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Welcome & Introductions

Dr. Hagemeister's slides are available for download at
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Diagnosis and Treating Slow Growing Non-Hodgkin Lymphomas

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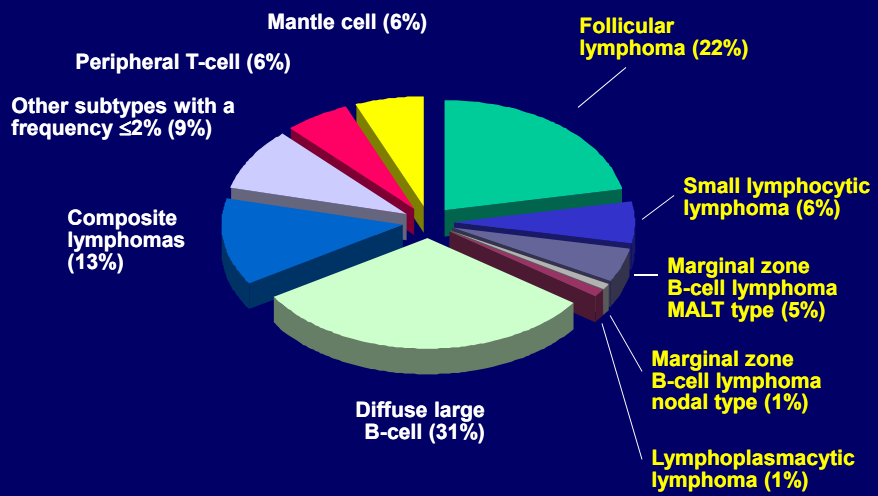
Lymphoma: A Model for Basic Science and Clinical Research

- "Staging"– does the extent of disease make a difference?
- Combinations of drugs - better than "single-agent" therapies?
- Cytogenetics – a tool for better classification and basic science?
- Radiotherapy – a useful treatment?
- Prognostic factors – determining outcome?
- Antibody therapy – new targeted treatment?
- Gene Microarray Studies – understanding the basic cause of cancer?
- Molecular Studies-testing minor variations that make a difference?

Frequency of Lymphoma Subtypes in Adults



Armitage et al. J Clin Oncol. 1998;16:2780–2795.

Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

- Diagnosis
  - Possible Causes
  - Pathology
  - Clinical Evaluation
- Therapy
  - Follicular Lymphomas
  - Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia
  - Mantle Cell Lymphomas
  - Marginal Zone Lymphomas
  - T Cell Lymphomas

Possible Causes of Lymphomas

- Aging
- Immunodeficiency/ Immunosuppression
  - Congenital - Ataxia telangiectasia, Wiskott-Aldrich, SCID
  - Acquired – HIV infection, organ transplant, aging, autoimmune disease
  - Drug induced – Immunosuppressants, organ or allogeneic SC transplantation
- Environmental/Toxic Exposure
  - Agent orange, dioxins, PCBs, pesticides, herbicides, solvents
- Radiation
  - Atomic bomb exposure, Nuclear reactor accidents, Therapeutic RT
- Chemotherapy
  - Methotrexate and other immunosuppressive drugs suspected
- Viruses
  - EBV, HIV, HTLV-1, Hepatitis C, Human Herpesvirus 8
- Bacteria
  - H. Pylori, B. burgdorferi, C. jejuni, C. psittaci

Primary Immunodeficiency Disorders Associated with NHL

- Wiskott-Aldrich Syndrome
- Ataxia Telangiectasia
- Common Variable Immunodeficiency
- X-Linked Immunoproliferative Syndrome
- SCIDS – "Bubble Boy"
- Autoimmune Lymphoproliferative Syndrome (ALPS)
- Job's Syndrome (subcutaneous abscesses)

Autoimmune Disorders Associated with Development of Lymphomas

- Hashimoto's Thyroiditis
- Sjogren's Syndrome
- Rheumatoid Arthritis
- Systemic Lupus Erythematosis
- Sprue, Inflammatory Bowel Disease
- Autoimmune Hemolytic Anemia and Immunopathic Thrombocytopenic Purpura
- Dermatitis Herpetiformis

Models for Increased Risk of NHL in Patients with Autoimmune Disorders

- Chronic Immune Stimulation by Self Antigens
  - Defective apoptosis of B-cells
  - Impaired T-Cell function
  - Secondary inflammation
- Genetic Factors
  - Defects in inherited self-tolerance genes (TNF and IL-10 polymorphisms) with increased TNF, and increased NF-KB
  - Other polymorphisms possibly associated (IL-7, IL-12, IL-13, and Interferon-gamma)
- Environmental Factors
  - Dietary antigens (as in gluten, intestinal inflammation, and lymphoma)
  - Abnormal response to viral or other infectious agents.

Relative Risks of NHL for Patients with Selected Autoimmune Diseases

Disorder	DLBCL	CLL	T-Cell	MCL	MZL	LPL
RA	1.8*	1.4	1.9	1.2	1.4	2.5*
SS	11*	--	UD	UD	28*	--
SLE	6.2*	--	UD	UD	--	--
Celiac Dz	2.8*	0.5	17*	3.3	UD	3.4
DM (Type1)	1.3	3.6*	UD	5.0*	2.8	3.9

Autoimmune Diseases for which there are cases, but there either no cases in the "Control Group" or the Relative Risk of NHL is not statistically significant include: Crohn's disease, Ulcerative Colitis, Sarcoidosis, and Psoriasis

* P < 0.05; UD: No cases in the control group; --: Too few cases in the AD or the control group

Smedby et al. JNCI 98: 51-60, 2006.

Clinical Features of 126 Patients with RA and Risk of Lymphoma (2905 Controls)

Feature	RRisk of NHL
Male : Female	0.8 : 9.2
Duration of Disease <5 : ≥5 yrs	2.4 : 1.4
Family history Autoimmune Disorders	1.1
ESR > 45	2.8
Severe Small : Severe Large Joint Damage	10.5 : 29.3
Steroids/NSAIDS Therapy	1.5
NSAIDS > 10 yrs	1.9
Immunosuppressant Therapy	3.5
Immunosuppressants > 10 yrs	5.8

Dias and Isenberg. Nature Reviews/Rheumatology 3: 361-368, 2011.

Drugs Associated with Development of Lymphoproliferative Disorders

- TNF-Blockers (Used for other inflammatory disorders besides those listed)
  - Eternacept: Approved for RA, psoriasis, ankylosing spondilitis
  - Associated with NHL in RA (one study), maybe other solid tumors
  - Infliximab: For RA, Crohn's, amylosing spondylitis, psoriasis, UC
  - Combined with azathioprine or 6-MP, associated with hepatosplenic T-cell NHL
  - Adalimumab: Same as eternacept
- Alemtuzumab
  - In combination With CHOP for aggressive T-cell NHL
  - 3/20 developed EBV+ lymphoproliferative disorders
- Methotrexate in rheumatoid arthritis patients
  - Reports of regression following discontinuation
  - WHO Iatrogenic Immunodeficiency-associated LPD

Hoshida et al. J Rheum 34: 3222-331, 2007. Callen. Sem Cutan Med Surg 26: 8-14, 2007.

Clinical Features of Lymphomas in 76 Patients with RA

Feature	MTX-LPD	Non-MTX LPD	All Cases	Controls
All Pts	48	28	76	150
Med. Age	67	66	66#	58
Percent male	32	19	28*	62
Mo from RA-LPD	132@	240	144	NA
Percent Stage I/II	38	40	38+	28
5 yr OS, %	59	53	59^	75

Comparisons with P = 0.05:
RA cases with LPDs were older than were controls
• More women had LPDs with RA than did men compared with controls
@ MTX-LPDs occurred earlier in diagnosis of RA than did non-MTX-LPDs
+ RA-LPDs were more often early staged than controls
^ 5-yr OS rates were worse for RA-LPDs that were controls

Hoshida et al. J Rheum 34: 322-331, 2007.

