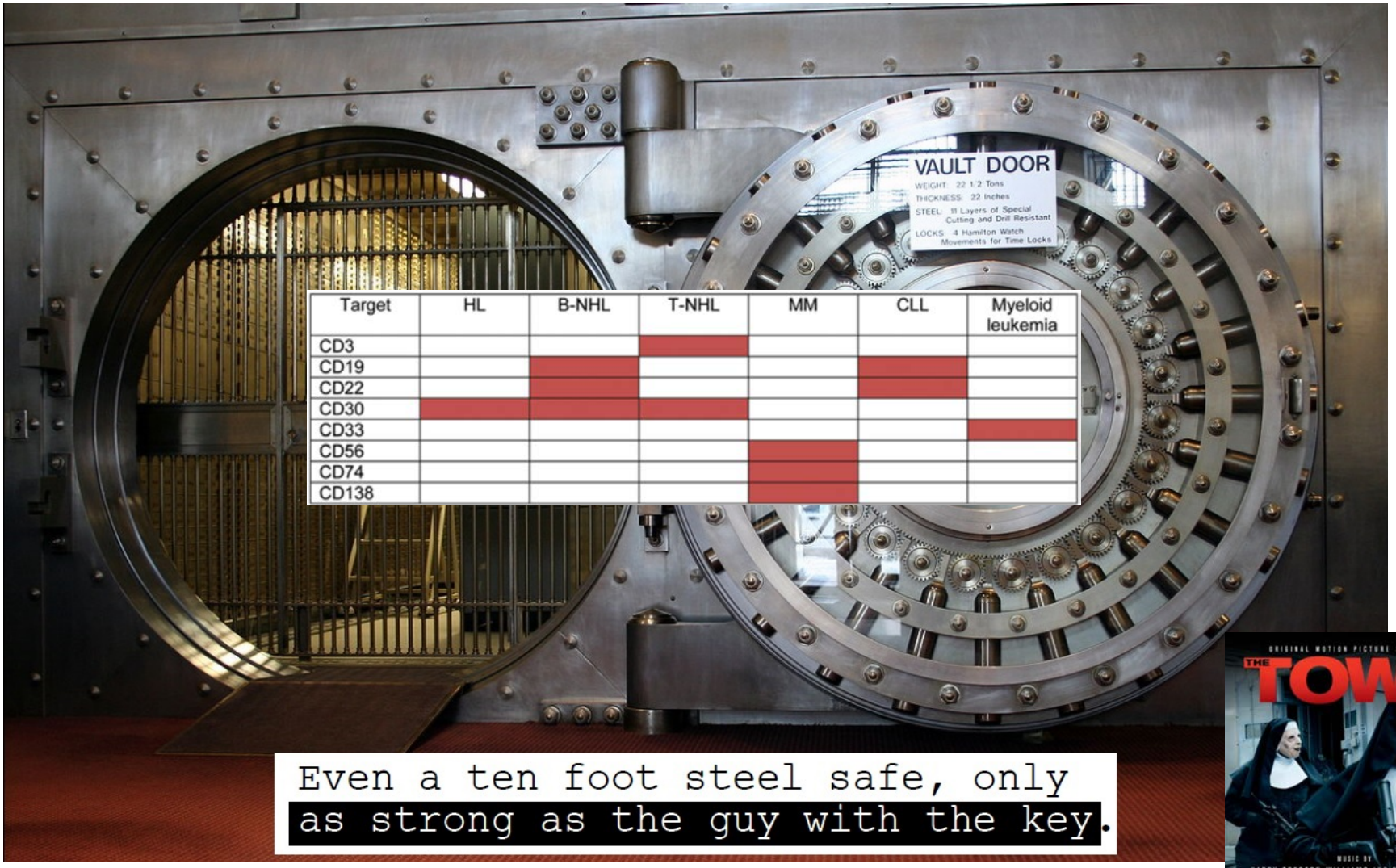
Laboratory studies indicate a leukocyte count of 12,000/ul, with 65% lymphocytes.

