

**Treating Chronic Lymphocytic Leukemia (CLL):
Evaluating and Managing Options**



Welcome & Introductions

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Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options

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Disclosure

Rajat Bannerji, MD, PhD

has no affiliations with commercial interests to disclose.

Thursday, June 11, 2015

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Objectives

- How chronic lymphocytic leukemia (CLL) is diagnosed
- How chromosome changes are used to plan treatment
- Standard and emerging therapies for CLL
- Side effects management
- The importance of open communication with your healthcare team

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DIAGNOSIS

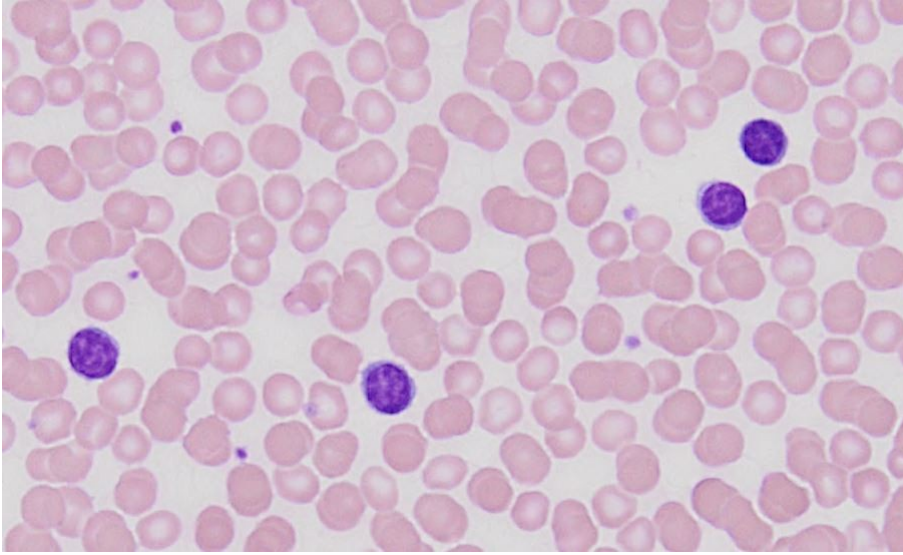
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CLL

- Most common adult leukemia in the US
- A cancer of B-lymphocytes (B-cells) which can accumulate in the blood, the bone marrow, in lymph nodes and in the spleen or liver
- Incidence is 6 per 100,000
- ~ 15,000 new cases/ year in the US
- Often discovered due to an incidental blood count test
- Median age at diagnosis 70 for men; 74 for women
- Male : female ~ 2:1
- Variable clinical course
- ~ 25% of patients require therapy at diagnosis
- Half of the rest may progress quickly; others progress slowly if at all

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CLL cells in a peripheral blood smear



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Signs and Symptoms of CLL

- Signs
 - Enlarged lymph nodes
 - Enlarged spleen or liver
 - Rash
- Symptoms
 - Fatigue
 - Drenching night sweats
 - Unexplained fevers
 - Unintentional weight loss

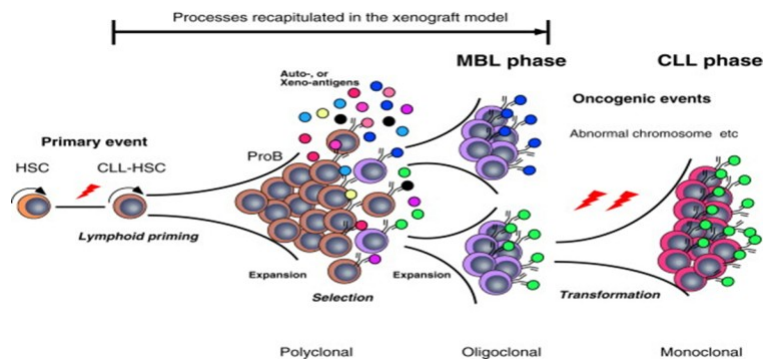
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Diagnosis

- At least 5000 B-lymphocytes/uL of blood
- Certain identifying proteins on the CLL cells (CD 5, CD19, CD20, CD23, slg (dim) by flow cytometry)
- All the CLL cells have the same light chain (kappa or lambda restriction); they are all the same or “clonal.”
- Fewer than 55% of the CLL cells are prolymphocytes (a name for activated lymphocytes) which are a larger more aggressive looking lymphocyte.
- Big lymph nodes, a big liver or spleen without CLL cells in the blood is called is Small Lymphocytic Lymphoma (SLL)
- Fewer than 5000 B lymphocytes/uL without any signs or symptoms of CLL is monoclonal B-lymphocytosis (MBL)
 - found in ~ 5% of healthy individuals age > 40
 - Incidence increases with age
 - sensitive flow cytometry techniques detect ~ 12% incidence

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A Model of How CLL May Develop in an Individual



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What else could it be?