Other Inflammatory Disorders for Which There May Be an Increased Risk of NHL

- Hashimoto's thyroiditis (local MZL excepted)
- Polymyositis/Dermatomyositis (small #s)
- Psoriasis (problems in pathology)
- Spondylarthropathies (small #s)
- Systemic Sclerosis (small #s)
- Wegener's granulomatosis (problems with pathology)

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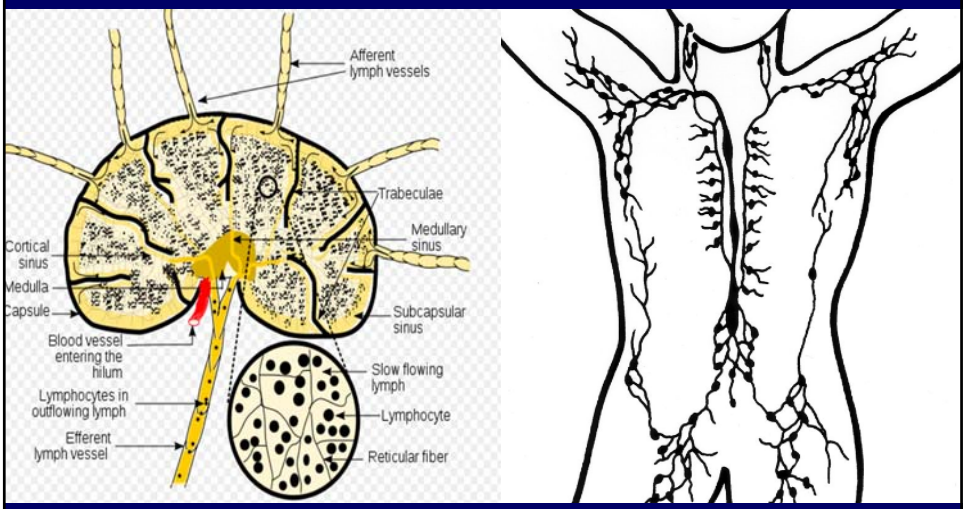
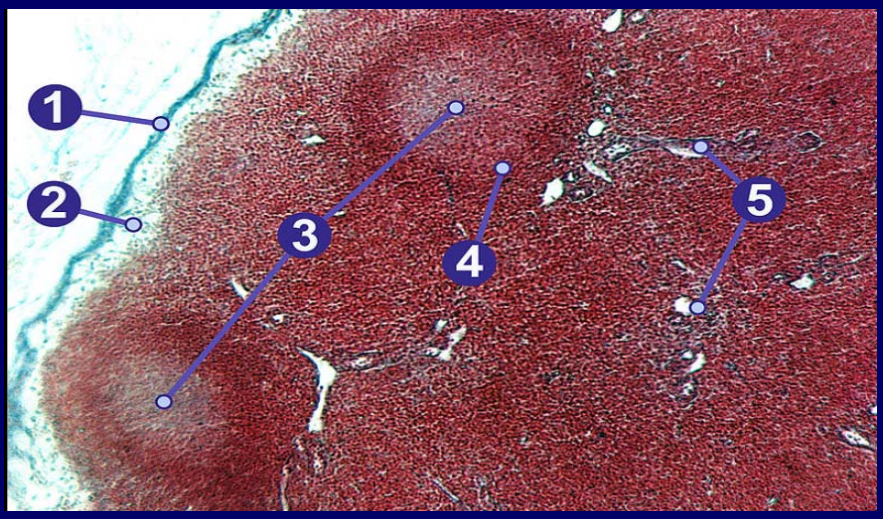
Lymph Nodes and Lymphatic Vessels: Important Parts of the Immune System

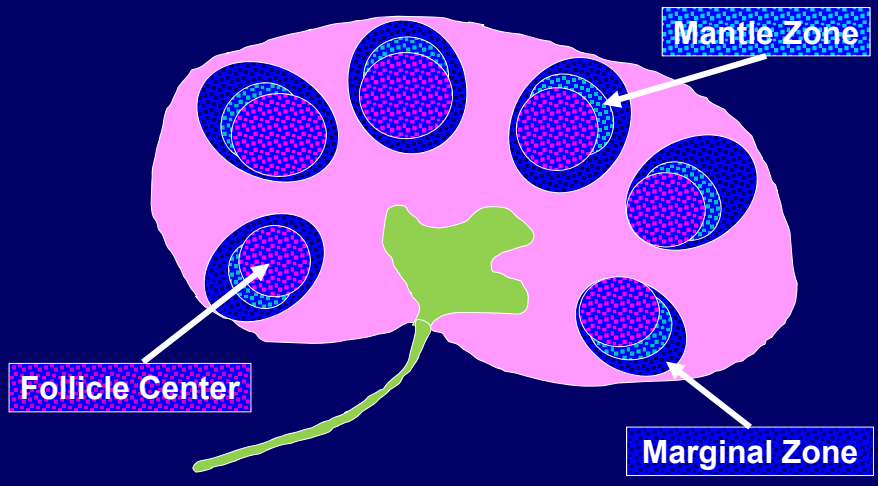


A Normal Lymph Node Under the Microscope

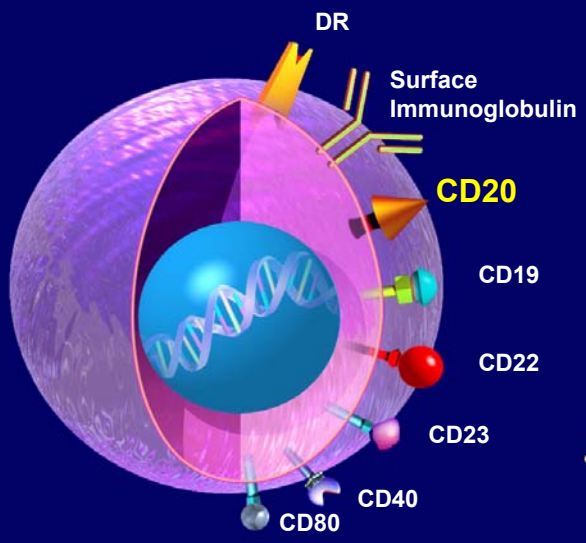


1. Capsule; 2 Subcapsular sinus; 3 Follicle (Germinal Center);
4. Lymphoid Nodule; 5. Trabeculae.

Some Lymphomas Get Their Names from Where the Normal Cell Counterpart Is Found



Examples of Various Proteins on the Surface of B Cell Lymphomas

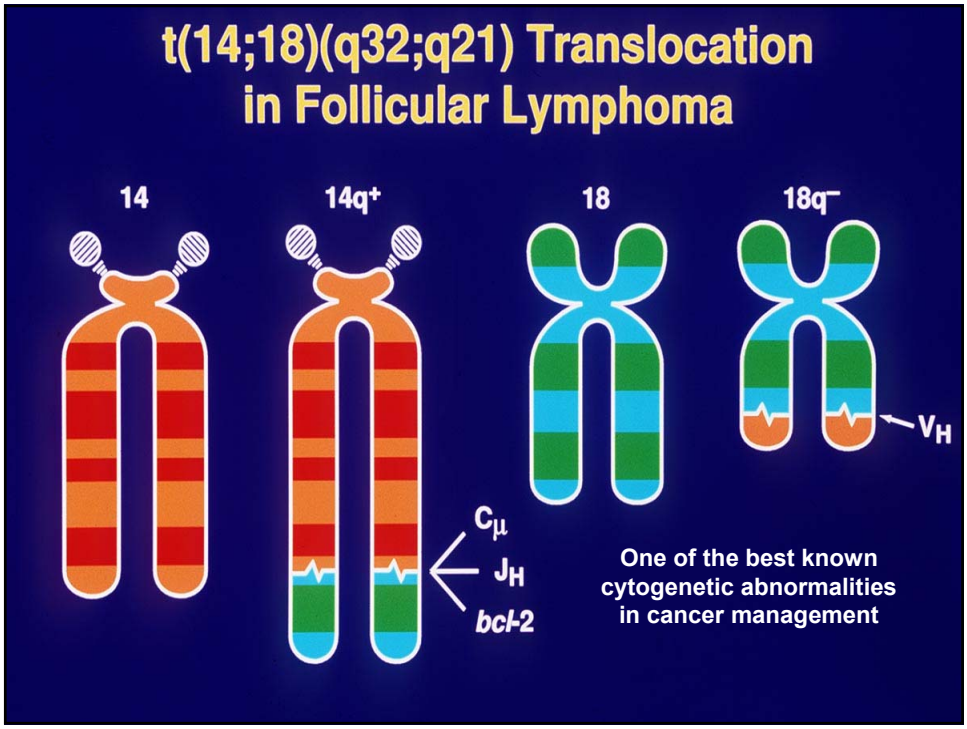


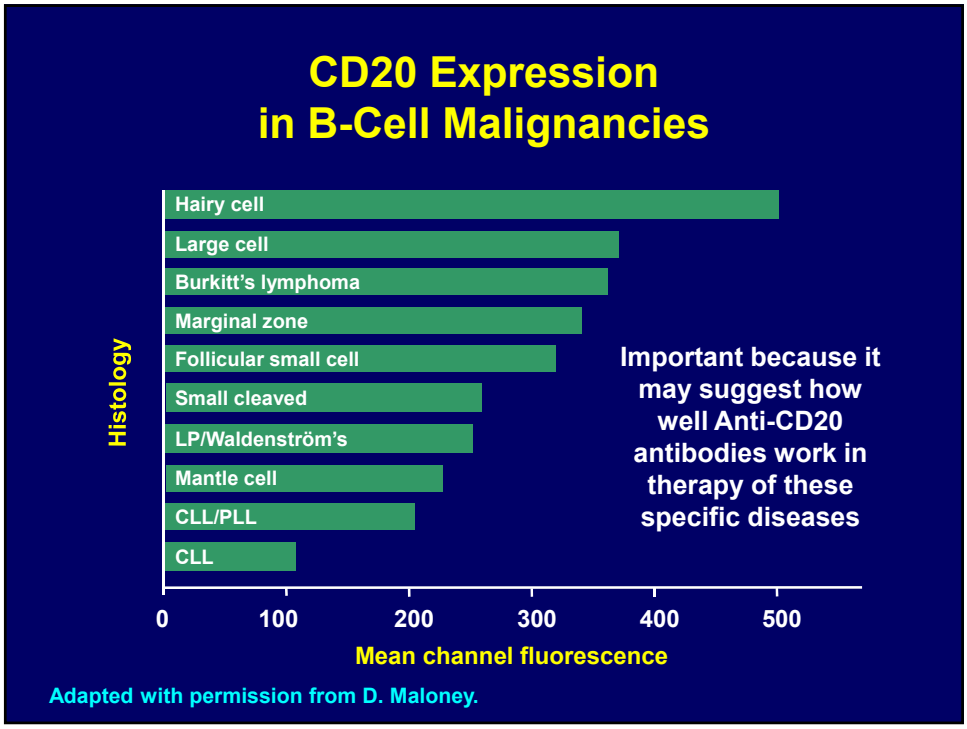
"Markers" That Make a Difference in Diagnosis of Indolent Lymphomas