CT scans show diffuse cervical, axillary, abdominal, and pelvic lymphadenopathy and splenomegaly.

Which of the following diagnostic studies should be performed next?

A. Bone marrow biopsy
B. Excisional biopsy of an enlarged node
C. Fine-needle lymph node biopsy
D. Lumbar puncture
E. PET/CT scan

Finding a Key



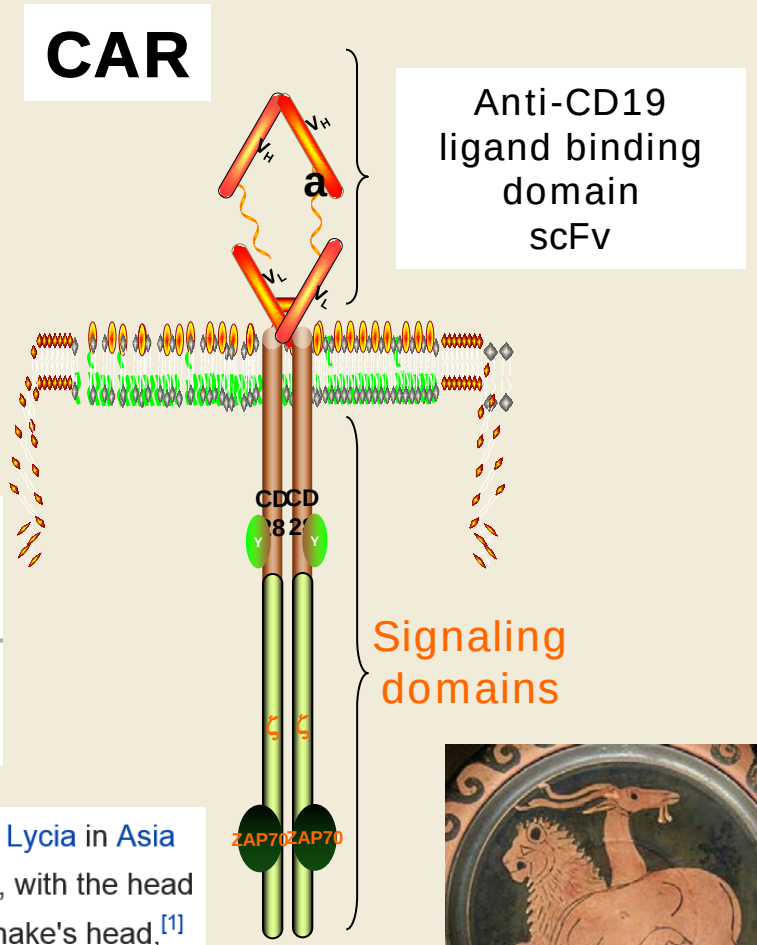
Target	HL	B-NHL	T-NHL	MM	CLL	Myeloid leukemia
CD3			■			
CD19		■			■	
CD22		■			■	
CD30	■	■	■			
CD33						■
CD56				■		
CD74				■		
CD138				■		

CAR19


Lymphoma
Cancer
Is your cancer therapy
SPECIFIC,
ADAPTABLE,
and DURABLE?
It's time to consider
IMMUNOTHERAPY
as an important treatment in your fight against cancer.
hiding in plain sight

What is CART19?
(C-himeric A-ntigen R-eceptor)

- Autologous T cells collected by leuka-pheresis were transduced with a lentivirus encoding the anti-CD19 scFv linked to co-stimulatory domains.
- Gene-modified T cells were expanded and activated ex vivo by exposure to anti-CD3/CD28 beads.