- Mantle Cell Lymphoma
- Hairy Cell Leukemia
- Marginal Zone Lymphoma
- Follicular Lymphoma
- Mucosa Associated Lymphoid Tissue (MALT) Lymphoma
- Lymphoplasmacytic Lymphoma
- Prolymphocytic Leukemia (T-cell PLL or B-cell PLL)

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CHROMOSOME CHANGES AND IMPLICATIONS FOR TREATMENT

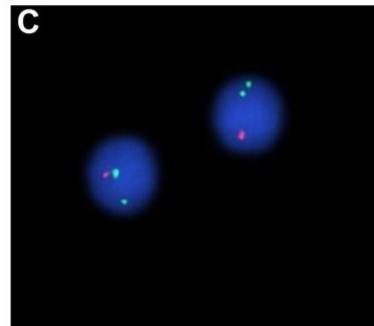
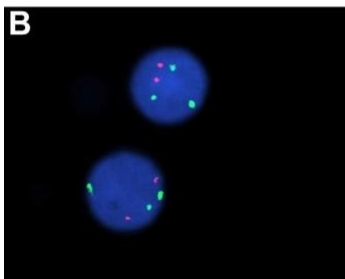
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Common Chromosome Changes in CLL

- Detected by the Fluorescence In Situ Hybridization (FISH) test
- Deletion of chromosome 13q
 - improved prognosis
 - loss of miR 15a and miR 16-1 activates BCL2, MCL1, CCND1, WNT3A
- Trisomy chromosome 12
 - unknown mechanism of leukemogenesis
- Deletion of chromosome 11q (loss of ataxia-telangiectasia mutated gene)
 - ATM activates Chk1 and Chk2; pauses the cell cycle to allow for DNA repair
 - poor prognosis
- Deletion of chromosome 17p (loss of p53)
 - p53 – activates DNA repair; initiates apoptosis
 - poor prognosis; treatment resistance

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Genomic aberrations are frequently detected by FISH in CLL-like MBL clones.



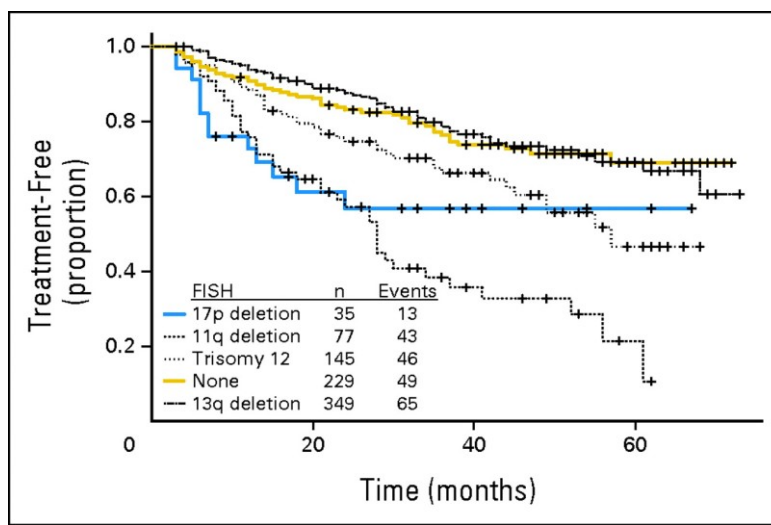
Claudia Fazi et al. *Blood* 2011;118:6618-6625

Clinical Implications of Chromosome Changes

- The time from diagnosis of CLL to needing treatment for CLL varies according to the chromosome changes found in a patient's CLL cells.
- Average survival varies according to the chromosome changes. High risk chromosome changes may predict for shorter survival.
- How well different treatments work in controlling CLL varies according to chromosome changes.
- Some treatments, such as the monoclonal antibody alemtuzumab (Campath) or bone marrow transplantation, work equally well regardless of chromosomal changes.

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Time to first treatment by FISH results



Wierda W G et al. JCO 2011;29:4088-4095

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Impact of molecular markers on prognosis in chronic lymphocytic leukemia

Marker		Frequency, %	TTT, mo	OS, mo	Reference
Cytogenetics	del 13q	55	92	133	Dohner et al 2000 ³
	Normal	18	49	111	
	Trisomy 12	16	33	114	
	del 11q	13	13	79	
	del 17p	9	9	32	
IgVH	Mutated	47	110	300*	Rassenti et al 2004 ²²
	Unmutated	53	42	115*	Hamblin et al 1999 ⁸
ZAP70	Negative	54	110	NS	Rassenti et al 2004 ²²
	Positive	46	35	NS	
CD38	Negative	67	94	193*	Rassenti et al 2008 ³⁷
	Positive	33	40	109*	Hamblin et al 2002 ²⁷

(Gribben, JG. Hematology 2008; 444-9).