- "Markers" are sugar/protein complexes that are produced by cells
- They can be produced by both cancer cells and normal cells
- These can be studied under the microscope to identify certain types of lymphomas

Marker	FL	SLL/CLL	MCL	MZL	T Cell
CD20	Pos	Pos	Pos	Pos	Neg
CD10	Pos	Neg	Neg	Neg	Neg
CD5	Neg	Pos	Pos	Neg	Pos
CD23	Neg	Pos	Pos	Neg	Neg
Cyclin D1	Neg	Neg	Pos	Neg	Neg
Cytogenetics	t(14;18)	Various	t(11;14)	Various	Various

- CD: Cluster of Differentiation
- Not all are absolute: There are often variations in positivity/negativity
- Note: The genetics are only in the cancer cells


t(14;18)(q32;q21) Translocation
in Follicular Lymphoma
14
14q+
18
18q−
Cμ
JH
bcl-2
VH
One of the best known
cytogenetic abnormalities
in cancer management


CD20 Expression
in B-Cell Malignancies
Hairy cell
Large cell
Burkitt's lymphoma
Marginal zone
Follicular small cell
Small cleaved
LP/Waldenström's
Mantle cell
CLL/PLL
CLL
Histology
0
100
200
300
400
500
Mean channel fluorescence
Important because it
may suggest how
well Anti-CD20
antibodies work in
therapy of these
specific diseases
Adapted with permission from D. Maloney.

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How Are Patients Found to Have Slow-Growing (Indolent) Lymphomas?

The fastest growing cancer is a lymphoma; the slowest growing cancer is a lymphoma

The most common “presentation” is a painless lump, but pain can be an important initial clue to diagnosis in aggressive lymphomas

Other symptoms depend upon the location of the disease: back, chest, or abdominal pain can occur with slow-growing lymphomas

Bone marrow involvement can result in low blood counts (hemoglobin, platelets)

Unusual sites of disease: Gastrointestinal Tract, Kidney, Lung, and Other Organs

Tests in the Evaluation of Indolent NHL

- A Biopsy: The most important test
  - FNA (Fine needle aspirate)
    - Usually inadequate (loose cells)
  - "Excisional" biopsy recommended
  - CORE biopsy (larger needle) may be as good
    - Evaluates nodal "architecture"
- Xrays (Radiographs) and Other Tests
  - CAT (computerized axial tomography) Scan
    - Most common method to evaluate disease extent (nodes, organs)
  - PET (Positron Emission Tomography) not mandatory.
  - Bone Marrow Biopsy useful, and necessary in some
  - Other special tests may be useful
    - MRI (Magnetic Resonance Imaging)
    - Gastroscopy or Colonoscopy

Indolent Lymphomas: Problems and Questions

- Should FL, SLL/CLL, and MZLs be treated differently?

  A. Marrow Involvement

  1. Follicular Lymphomas rarely cause blood involvement although marrow is positive
  2. SLLs can be diseases with massive lymph node involvement, and yet very minimal marrow disease
  3. MZLs involve the bone marrow sometimes, but most often in the splenic type

Indolent Lymphomas: Problems and Questions

B. Extranodal Disease

1. FLs rarely present with disease outside of lymph nodes, esp. Gastrointestinal sites, until transformation
2. SLLs can be indistinguishable from MZLs when disease is present outside of nodes
3. MZLs often have disease outside of the lymph nodes, but the nodal form is poorly defined

Indolent Lymphomas: Problems and Questions

C. Risk of Transformation

1. FLs have the perhaps the highest risk, but when and how the diagnosis is made can be difficult: Bulkiness, Pure DLCL, CT type?
2. Grading of FLs is very subjective: FLCL?
3. Transformation may not be such a bad thing at initial diagnosis
4. SLL/CLLs transform infrequently and may be a very poor risk feature: Richter's Syndrome
5. MZLs transform at an unknown rate, despite classic involvement outside of lymph nodes

Indolent Lymphoma: Treatment Choice Considerations

- Efficacy
- Patient's age
- Prior therapies
- Safety profile
- The FLIPI (Follicular Lymphoma International Prognostic Index)
- Patient Choice
- Future therapies
- AE management
- QOL
- Treatment goals and expectations
- Even with advanced disease, Observation is an option

Indications for Treatment by GELF Criteria

Involvement of 3 nodal sites, each with a diameter of ≥ 3 cm

Any nodal or extranodal tumor mass with a diameter of ≥ 7 cm

B symptoms

Splenomegaly

Pleural effusions or peritoneal ascites

Cytopenias (leukocytes < 1.0×10^9/L and/or platelets < 100×10^9/L)

Leukemia (> 5.0×10^9/L malignant cells)

GELF = Groupe d'Etude des Lymphomes Folliculaires.
Solal-Celigny et al. JCO 16: 2332-2338, 1998.

Standard Regimens for Therapy of Indolent Lymphomas

- Initial Therapy
  - Single-Agent Rituximab
  - Bendamustine + Rituximab
  - R-CHOP
  - Fludarabine-like Regimens
- Relapsed Disease
  - Any of the above
  - Lenalidomide + Rituximab
- Regimens not often used
  - Platinum-, Gemcitabine-, Etoposide-Based Regimens

Novel Therapies in Treatment of Lymphomas

moAbs	Anti-CD20 (obinutuzumab and ofatumumab), as well as other antigens on the cell surface (eg, CD19, CD22)
IMiDs	Lead drug is lenalidomide, which has efficacy in multiple NHL subtypes (ie, MCL, FL, DLBCL, T-cell lymphoma)
PI3K and BTK Inhibitors	Have effects in CLL and subtypes of aggressive and indolent lymphomas
BCL2 Inhibitors	Induce expression of costimulatory molecules and tumor immunity in melanoma, Hodgkin lymphoma, and NHLs
PD-1 moAbs	Effective in Hodgkin's and other lymphomas
CAR T-Cell Therapy	Significant activity, especially in aggressive lymphomas and leukemias

Btk: Bruton's tyrosine kinase; CAR: chimeric antigen receptor; CLL: chronic lymphocytic leukemia; IMiD: immunomodulatory drug; mAbs: monoclonal antibodies; MCL: mantle cell lymphoma; NHL: non-Hodgkin lymphoma; PI3k: phosphoinositide-3-kinase;; PD-1: programmed death-1

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WHO Histologic Grading of Follicular Lymphoma

Grade	Histology	Clinical Behavior
1	0-5 centroblasts/HPF	Indolent
2	6-15 centroblasts/HPF	Indolent
3a	>15 centroblasts/HPF, centrocytes present	Indolent-Aggressive
3b	>15 centroblasts/HPF, centrocytes absent; centroblasts in large sheets	Aggressive (similar to LCL)

Nathwani et al. Intnl Agency Res Ca Press, Lyon 162-168, 2001.

Mortality According to FLIPI Index Using "NoLASH"

Risk Group	Number Factors	% Patients (n = 1795)	5-year OS (%)	10-year OS (%)	RR
Good	0-1	36	91	71	1
Intermediate	2	37	78	51	2.3
Poor	≥ 3	27	53	36	4.3

No = 5 or more Nodal Sites of Involvement

L = Elevated LDH

A = Age Greater than 60

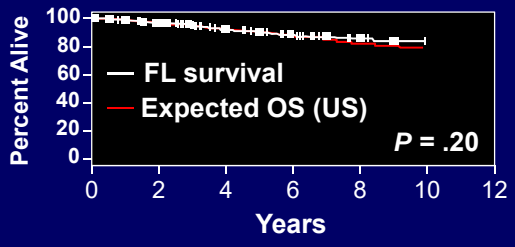
S = Stage III – IV

H = Hemoglobin 12 or Less

Solal-Celigny et al. Blood 104: 1258-1265, 2004.