Chimera (mythology)

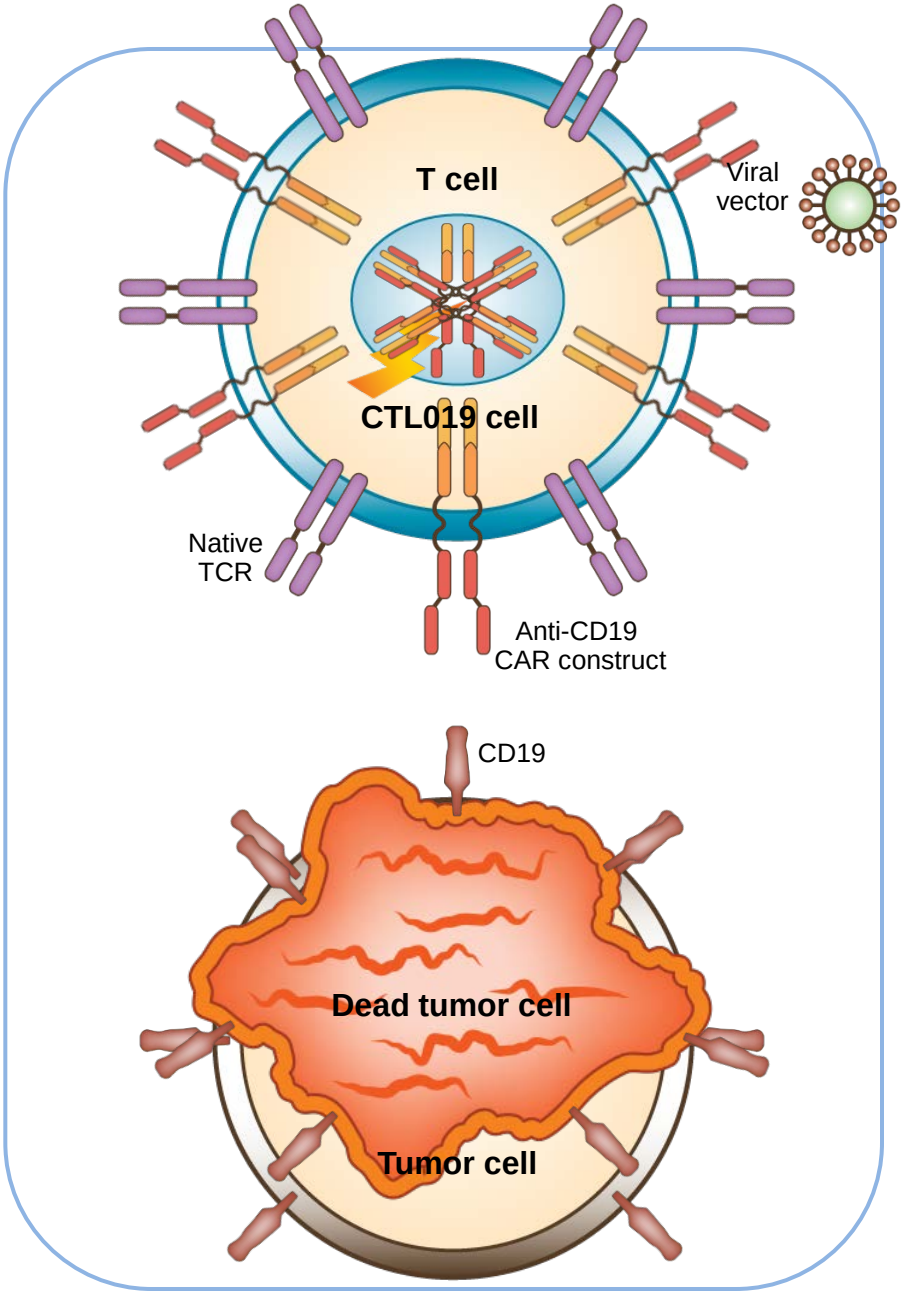
From Wikipedia, the free encyclopedia

The **Chimera** was a monstrous fire-breathing hybrid creature of Lycia in Asia Minor, composed of the parts of more than one animal. Usually depicted as a lion, with the head of a goat arising from his back and also dragon, and a tail that might end with a snake's head,[1]

Porter DL et al. *Proc ASH* 2012;Abstract 717.