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Some treatments work less well with high risk chromosome changes

Line of therapy	1 st line	Relapsed
ORR/CR	88% / 23%	59% / 9%
PFS	33.8 months	15.2 months
Del 17p RR/CR	37.5% / 0%	7.1% / 7.1%
Del 17p PFS	7.9 months	6.8 months

- Bendamustine – rituximab treatment in untreated (1st line) and previously treated (relapsed) CLL patients
- A lower overall response rate (ORR) and lower complete response rate (CR) in patients with deletion chromosome 17p
- Shorter progression free survival (PFS) in patients with deletion chromosome 17p

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IgVH somatic hypermutation

- IgVH unmutated (pre-germinal center naïve B cell?)
 - advanced stage
 - decreased survival
 - poor risk cytogenetics
 - progressive disease
- IgVH mutated (post-germinal center memory B-cells?)
 - < 98% homology with germline
 - improved survival
 - good risk cytogenetics (del 13q14)
 - stable disease

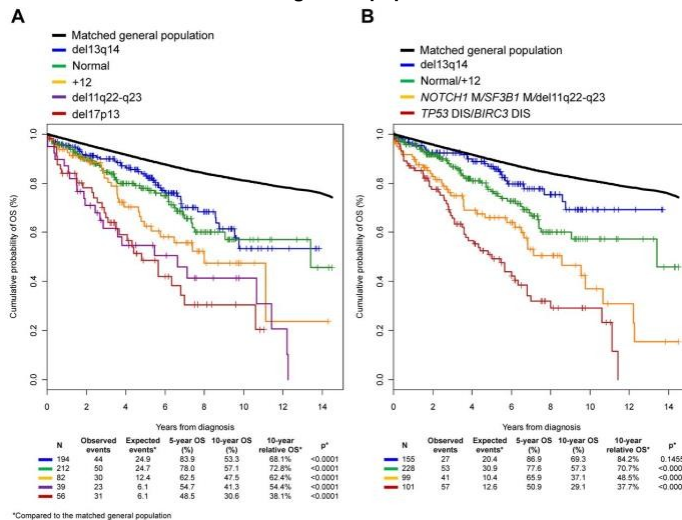
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Prognostic Markers and Treatment Decisions

- As CLL biology is deciphered, new prognostic and predictive biomarkers have been proposed
- Currently there is no data to support molecular risk based therapy in CLL outside of a trial
 - German CLL Study Group - Phase III FCR vs Obs in Patients With High-Risk, Previously Untreated Binet Stage-A CLL
 - CALGB - Phase III of Early Versus Delayed CIT (Flu-R) asymptomatic, previously untreated patients with genetically high-risk (unmutated IgVH) CLL
- Exception – patients with del 17p should be offered a trial or treatments shown effective independent of p53 status

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Observed OS in patients from the training series compared with the expected OS in the matched general population.



Daive Rossi et al. *Blood* 2013;121:1403-1412

A partial list of NCCN Recommendations for del17p CLL

- Clinical trial
- Ibrutinib
- Rituximab plus high dose methylprednisolone
- FCR or FR chemo-immunotherapy
- Obinutuzumab plus chlorambucil
- Alemtuzumab with or without rituximab
- Relapsed/Refractory patients (partial list)
 - Ibrutinib
 - Idelalisib with or without rituximab
 - Lenalidomide with or without rituximab
 - Ofatumumab

TREATMENT

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Indications for Treatment

- Constitutional symptoms
 - Weight loss $\geq 10\%$ in past 6 months; fatigue; fever; night sweats
- Anemia (hgb < 11 g/dL) and/or thrombocytopenia ($< 100,000$)
- AIHA and/or ITP poorly responsive to steroids
- Massive splenomegaly and/or lymphadenopathy
- Lymphocyte doubling time < 6 months (should not be the sole factor to determine Rx)
- There is no absolute lymphocyte count that mandates treatment in an asymptomatic patient

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Evolution of CLL 1st line Treatment

- chlorambucil:
 - Various schedules and doses (10mg/m²/day on days 1-7 Q 28-days; 40 mg/m² on day 1 every 28 days; 0.4-0.8mg/kg days 1-14 every 28-days)
 - RR 30%-50%; CR ≤ 5%; PFS 12-18 months
 - Chlorambucil + rituximab improves ORR to 80%; CR 9-19%; PFS 24 months.
- fludarabine (1980's):
 - RR 70% and CR 30%-40% in Phase 2; CR 10% in Phase 3
 - improved PFS; no change in OS (fludarabine vs CHOP - Blood 2001;98:2319-2325)
- fludarabine + cyclophosphamide:
 - RR 90%; improved PFS
 - Increased risk of treatment related MDS/AML with FC (8.2% at 7 years) compared to fludarabine alone (4.6% at 7 years).