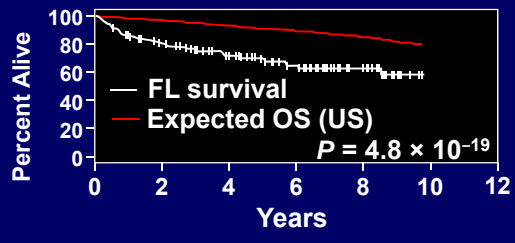
Prognosis of FL: OS Related to Duration of EFS Following Initial Therapy

- EFS: absence of progression, relapse, retreatment, or death



Patients with EFS > 1 Yr

Similar OS rate to that of the general US population



Patients with EFS < 1 Yr

Significantly inferior OS rate compared with the general US population

Maurer et al. Blood 124: 2014 (Abst 1664).

Disease and Patient Features of FL with POD in 24 Months Versus Others

- Retrospective analysis of patients in LymphoCare Study
- Therapy: R-CHOP-588 pt; R-CVP-280; R-Flu-207
- Comparison of those with POD < 24 vs > 24 mo (Reference)

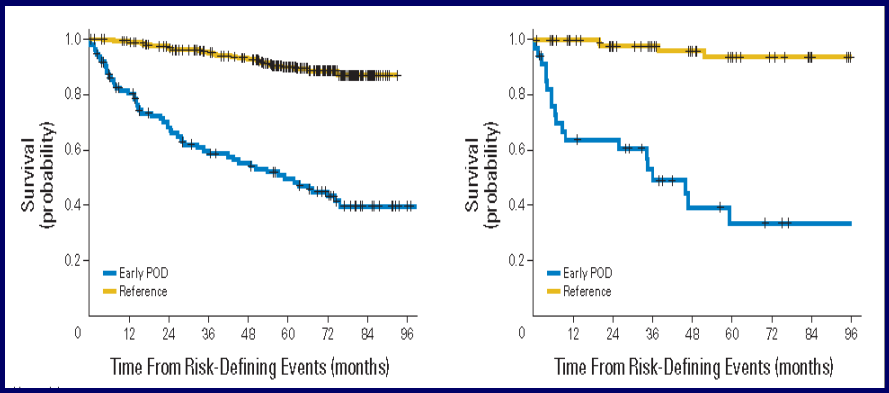
Features	Early POD, N (%)	Reference, N (%)	P
No. Pts Total	110	420	
Female	38 (35)	200 (48)	NS
Gr 1-2	63 (66)	227 (60)	
3	33 (34)	150 (40)	0.33
Missing	14	43	
FLIPI 0-1	10 (12)	92 (26)	
2	29 (34)	119 (34)	
3-5	47 (55)	140 (40)	0.007
Missing	24	69	

Casulo et al. JCO 33: 2516-2522, 2015.

OS According to POD Less Than or More Than 24 Months From Start of Therapy

The LymphoCare Datbase

U Iowa and Mayo Database (Validation Set)

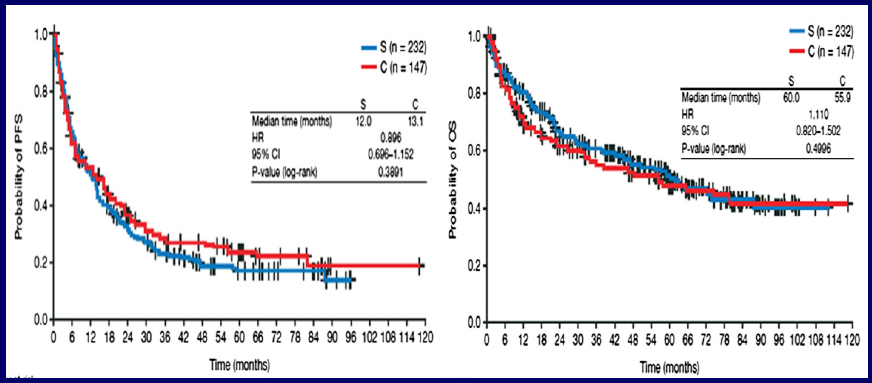


By MVA, PS ≥ 2, Age > 60 and ≥ 4 Nodal Sites (FLIPI features) and POD < 24 Mo were adverse features for OS.

Casulo et al. JCO 33: 2516-2522, 2015.

Transformed FL Outcomes from the LymphoCare Database

- PFS and OS rates were not statistically different for those with suspected (S) versus confirmed (biopsy-proven)T-FL

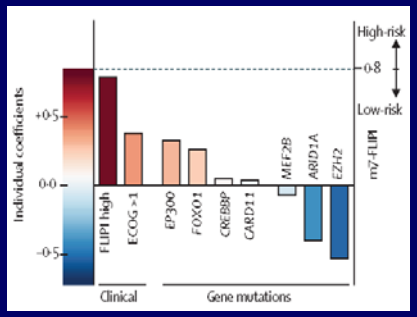


- Clinical features of ST-FL (Vancouver): LDH >2XNL, rapid single node growth, new ENS, new B SX, hypercalcemia (not collected in this study)

Wagner-Johnston et al. Blood: 126: 851-827, 2015.

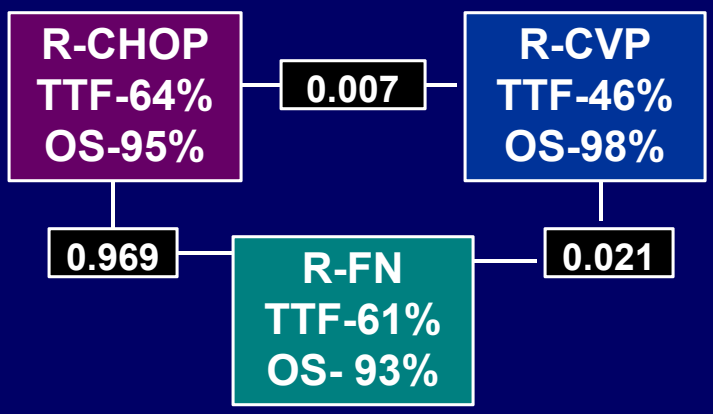
The M7-FLIPI: A Prognostic Model for Prediction of POD24

- Evaluation of 74 genes from 151 pts with FL who received R-CHOP and interferon maintenance.
- Selected genes that appeared mutated in more than 5 patients
- Calculated FFS models using high Risk FLIPI and other clinical and lab features
- Generated models that incorporated molecular features of 7 genes providing best FFS discrimination
- Validated: BCCA Cohort receiving R-CVP and MR.



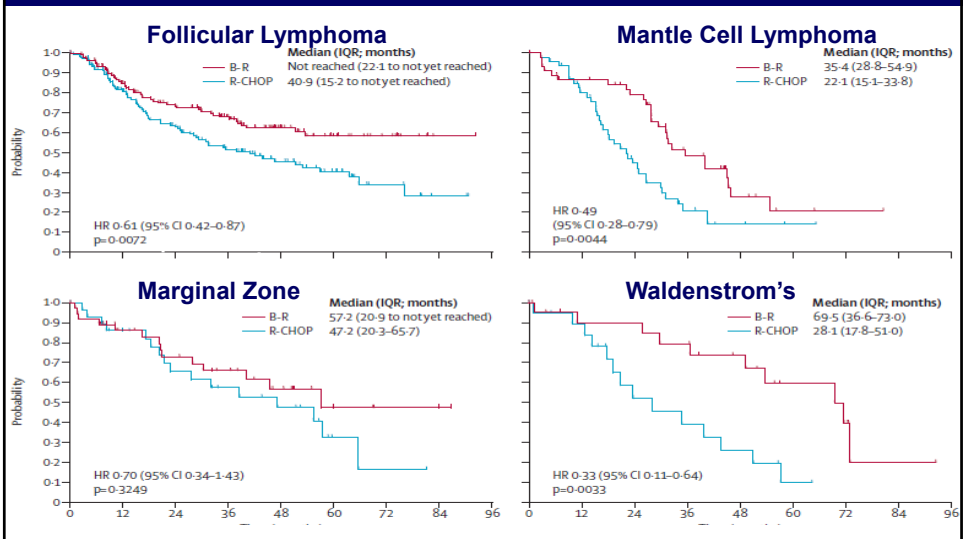
Pastore et al. Lancet Oncol 16: 2015.

Foll05 Trial: R-CVP vs R-CHOP vs R-FN: 3 Year TTF and OS Results



Federico et al. ASCO 2012 (abst 8006).

BR vs R-CHOP for Indolent Lymphomas



Rummel et al. Lancet 381: 1203-1210, 2013.