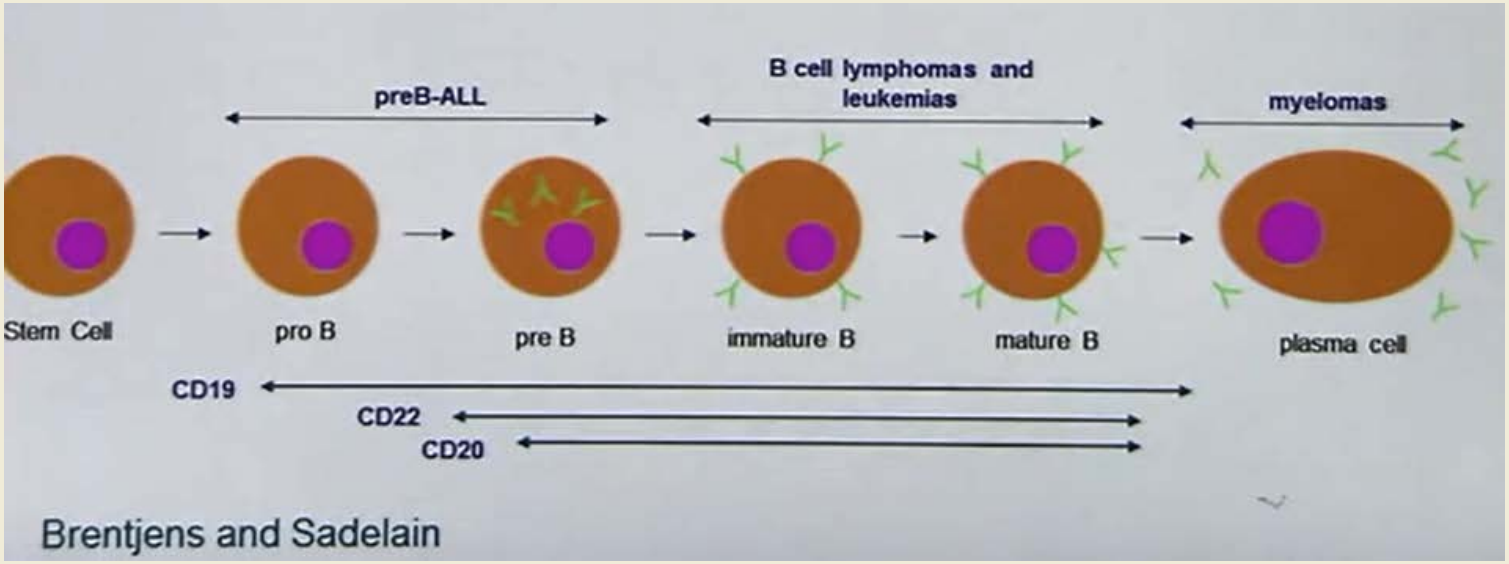
How does CART19 work? Redirecting the Specificity of T cells

- Gene transfer technology used to stably express CARs on T cells
  - confer novel antigen specificity
- Many manufacturing systems use retroviral transduction, some use lentiviral, and some the non-viral Sleeping Beauty transposon system