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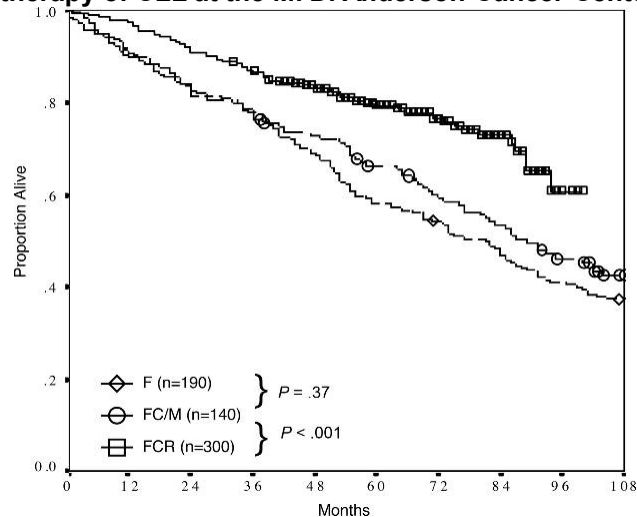
FCR (fludarabine, cyclophosphamide, rituxan)

- MDACC Phase 2 trial of 300 pts
 - RR 95%; CR 72%
 - TTP 80 months
- German Phase 3 of FCR vs FC (n=817)
 - FCR 95% RR/ 52% CR/ PFS 52 months
 - FC 88% RR/ 27% CR/ PFS 33 months
 - An overall survival advantage was shown for the first time in CLL. 3-yr OS 87% (FCR) vs 83% (FC) (p=0.01)
- Not all chemoimmunotherapy triplets are the same
 - FC-alemtuzumab vs FCR (French Phase 3 trial) stopped early due to excess deaths in the FCA arm (9% treatment related mortality); FCA also had an inferior CR rate.

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Survival of patients receiving fludarabine (F), fludarabine and cyclophosphamide or mitoxantrone (FC/M), and FCR as initial therapy of CLL at the M. D. Anderson Cancer Center



Tam, C. S. et al. Blood 2008;112:975-980

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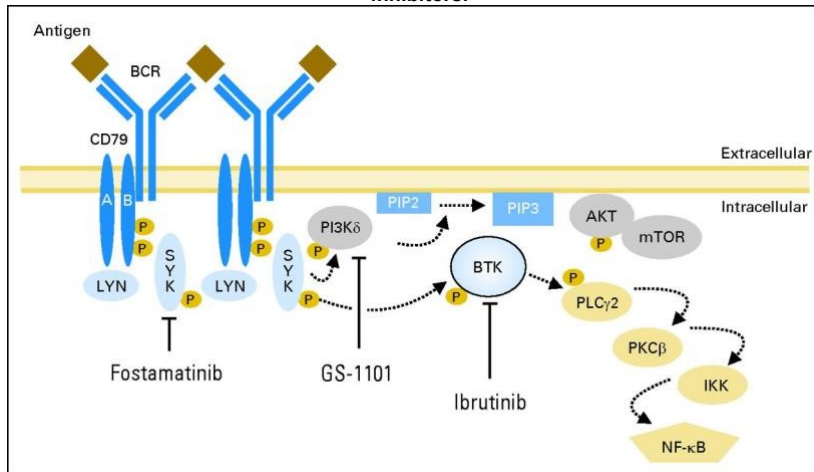
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B cell receptor (BCR)

- A transmembrane immunoglobulin (Ig), often IgM, associated with Ig-alpha (CD79A) and Ig-beta (CD79B) chains.
- BCR is the antigen receptor and promotes B cell growth, proliferation and survival
- BCR activation drives some B cell malignancies including CLL
 - Auto-Ag stimulation drives chronic lymphocytic leukemia (CLL) marked by restricted repertoire of IGHV genes.
- Proteins which transmit the BCR signal are targets for the treatment of CLL
 - Bruton's tyrosine kinase (BTK) is the target of the drug ibrutinib
 - Phosphatidylinositol-3-kinase (PI3K) is the target of the drug idelalisib
 - Spleen tyrosine kinase (SYK) – no drug in late stage development

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Antigen-dependent B-cell receptor (BCR) signaling and its targeting by small-molecule inhibitors.