R^2 for Untreated FL: Response by Tumor Burden and Molecular Features

By GELF Criteria (N=46)

High Tumor Burden (N=22, 48%)				Low Tumor Burden (N=24, 52%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1 (5%)	21(95%)	100%	1(4%)	4(17%)	19 (79%)	96%

By Bulk of Disease (N=46)

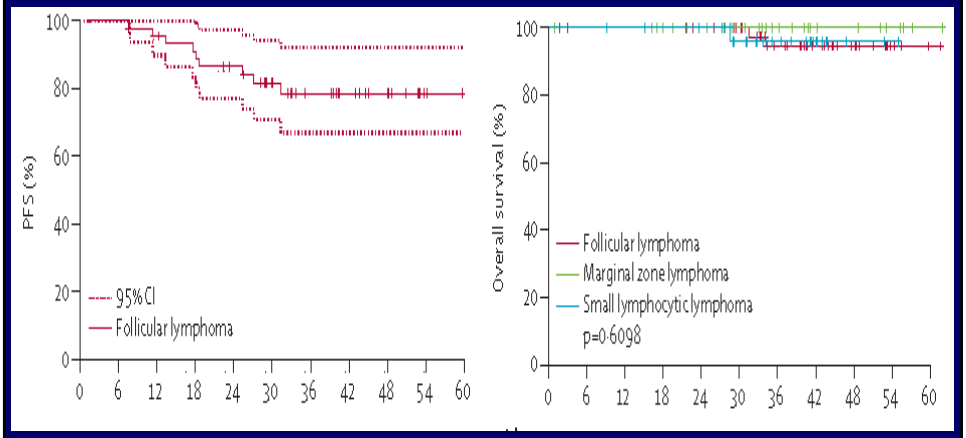
Bulky (N=13, 28%)				Non-Bulky (N=33, 72%)			
SD	PR	CR/CRu	ORR	SD	PR	CR/CRu	ORR
0	1(8%)	12(92%)	100%	1(3%)	4 (12%)	28 (85%)	97%

Molecular Response (N=44 Evaluable, Marrow and Blood)

	PCR Positive	PCR Negative
PRETREATMENT	17(41%)	26(59%)
POST CYCLE 3	5(11%)	39(89%)
POST CYCLE 6	2(5%)	42(95%)

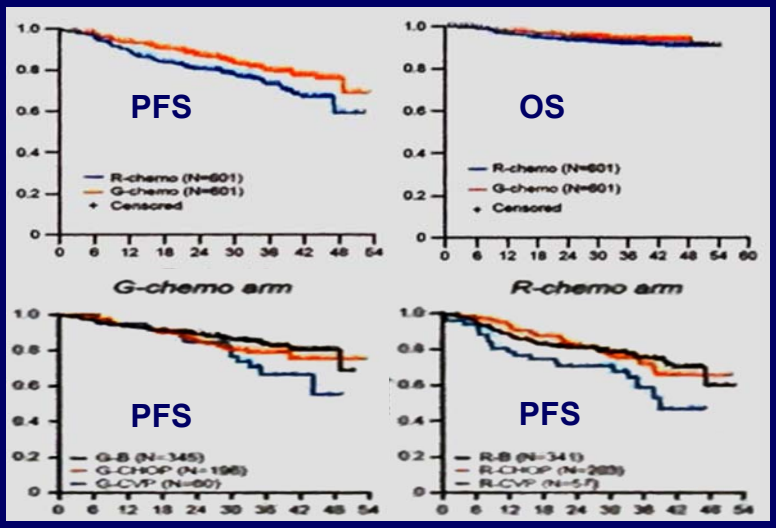
Fowler et al. Lancet Oncol 15: 1311-1318, 2014.

R2 for Untreated follicular and Other Indolent NHLs: PFS and OS Results



Fowler et al. Lancet Oncol 15: 1311-1318, 2014.

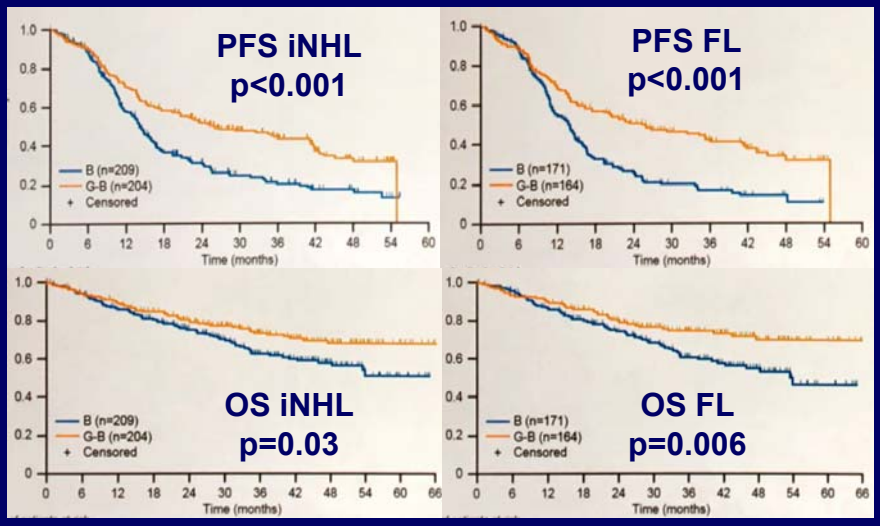
Obinutuzumab-CIT vs Rituximab-CIT for Untreated FL: The Gallium Study



Marcus et al. ASH 2016, abstract 6.

Results for other iNHLs pending.

Phase 3 Obinutuzumab/Bendamustine vs Bendamustine for R-Refractory FL



Cheson et al. ASH 2016, abstract 615.

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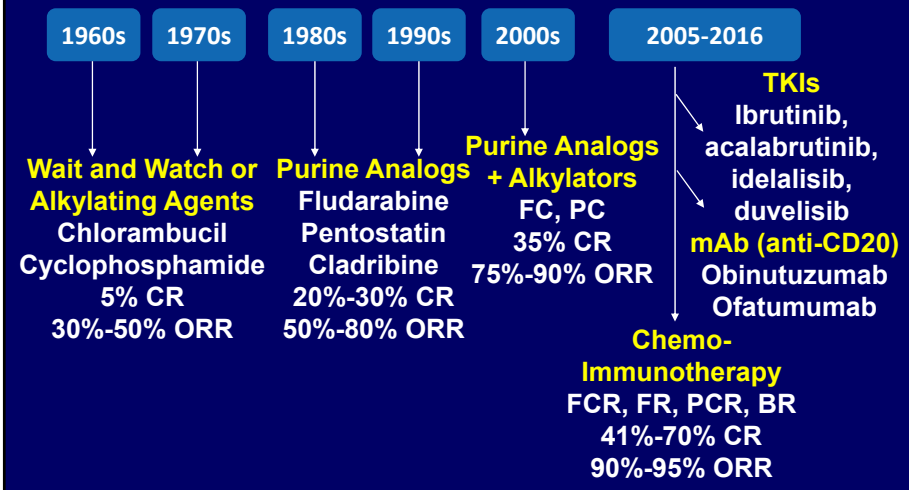
CLL Management—How Far We've Come[1]

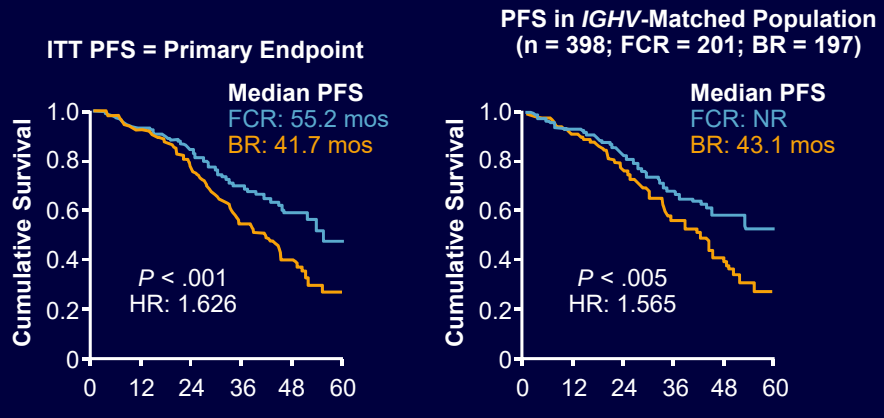


Rai KR, Jain P. Am J Hematol. 2016;91:330-340.

Traditional and Newer PFs associated With Inferior OS in CLL

- Traditional PFs
  1. Advanced stage at diagnosis
  2. Short lymphocyte doubling time
  3. Diffuse pattern of bone marrow disease
  4. Advanced age / male
  5. ↑ β-2 microglobulin or circulating CD23
  6. ↑ prolymphs (PLL)
- Newer PFs
  1. FISH cytogenetics
     - 17p del: agg dz
     - 11q del: agg dz
     - 13q del: indolent dz
  2. Unmutated IgV_H (<2% homology with germline)
  3. ZAP70 (≥ 20% positive)
  4. CD38 (≥ 30% positive)

FCR vs BR in Pts With Advanced CLL: PFS



Eichhorst B, et al. ASH 2014. Abstract 19

MR After FCR for Untreated CLL: The French FILO CLL 2007 Trial

- 409 pts with untreated CLL, ≥65 yrs, in CR/PR. No del(17p).
- Therapy: 4 cycles of FCR, followed by MR (500 mg/m2 q 2 mo for 2 yr) vs Observation
- CR/CRi = 38%. Stratified by del(11q), CR/PR, and IGHV status.