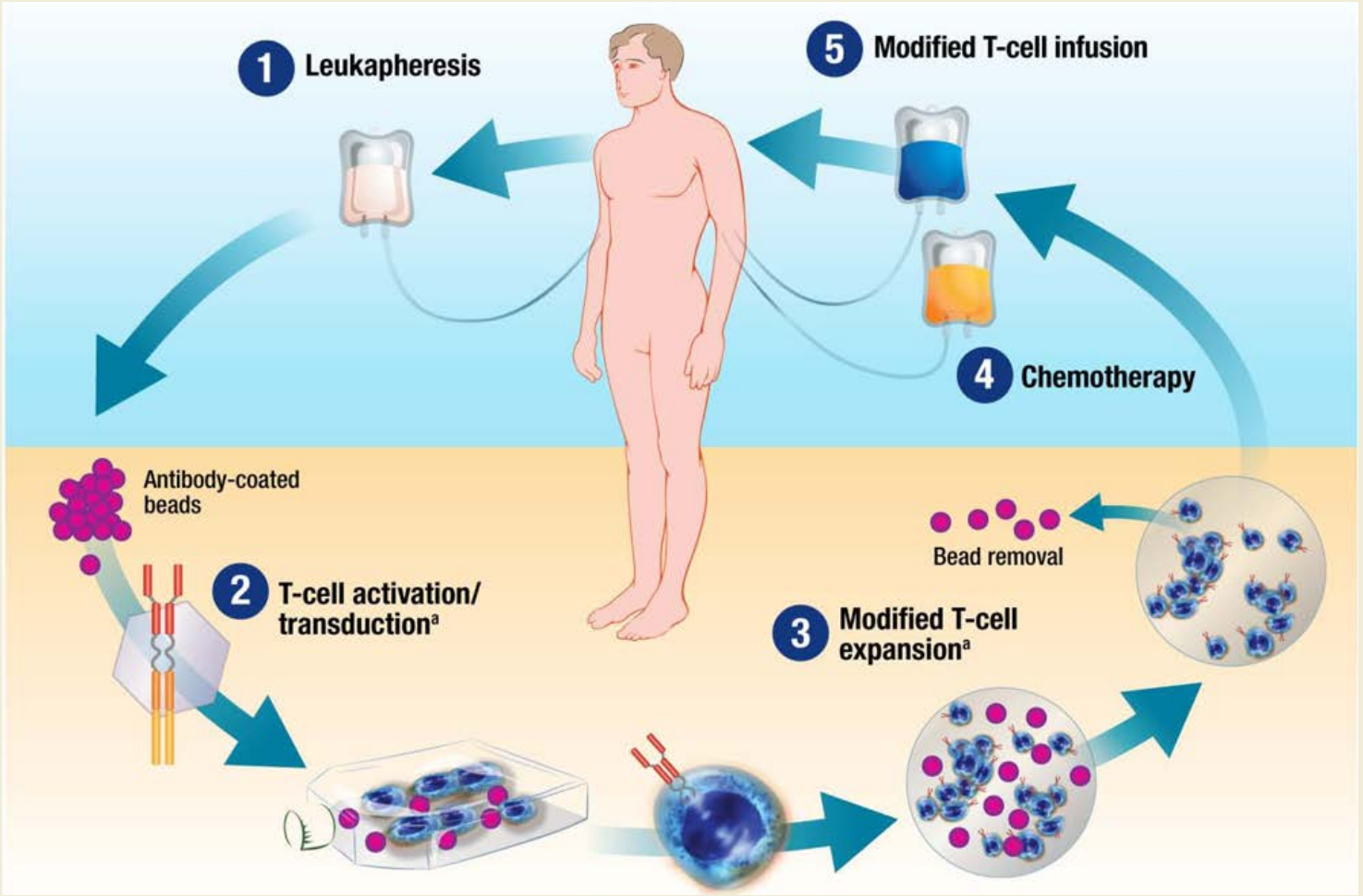


Why CD19?

- CD19 expression is restricted to B cells
- CD19 is not expressed on marrow stem cells
- CD19 is expressed on the surface of most B cell malignancies
- Antibodies against CD19 inhibit growth of tumor cells