Wiestner A JCO 2013;31:128-130

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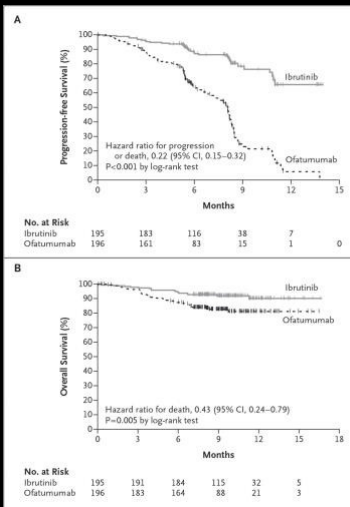
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Ibrutinib

- An oral BTK inhibitor
- The dose is 420mg once daily
- The RESONATE clinical trial compared ibrutinib to the monoclonal antibody ofatumumab in 391 patients with previously treated CLL (NEJM 2014; 371:213-23)
- Progression free survival favored ibrutinib (median PFS not reached vs 8.1 months)
- Overall survival at 12 months favored ibrutinib (90% vs 81%)
- The results were similar for patients with the poor risk deletion of chromosome 17p as for other patients
- Ibrutinib is FDA approved for the 2nd line treatment of CLL and for the initial treatment of CLL with del 17p

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Progression-free and Overall Survival.



Byrd JC et al. N Engl J Med 2014;371:213-223.



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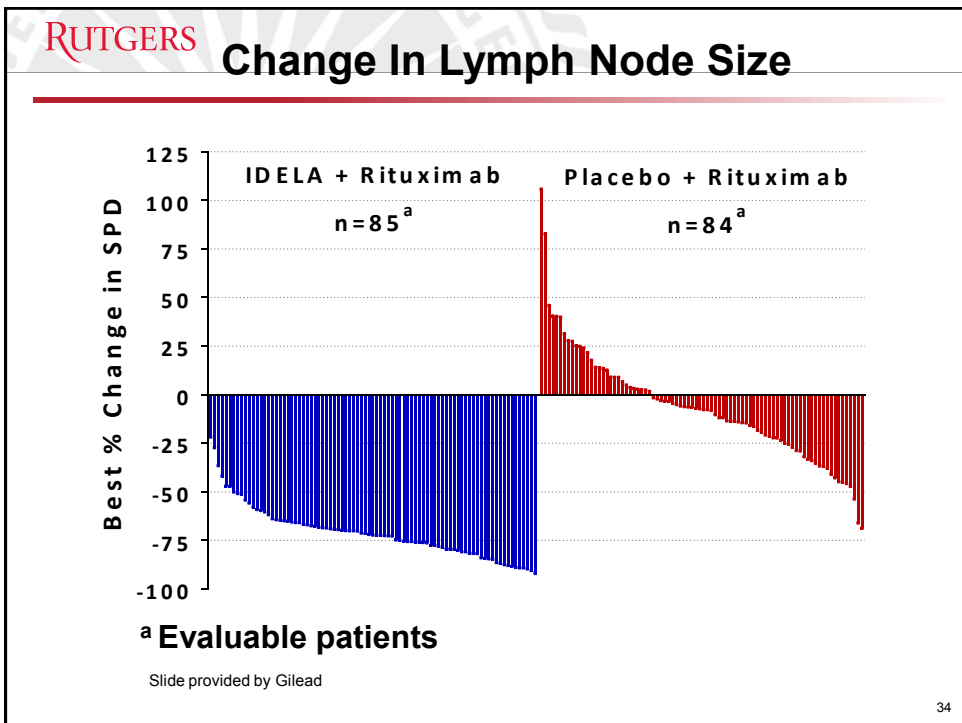
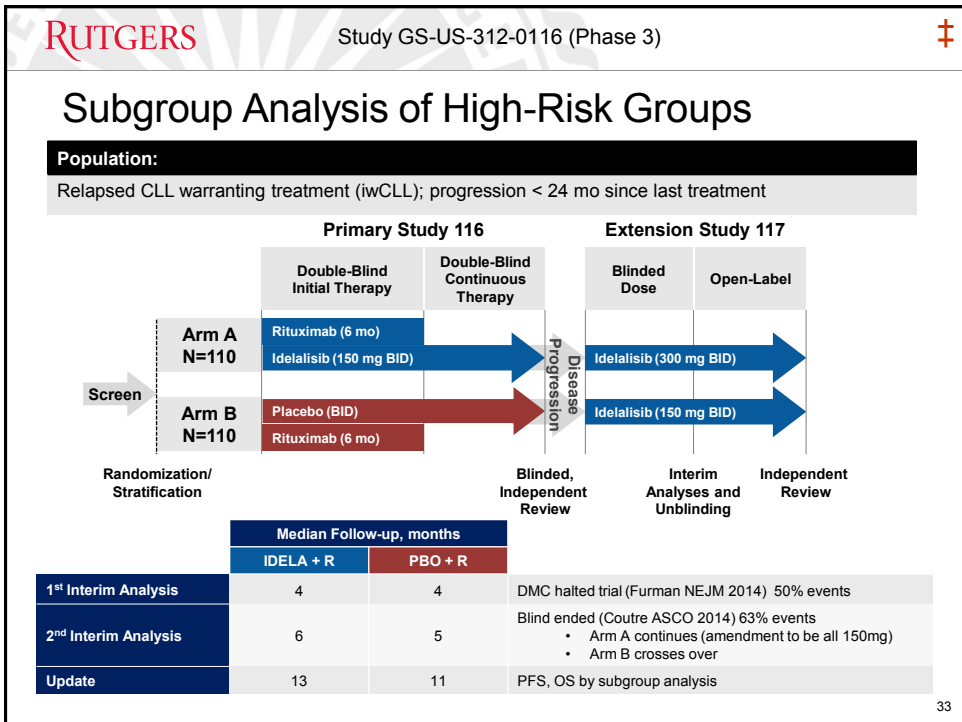
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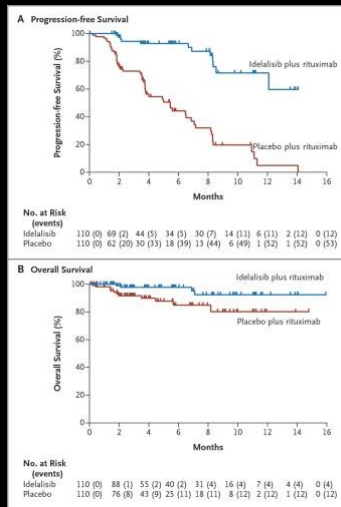
Idelalisib