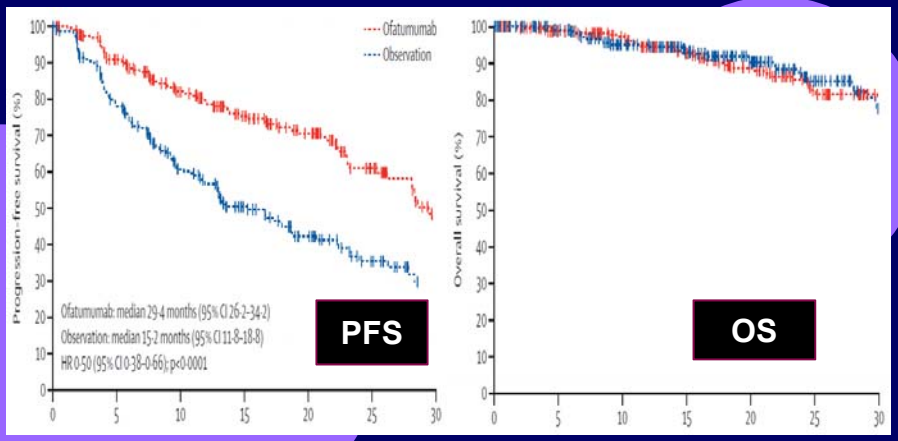
	Maintenance R (202)	Observation (207)
Median PFS (mo)	59.3	49
3 Yr PFS (%)*	83	64.2
3 Yr OS (%)	92.6	87.2
Secondary Cancer	15.3	11.1
Heme SAEs*	6.9	1.9
Infectious SAEs*	18.8	10.1

- PFS also better with MR for those with/without del(11q) or unmutated IGHv

Dartigeas et al. ASCO 2016 (abst 7505). * P < 0.05.

Maintenance Ofatumumab vs Observation for 2nd or 3rd CR/PR: The PROLONG study

After a median follow-up of 19.1 months

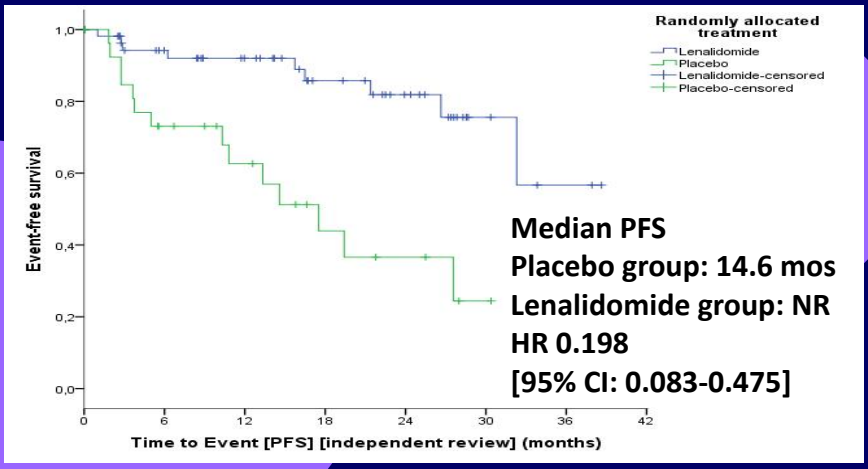


van Oers et al. Lancet Oncol 2015;16:1370-79

Approved by FDA

Maintenance Len After Initial Therapy for "High –Risk" Disease: CLL M1 Study

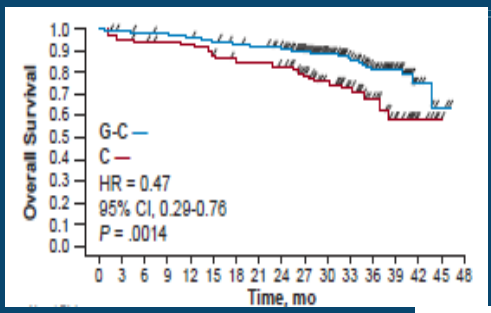
- Median observation time of 17.7 months



Median PFS
Placebo group: 14.6 mos
Lenalidomide group: NR
HR 0.198
[95% CI: 0.083-0.475]

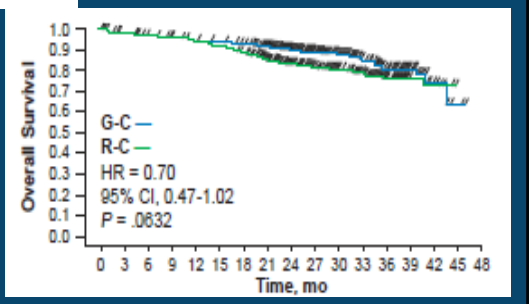
Fink et al. ASH 2016

CLL11 Results: OS in Older Patients



Obinutuzumab-chlorambucil is associated with significant OS benefit vs chlorambucil[a]

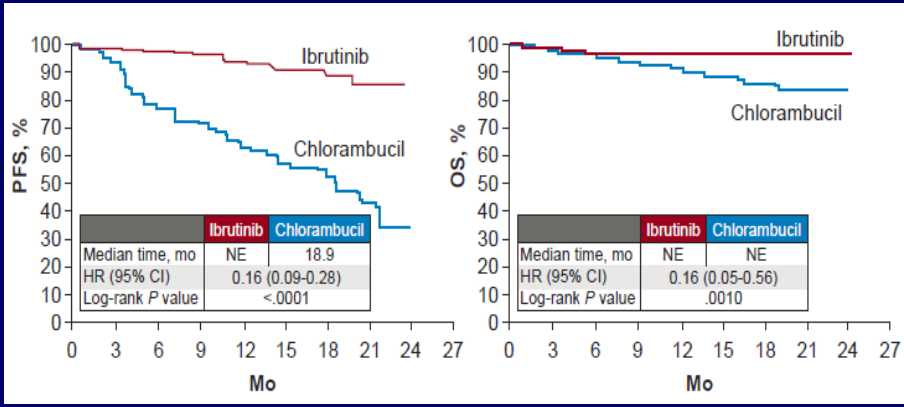
No statistically significant difference in OS is noted vs rituximab-chlorambucil[a]



[a] OS results are not yet mature

1. Goede V et al. *Leukemia*. 2015;29:1602-1604.

Ibrutinib (BTK Inhibitor) for High-Risk CLL: RESONATE-2 Survival Outcomes

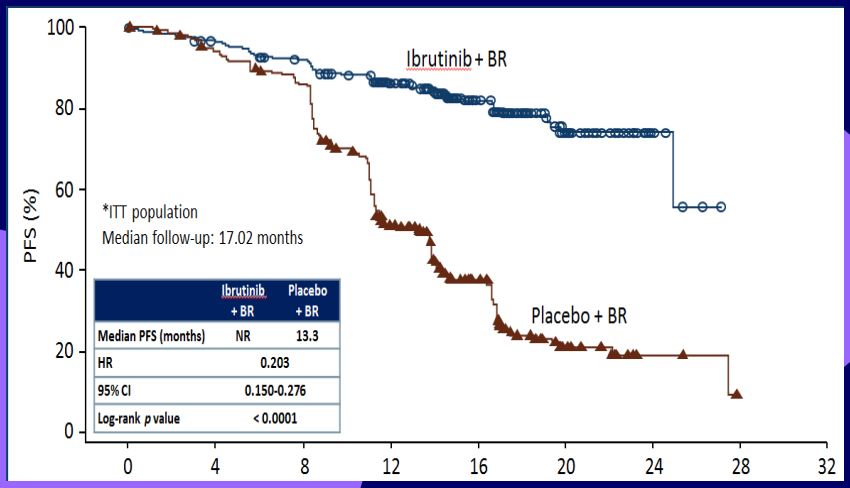


CR rate improved from 11% to 18% with longer f/u: at 29 mo: 88% reduction in risk of PD or death with ibrutinib vs CHL

Tedeschi A et al. ASH 2015. Abstract 495.

Barr et al: ASH 2016. Abstract 234.