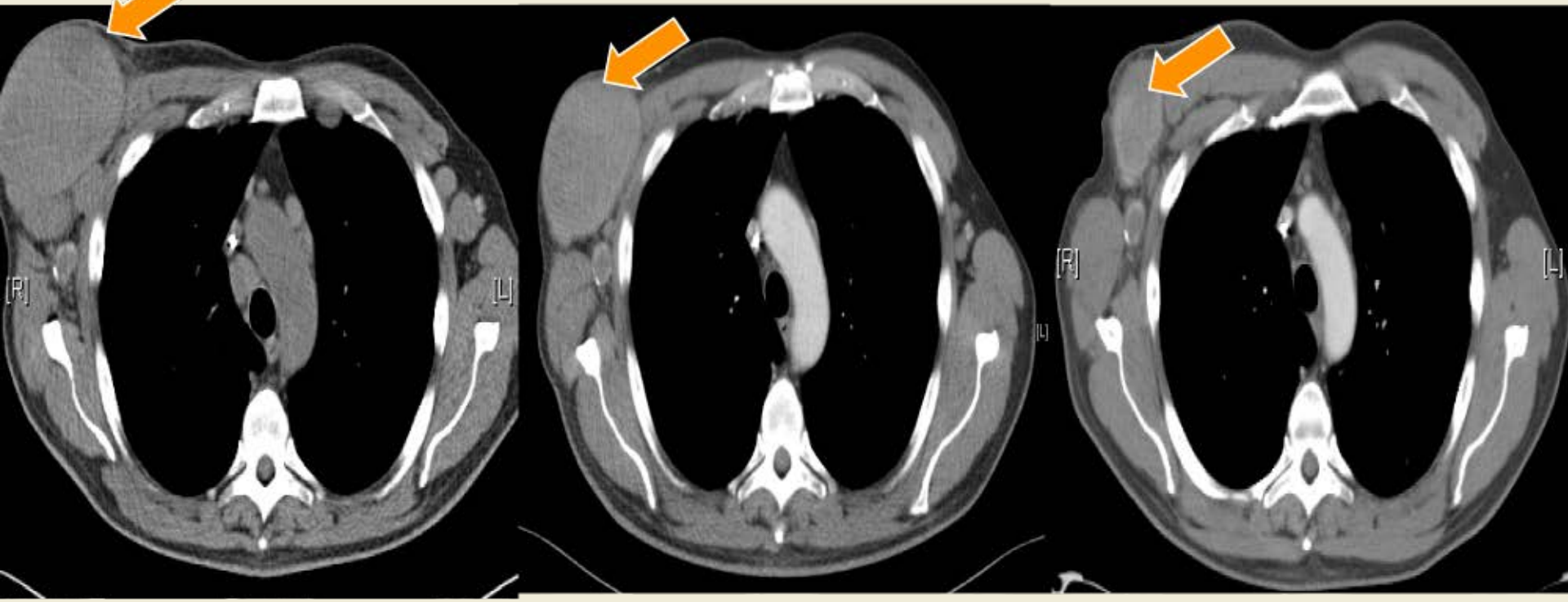
Overview of CTL019 Therapy



[a] Transduced ex vivo with a lentivirus encoding anti-CD19 scFv linked to 4-1BB and CD3-ζ signaling domains

Porter DL et al. *Proc ASH* 2013;Abstract 4162.