- An oral phosphatidylinositol 3-kinase delta (PI3K-delta) inhibitor
- The dose is 150mg twice a day
- Phase 3 clinical trial of idelalisib plus rituximab vs placebo plus rituximab in 220 patients with relapsed CLL (NEJM 2014; 370: 997-1007)
- Progression free survival favored the idelalisib plus rituximab group (not reached vs 5.5 months)
- Overall survival at 12 months also favored the idelalisib group (92% vs 80%)
- The overall response rate favored idelalisib (81% vs 13%). All the responses were partial responses.
- Idelalisib plus rituximab were equally active in patients with del 17p as in other patients
- Idelalisib in combination with rituximab is FDA approved for the treatment of patients with relapsed CLL

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Progression-free and Overall Survival.



Furman RR et al. N Engl J Med 2014;370:997-1007.



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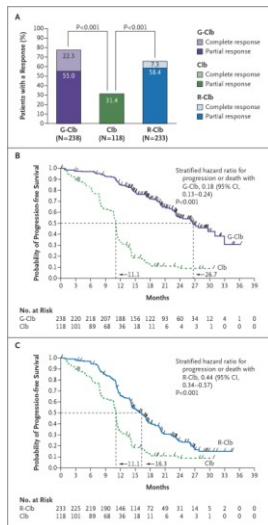
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Anti-CD20 Monoclonal Antibodies to Treat CLL

- Rituximab
 - Standard dose (375 mg/m² q week x 4) has low RR: 5%-14%
 - Works best to augment chemotherapy responses and improve survival (Blood 2005;105:49-53)
 - Flu+R vs Flu: RR 84% vs 63%; CR 38% vs 20%
 - 2-yr PFS 67% vs 45%; 2-yr OS 93% vs 81%
- Ofatumumab
 - Binds to a different part of the CD20 molecule than rituximab
 - ORR 58% fludarabine alemtuzumab refractory CLL and 47% in bulky fludarabine refractory CLL
 - PFS ~ 6 months in both populations
 - Lower response rate in del17p patients
- Obinutuzumab - high affinity 3rd generation Mab
 - Phase 3 trial of obinutuzumab plus chlorambucil vs rituximab plus chlorambucil vs chlorambucil resulted in FDA approval for obinutuzumab

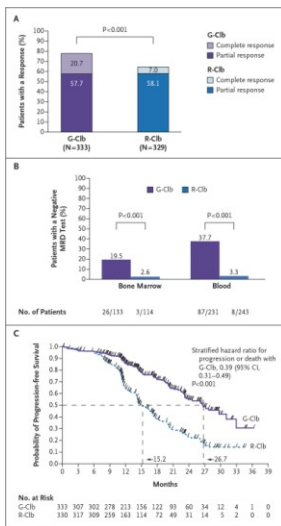
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Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil or Rituximab–Chlorambucil versus Chlorambucil Alone.



NEJM 2014; 370: 1101-10

Response Rates and Progression-free Survival with Obinutuzumab–Chlorambucil versus Rituximab–Chlorambucil.



NEJM 2014; 370: 1101-10

Allogeneic Hematopoietic Stem Cell Transplant

- Poor prognosis chromosome changes do not effect the success of transplant
- Transplant may cure some patients
- Transplant is possible in a minority of CLL patients. The recipient must be healthy and a suitable donor must be found.
 - Even with modern transplant techniques there is a 15% to 30% death rate during the first 2 years following transplant.
 - The majority of patients will suffer graft-vs-host disease; with 25% suffering chronic GVHD
- Long term (5 year) survival rates of 45% to 60% have been reported in CLL transplant studies.