Ib + BR vs PL + BR for Rel CLL: HELIOS



- **Investigator-assessed HR for ib + BR vs pl + BR: 0.201 (CI: 0.145-0.278)**
- **No Richter's observed on the ib and 3 on the pl arms**

Chanan-Khan et al. ASCO 2015; LBA 7005

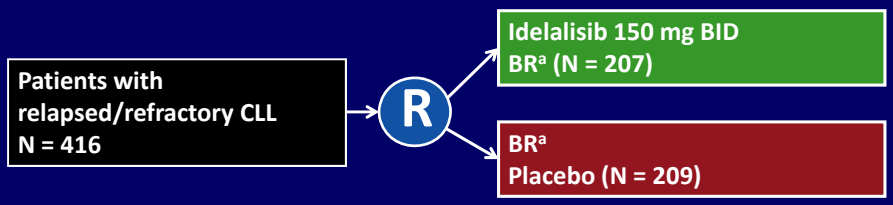
Idelalisib (PI3Kδ Inhibitor): Phase 3 Summary in CLL[1]

- Phase 3 summary of efficacy in relapsed/refractory CLL (N = 220)
  - 150-mg BID dose tested
  - Patients with decreased renal function, previous therapy-induced myelosuppression, or major coexisting illnesses

Efficacy Outcomes	Idelalisib + Rituximab	Rituximab	*P*
ORR, %	81	13	<.001
Median PFS, months	Not reached	5.5	<.001
12-month OS, %	92	80	.02
HR for PFS (progression or death) = 0.15 HR for OS (death) = 0.28			

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

Idelalisib + BR for Relapsed/Refractory CLL[1]



- Primary endpoint: PFS

Idelalisib + BR:
- Reduced risk of both PD and death
- Increased PFS
- Increased OS (HR 0.55; stratified *P* = .008)

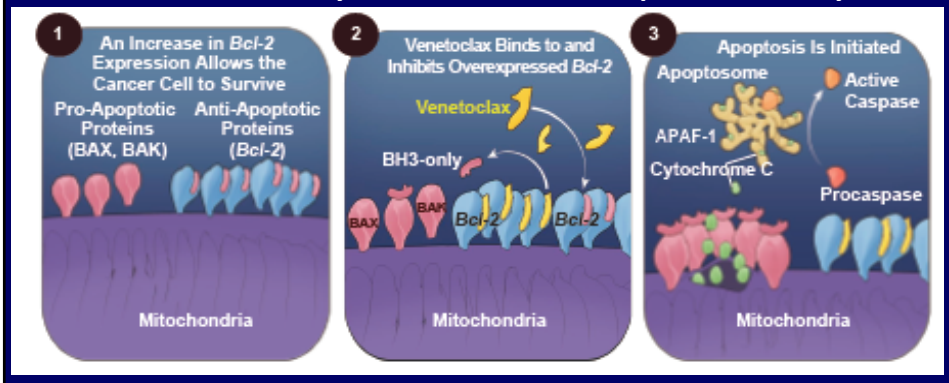
	Idelalisib + BR	BR
Median PFS, mo	23.1	11.1
HR, P	0.33, <.0001	

[a] Bendamustine 70 mg/m² days 1, 2 Q4W, cycles 1-6; rituximab 375 mg/m² cycle 1, 500 mg/m² cycles 2-6.

Zelenetz AD et al. ASH 2015. Abstract LBA-5.

Emerging Strategies for Therapy of Lymphomas: Bcl-2 Inhibition[1-3]

- Venetoclax: orally bioavailable, selective Bcl-2 inhibitor that induces apoptosis in CLL cells independent of p53
  - 79% ORR in early clinical studies in relapsed/refractory CLL[1]



Roberts et al. NEJM 2016;374:311-322. Stilgenbauer et al. ASH 2015. Abstract LBA-6. Konopleva et al. ASH 2014. Abstract 118.

Venetoclax Monotherapy: Phase 2 Study in Relapsed/Refractory del(17p) CLL (N = 107)[1]

Response and Main Safety Findings

Response, n (%)	IRC	Investigator
ORR	85 (79.4)	79 (73.8)
CR or CRi	8 (7.5)	17 (15.9)
nPR	3 (2.8)	4 (3.7)
PR	74 (69.2)	58 (54.2)

Safety Summary
• 40% grade 3/4 neutropenia; 22.4% baseline neutropenia (any grade)
• Infections in 72% of patients (20% grade ≥3)
• Laboratory TLS in 5 patients during the ramp-up period; no clinical TLS
• Most common SAEs: pyrexia (7%), AIHA (7%), pneumonia (6%), FN (5%)

Stilgenbauer et al. ASH 2015. Abstract LBA-6.

Diagnosing and Treating Slow-Growing Non-Hodgkin Lymphomas

- Diagnosis
  - Possible Causes
  - Pathology
  - Clinical Evaluation
- Therapy
  - Follicular Lymphomas
  - Small Lymphocytic Lymphoma and Chronic Lymphocytic Leukemia
  - Mantle Cell Lymphomas
  - Marginal Zone Lymphomas
  - T Cell Lymphomas

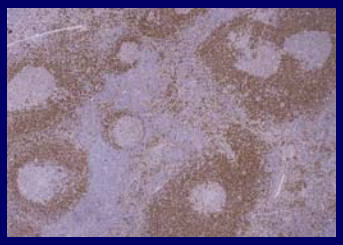
Diagnosis of Mantle Cell Lymphoma

- 5%-10% of B-cell NHL, with moderately aggressive course
- 74% male, median age 63 years
- >80% stage III/IV including marrow involvement
- Extranodal sites common: lymphomatous polyposis, gastrointestinal, soft tissue, or leukemic phase
- Classic translocation: >70% t(11;14); overexpression of cyclin D1 (bcl-1)
- CD19+, 20+, 5+, 23–, FMC7+, SOX11+
- In the past, prognosis was poor: chemoresponsive, but median survival 30 months with CHOP-type chemotherapy

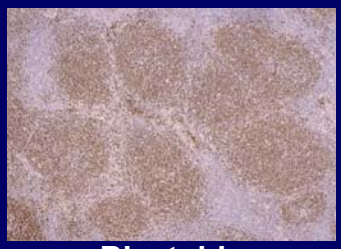
Fisher et al. Hematology, 221: 2004.

MCL Histologic Subtypes

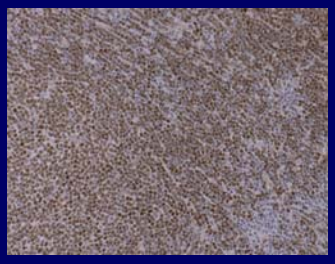
Mantle Zone



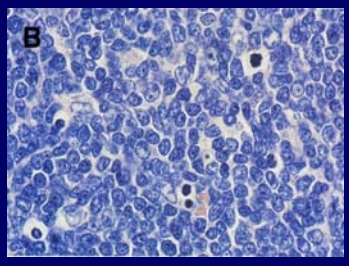
Nodular



Diffuse



Blastoid



Indolent Mantle Cell Lymphoma

- Characterization
  - Mantle Zone Lymphoma
    - With this pathology, only the Mantle Zone is involved by the disease
  - Any MCL (except Blastoid variant) with Ki-67 ≤ 10%
  - Mantle Cell Lymphoma involving the spleen and marrow only (usually do not have colon involvement)
  - Low MIPI and small tumor burden
- None of these have been studied in prospective trials

A Prognostic Index (M-IPI) for Patients With Advanced-Stage MCL

Patients with advanced MCL treated with first-line from 3 GLSG trials N=455

↓

Analysis based on a list of prognostic factors*

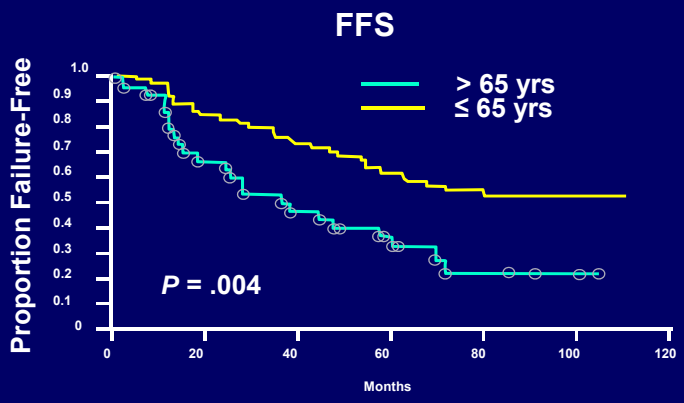
- Age (↑ 10 y, HR 1.42; *P*=0.0002)
- Sex
- ECOG PS (>1, HR 2.01; *P*=0.0088)
- Ann Arbor stage
- B-symptoms
- Number of ENS
- Number of involved nodal areas
- Tumor size
- Serum LDH (2 × ↑ LDH, HR 1.51; *P*<0.0059)
- WBC (10 × ↑ WBC, HR 2.56; *P*<0.0001)
- Platelet count
- Hemoglobin
- Albumin
- β2-microglobulin
- Ki-67

Hoster et al. ASH, 2006. Abstract 814.

R-HyperCVAD for MCL: FFS by Age

Initial R-HyperCVAD had 97 pts

Median age 61 (range 41-80); 1/3 pts > 65 y



Pts > 65y worse: med PFS just over 2y (delays / dose reduction / toxicity)

Romaguera et al. Brit Jnl Hematol 150::200-208, 2010.