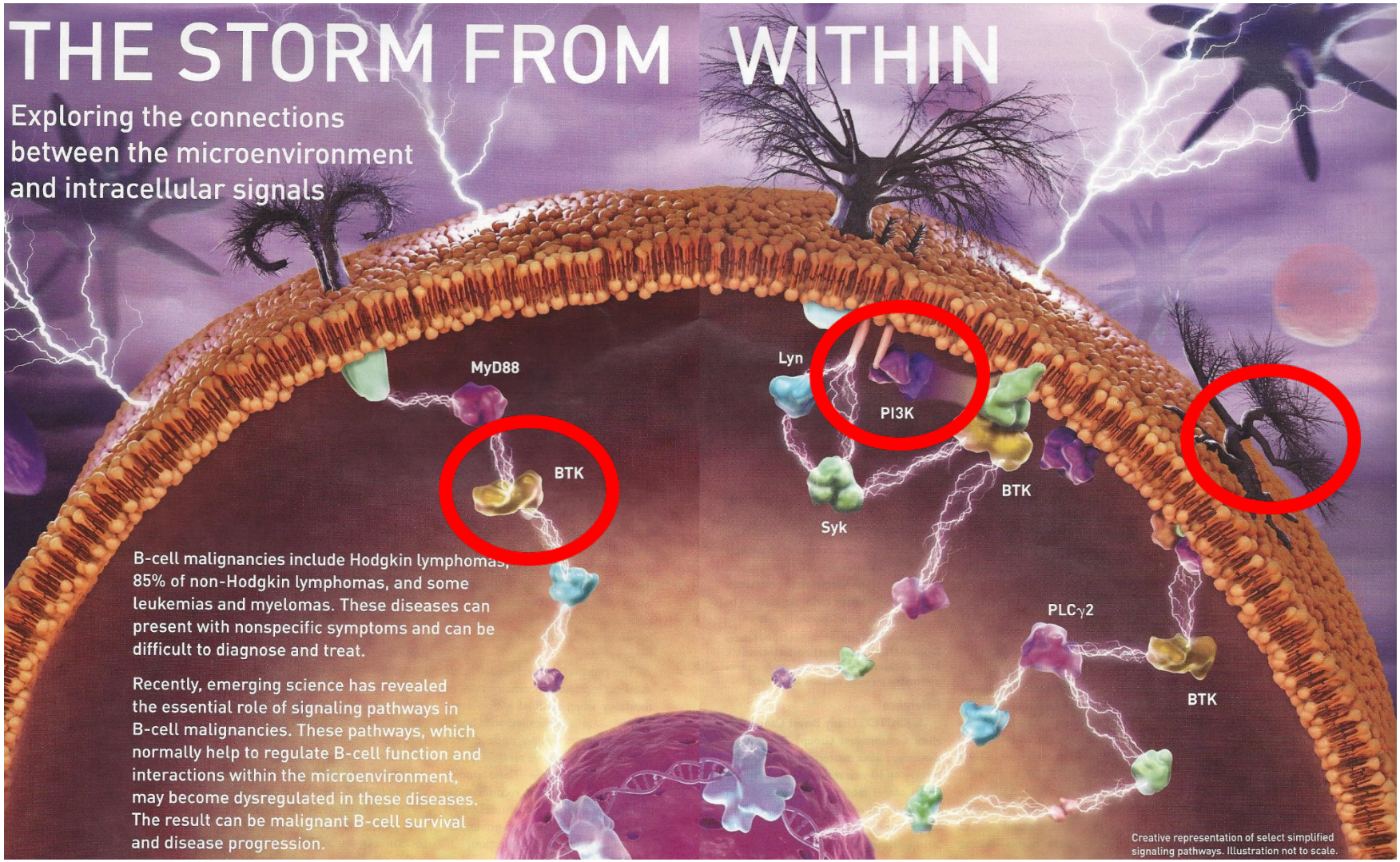
Ongoing Response in a Patient with Transformed CLL



10 prior therapies, transformed CLL, del(17p), ibrutinib resistant, XRT resistant

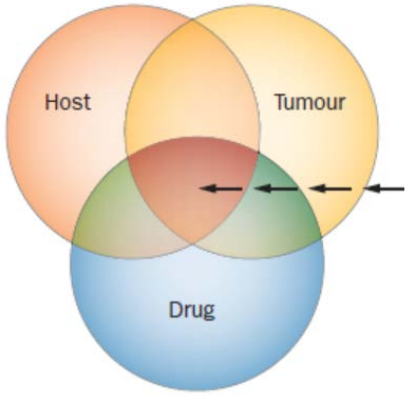
Porter DL et al. *Proc ASH* 2013;Abstract 873.

The Molecular Story



Conclusions

1. GA101 FDA approved for CLL 11/01/13.
2. Ibrutinib FDA approved for CLL 02/12/14.
3. Idelalisib FDA approved for CLL 07/23/14.
4. Future possible FDA approvals: ABT-199?
5. BCR pathway appears promising.
6. Ibrutinib has a unique profile with lymphocytosis.
7. Downsides include cost and infections.
8. Long term toxicity unclear.
9. Next generation molecules in development.



THANK YOU

"The right patient, the right drug, the right disease"

Munoz, Nature Reviews, 2012