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When to transplant in high risk CLL

- What is high risk CLL?
 - Refractory to purine analogs (drugs like fludarabine)
 - A short response (less than 24 months) to chemoimmunotherapy (FCR)
 - Deletion of chromosome 17p or TP53 gene mutations
- Recommendations from the European Society for Blood and Marrow Transplantation (EBMT)
 - Treatment with a novel agent (on clinical trial if possible) first
 - Consider transplant if no response to the novel agent.
 - Consider transplant following best response to the novel agent (since there is no long term follow-up > 3 years with any of the new targeted agents)
 - Consider transplant in patients with high risk CLL and low transplant risk (young, healthy patient with a matched donor)

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EMERGING THERAPIES

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Important Clinical Trails Currently Underway

- E1912 – Untreated younger patients (age 18 to 70)
 - Ibrutinib plus rituximab vs FCR
 - Goal enrollment is 519 patients; results expected in 2017
 - UK CLL 10 trial is also looking at this question
- A041202 – Untreated older patients (age 65 and above)
 - Ibrutinib vs Ibrutinib plus rituximab vs BR
 - Goal enrollment is 523 patients; results expected in 2018
- German CLL Study Group maintenance trial of lenalidomide following chemoimmunotherapy in high risk CLL (200 patients)
- 2nd line lenalidomide maintenance trial (Celgene; 400 patients)
- HELIOS study presented at the ASCO 2015 meeting in June. A Phase 3 study of BR-ibrutinib vs BR-placebo.

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Treatments in development

- Venetoclax (ABT-199)
 - Oral BCL2 inhibitor
 - Phase 1 combination studies of venetoclax plus rituximab and of venetoclax plus obinutuzumab in relapsed CLL were presented at the 2014 ASH meeting. Both studies showed the combinations to be safe and showed activity in this heavily pre-treated population.
 - Await the results of the Phase 2 study of venetoclax for the treatment of relapsed del17p CLL. The study is fully enrolled.
- Duvelisib (IPI-145)
 - Oral inhibitor of PI3K- gamma and delta isoforms
 - Phase 1 study in relapsed CLL showed the drug to be safe and have activity with 83% of patients having a greater than 50% reduction in lymph adenopathy
 - Phase 1b study proved the combination of duvelisib plus bendamustine and rituximab to be safe and active in patients with previously treated CLL.
 - Await the results of the on-going Phase 3 trial of duvelisib vs ofatumumab in patients with relapsed/refractory CLL

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Chimeric Antigen Receptor Modified T Cells (CAR-T) therapy of CLL

(NEJM 2011; 365:725-733 & ASH 2014 abstract # 1982)

- T-lymphocytes are collected from the patient's blood
- These T-cells are then genetically modified to express a T-cell receptor which targets CD 19, a protein on the CLL cell surface.
- The modified T-cells are then re-infused into the patient
- Early in data in CLL show 3 of 10 patients with a complete response sustained for 8 months to 2.5 years after treatment.
- Phase 2 study looking at 2 different doses of CAR-T cells randomized 30 patients with refractory or relapsed CLL
- Unique toxicities of CAR-T treatment include Cytokine Release Syndrome (CRS) and central nervous system toxicity

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TOXICITIES OF TREATMENT

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Treatment side effects

- All treatments have side effects. These are often referred to as “adverse events” or as “toxicities” in clinical trial reports.
- Some side effects may be immediate – such as having the chills and shakes during intravenous infusion with any one of the monoclonal antibody treatments (such as rituximab or obinutuzumab).
- Some side effects may occur days to weeks after the treatment has been finished – such as low white blood cell counts (neutropenia) following chemotherapy.
- The new oral medications also have toxicity and should not be assumed to be benign.
- Always request printed patient information for any cancer treatments you are to receive.

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Ibrutinib Adverse Events.

Table 2. Adverse Events.^a

Adverse Event	Grade 1-2	Grade 3-4	Total [‡]
<i>number of patients (percent)</i>			
Diarrhea	40 (47)	2 (2)	42 (49)
Upper respiratory tract infection	28 (33)	0	28 (33)
Fatigue	24 (28)	3 (4)	27 (32)
Cough	26 (31)	0	26 (31)
Arthralgia	23 (27)	0	23 (27)
Rash	23 (27)	0	23 (27)
Pyrexia	19 (22)	4 (5)	23 (27)
Edema, peripheral	18 (21)	0	18 (21)
Muscle spasms	16 (19)	1 (1)	17 (20)
Constipation	14 (16)	1 (1)	15 (18)
Dizziness	14 (16)	1 (1)	15 (18)
Headache	14 (16)	1 (1)	15 (18)
Hypertension	11 (13)	4 (5)	15 (18)
Nausea	14 (16)	1 (1)	15 (18)
Sinusitis	11 (13)	4 (5)	15 (18)
Contusion	14 (16)	0	14 (16)
Vomiting	13 (15)	1 (1)	14 (16)
Neutropenia [‡]	0	13 (15)	13 (15)
Oropharyngeal pain	13 (15)	0	13 (15)

^a Listed are adverse events that were reported in 13 or more of the 85 patients (≥15%), regardless of the cause.
[†] Seven grade 5 adverse events were reported: pneumonia, influenza-like pneumonia, cryptococcal pneumonia, chronic lymphocytic leukemia, Richter's syndrome, sarcoma, and the systemic inflammatory response syndrome. (The event terms are those deemed most appropriate by the investigator.)
[‡] Neutropenia did not lead to treatment discontinuation and was managed with the administration of growth factors in 5 of 13 patients.