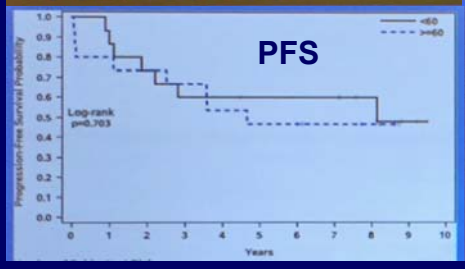
VcR-CVAD and MR for Untreated MCL

VcR-CVAD induction chemotherapy (21-day cycles, 6 cycles total)

Bortezomib† (Vc) 1.3-1.5 mg/m² IV, D1&4
Rituximab 375 mg/m² IV, D1
Cyclophosphamide 300 mg/m² IV q12h, D1-3
Doxorubicin 50 mg/m² IV CI, D1-2
Vincristine‡ 1-2 mg IV, D3
Dexamethasone 40 mg orally, D1-4

G-CSF 5 mcg/kg/day SQ D5/D6 until ANC 2000/mm³, OR
Pegfilgrastim 6 mg SQ D5/D6

Sex	Male	24 (80%)
	Female	6 (20%)
Age	Median 61 Range (48-74)	
	Age <60	15 (50%)
	Age ≥60	15 (50%)
ECOG PS	0	6 (20%)
	1	19 (63%)
	2	5 (17%)
MIPI	Low	12 (40%)
	Medium	8 (27%)
	High	10 (33%)
Stage	III	4 (13%)
	IV	26 (87%)
Blastic morphology		6 (20%)
Ki-67	<10	11 (37%)
	10-30	12 (40%)
	>30	5 (17%)
Elevated LDH		20 (67%)
Elevated β_2-microglobulin		20 (67%)



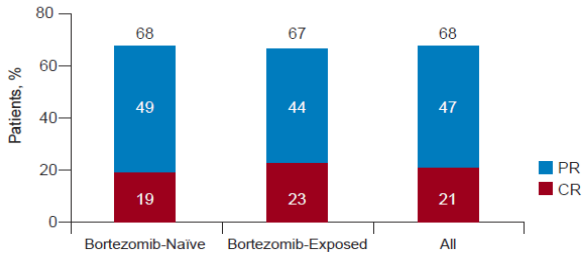
Chang et al. ASH 2016, abstract 149. **Tolerance better with Bor 1.3 and Vin 1**

BCR Inhibition in Relapsed MCL: Ibrutinib

Eligibility (N = 111)
- Patients with relapsed/ refractory MCL
- 1-5 prior lines of treatment
- No significant CV or GI disease

Bortezomib-naïve cohort (n = 63)
Ibrutinib 560 mg/d PO
28-d cycle until PD

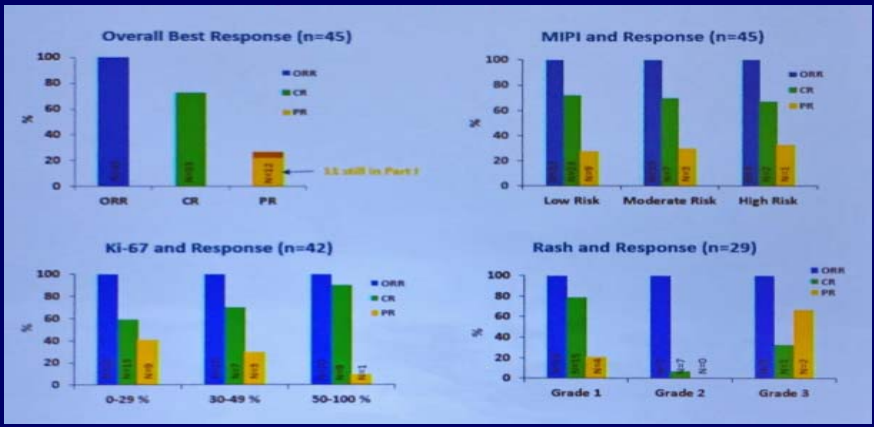
Bortezomib-exposed cohort (n = 48)
Ibrutinib 560 mg/d PO
28-d cycle until PD



Note: 560-mg daily dose approved in MCL (differs from CLL dose)

Wang ML et al. N Engl J Med. 2013;369:507-516.

Ibrutinib + Rituximab for Untreated MCL < 66: Responses by Features



CR 73%, ongoing. Better in those with high Ki-67%, but not affected by MIPI or degree of rash.

Wang et al. ASH 2016, abstract 147.

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  - **Marginal Zone Lymphomas**
  - T Cell Lymphomas

C

Outcome in Treatment Subsets of Stage IE Gastric MALT NHL: OS and EFS

Treatment	n	CR	PR	NC	5 Yr OS	5 Yr EFS
Antibiotics	45	67%	9%	24%	94%	75%
Local tx*	14	100%	0	0	92%	80%
Chemo	8	50%	12%	38%	75%	49%
CMT†	5	100%	0	0	80%	80%
Total	72	74%	7%	19%	89%	72%

* Surgery alone (n = 11), surgery and XRT (n = 2), or XRT alone (n = 1)
† Surgery and adjuvant chemotherapy

Pinotti G et al. *Leuk Lymphoma.* 1997;26:527-537.

Nongastric MALT Lymphoma: Presenting Sites

Primary Site	Percent (%)
Head and neck	30
Ocular adnexa	24
Lung	12
Skin	12
Intestinal tract/GU	8/1
Thyroid/Breast	7/2

From International Extranodal Lymphoma Study Group (IELSG), others

Cavalli F et al. Hematology. 2001:241-258.

Splenic Marginal-Zone Lymphoma: Clinical Presentation

- Typical presentation:
  - Splenomegaly
  - Circulating lymphoma cells
  - BM involvement
  - No enlarged nodes
- Rare lymphoma (<1% of all NHL)
- Also called splenic lymphoma with or without villous lymphocytes
- Was confused with Hairy Cell Leukemia

Nodal Marginal-Zone Lymphoma: Clinical Features

- B symptoms (14%)
- Stages I/II (29%) and III/IV (71%)
- Elevated LDH (36%)
- Bone marrow involvement (28%)
- 5-year survival (56%)

Nathwani BN et al. J Clin Oncol. 1999;17:2486-2492.

Therapy for Marginal Zone Lymphomas

- Few randomized trials
  - Good survival rates, even with active disease
  - Many different therapies work
  - Treatment depends on site of disease, and patient features
- Individualized Choices
  - Observation (no immediate therapy)
  - Radiation Therapy (often low dose)
  - Single-Agent Rituximab
  - Bendamustine/Rituximab
  - B-cell pathway drugs (Ibrutinib, Idelalisib)
  - Other novel agents being studied

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  - T Cell Lymphomas

The WHO Classification of PTCL

- **PTCL Leukemic**
  - Adult T cell leukemia/lymphoma (HTLV-1+)
- **PTCL, Predominantly Extranodal**
  - Extranodal NK/T cell lymphoma, nasal type
  - Enteropathy-type T cell lymphoma
  - Hepatosplenic T cell lymphoma (gamma/delta)
  - Subcutaneous panniculitis-type T cell lymphoma
  - Indolent: Mycosis fungoides/Sezary syndrome
    Primary cutaneous ALCL
- **PTCL, Predominantly Nodal**
  - Peripheral T cell lymphoma, NOS
  - Angioimmunoblastic T cell lymphoma, AILD-like
  - Anaplastic large cell lymphoma (T and Null cell)

Initial Therapy of PTCL

- **Relative rarity and heterogeneity of subtypes has limited clinical trials for these entities**
  - **Cell size does not correlate well with prognosis**
- **Most series indicate a higher relapse rate and poorer survival for PTCL, NOS vs DLBCL**
  - **Important to recognize ALCL, ALK+, containing the t(2;5) translocation → high curability with CHOP alone**
- **CHOP therapy has been the most commonly utilized front-line therapy**
  - **ORR ~ 60-70%, CR ~ 40-60%**
  - **Relapse @ 2 years > 70-80% in most series**

Initial Therapy of PTCL

- HyperCVAD often used for ATCL and other highly aggressive variants: PTCL trial at MDACC demonstrated no real benefit
- ACVBP may be better than CHOP in GELA trials
- EPOCH has activity in both front-line and relapsed settings
- Nucleoside analogues (fludarabine, cladribine, pentostatin) are more often used in MF or PTCL with cutaneous involvement
  - Inhibit adenosine deaminase, high concentrations in T-cells
  - ORR 20-70%, CR 3-25%, DR often < 6 months
- Improved therapies are needed !

Diagnosing and Treating Slow Growing Non-Hodgkin Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

someday is today®

Q&A Session

Ask a question by phone:

- Press star (*) then the number 1 on your keypad.

Ask a question by web:

- Click "Ask a question"
- Type your question
- Click "Submit"

Due to time constraints, we can only take one question per person. Once you've asked your question, the operator will transfer you back into the audience line.

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Diagnosing and Treating Slow Growing Non-Hodgkin Lymphomas

LEUKEMIA & LYMPHOMA SOCIETY® fighting blood cancers

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SUPPORT RESOURCES

- **Online Chats: Online moderated chat forums: www.LLS.org/chat**
- **Questions to ask your treatment team: www.LLS.org/whattoask**
- **Free education materials: www.LLS.org/booklets**
- **Past NHL education programs: www.LLS.org/programs**
- **Additional information on NHL: www.LLS.org/NHL**
- **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**

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