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


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Idelalisib Toxicity

- Idelalisib carries a “black box” warning for fatal and/or severe diarrhea or colitis, liver toxicity, pneumonitis and intestinal perforation.
- Severe neutropenia is seen in 31% of patients
- Severe diarrhea or colitis occurred in 14% of patients
 - Diarrhea occurred in almost all patients
- Elevated liver function tests occurred in almost half of all patients with severe abnormalities in 14% of patients
- An expert panel’s recommendations to manage idelalisib toxicity has been published (Leukemia and Lymphoma 2015; early online. DOI: 10.3109/10428194.2015.1022770).

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Adverse Events of Grade 3 or Higher, Safety Population.

Table 2. Adverse Events of Grade 3 or Higher, Safety Population.*

Event	Obinutuzumab–Chlorambucil vs. Chlorambucil Alone		Rituximab–Chlorambucil vs. Chlorambucil Alone		Obinutuzumab–Chlorambucil vs. Rituximab–Chlorambucil	
	Obinutuzumab–Chlorambucil (N=241)	Chlorambucil Alone (N=116)	Rituximab–Chlorambucil (N=225)	Chlorambucil Alone (N=116)	Obinutuzumab–Chlorambucil (N=336)	Rituximab–Chlorambucil (N=321)
	<i>number of patients (percent)</i>					
Any event	175 (73)	58 (50)	125 (56)	58 (50)	235 (70)	177 (55)
Infusion-related reactions	51 (21)	—	9 (4)	—	67 (20)	12 (4)
Neutropenia	84 (35)	18 (16)	60 (27)	18 (16)	111 (33)	91 (28)
Anemia	11 (5)	5 (4)	10 (4)	5 (4)	14 (4)	12 (4)
Thrombocytopenia	27 (11)	5 (4)	8 (4)	5 (4)	35 (10)	10 (3)
Leukopenia	13 (5)	0	3 (1)	0	15 (4)	3 (1)
Infections	27 (11)	16 (14)	30 (13)	16 (14)	40 (12)	44 (14)
Pneumonia	8 (3)	4 (3)	11 (5)	4 (3)	13 (4)	17 (5)
Febrile neutropenia	4 (2)	5 (4)	4 (2)	5 (4)	8 (2)	4 (1)

*The safety population included all patients who received at least one dose of study medication. Shown are adverse events of grade 3, 4, or 5 with an incidence of 3% or higher in any treatment group, irrespective of whether the event was considered related or unrelated to treatment by the investigators.

COMMUNICATION

Open Communication is Critical

- Feel free to ask questions of your health care team
 - Ask for clarification of anything you are not sure about regarding your diagnosis and plan of care
 - Ask for explanations of anything you don't understand such as unfamiliar terms or new medications
 - Have an advocate go with you to your appointments – ask a family member or a friend
- Feel free to ask about clinical trials and for 2nd opinions
 - Your local oncologist may refer you to an academic medical center
 - An academic expert can work with your local oncologist in your care and is a resource regarding information on new treatments or to provide advice for complicated cases
- Resources:
 - National Cancer Institute <http://www.cancer.gov/>
 - ClinicalTrials.gov <https://clinicaltrials.gov/>

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**Treating Chronic Lymphocytic Leukemia (CLL):
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Question-and-Answer Session

Dr. Bannerji's slides are available for download at
www.LLS.org/programs

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Treating Chronic Lymphocytic Leukemia (CLL): Evaluating and Managing Options



The Leukemia & Lymphoma Society (LLS) offers:

- **Live, Online Chats** that provide a friendly forum to share experiences with others.
 - **WEBSITE:** www.LLS.org/chat
- **What to ask:** For a list of suggested questions to ask about certain topics, download and print any of the following guides.
 - **WEBSITE:** www.LLS.org/whattoask
- **Free education materials:** www.LLS.org/publications
- **Past CLL education programs:** www.LLS.org/programs
- **Information Resource Center:** Speak one-on-one with an Information Specialist who can assist you through cancer treatment, financial, and social challenges.
 - **EMAIL:** infocenter@LLS.org **TOLL-FREE PHONE:** (800) 955-4572