

Living with  
**Slow-Growing  
Lymphoma**



## **Welcome & Introduction**

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*Senior Director, Patient Services Programs*  
The Leukemia & Lymphoma Society

## **Follicular and Other Slow Growing Lymphomas**

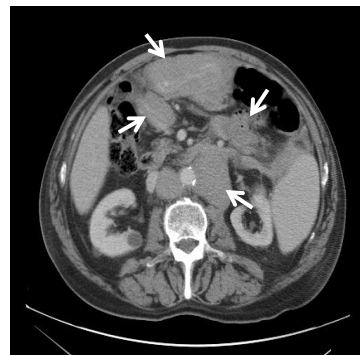
**Stephen Ansell, MD, PhD**  
Mayo Clinic

## Learning Objectives

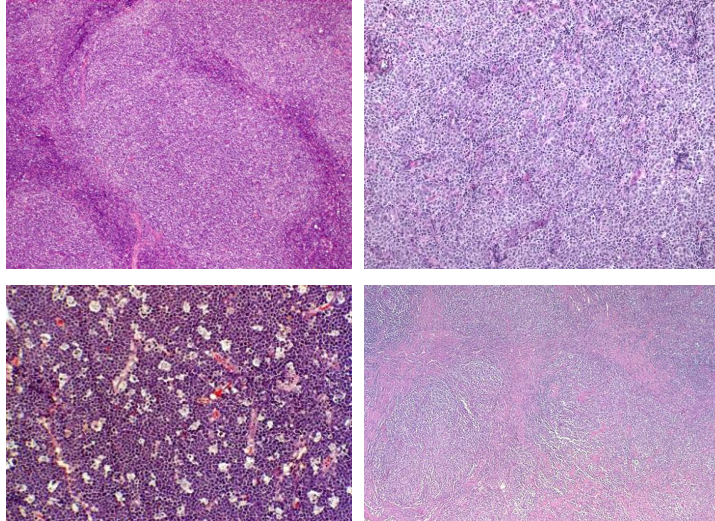
- Start with an overview of Follicular and other slow growing lymphomas
- Discuss current and emerging treatments, including stem cell transplantation.
- Discuss the role of clinical trials in the advancement of treatment.
- Review side effects of the various management strategies.

## Patient with Enlarged lymph nodes, Abdominal fullness and Fatigue

- 43 year old accountant
- Lymph nodes in neck, axilla, abdomen and groins
- Hgb 10.5g/dl. WBC and platelets - normal.
- LDH mildly elevated
- Biopsy shows B-cell lymphoma
- Bone marrow negative



## Histology - What kind of lymphoma does the patient have?



## WHO Classification for B-cell malignancies

<u>Classification</u>	<u>% of total cases</u>
<i>Peripheral B-cell neoplasms</i>	
Precursor B lymphoblastic leukemia/lymphoma	
<i>Mature B-cell neoplasms</i>	
CLL/small lymphocytic lymphoma	6.7
B-cell prolymphocytic leukemia	
Lymphoplasmacytic lymphoma	1.2
Splenic marginal zone lymphoma	<1
Extranodal marginal zone B-cell lymphoma of MALT (MALT Lymphoma)	7.6
Nodal marginal zone lymphoma	1.8
Follicular lymphoma	22.1
Mantle cell lymphoma	6.0
Diffuse large B-cell lymphoma	30.6
Mediastinal (thymic) large B-cell lymphoma	2.4
Intravascular large B-cell lymphoma	
Primary effusion lymphoma	
Burkitt lymphoma/leukemia	<1
Hairy cell leukemia	
Plasma cell myeloma	
Solitary plasmacytoma of bone	

## The Patient has Questions -

- Does she need treatment? Should she just "watch and wait"?
- Does she need chemotherapy - wouldn't rituximab alone be enough?
- If she receives chemotherapy, which chemotherapy regimen is best?
- Would maintenance rituximab after initial therapy add anything?
- Would stem cell transplantation add more?

## Current Treatment Options -

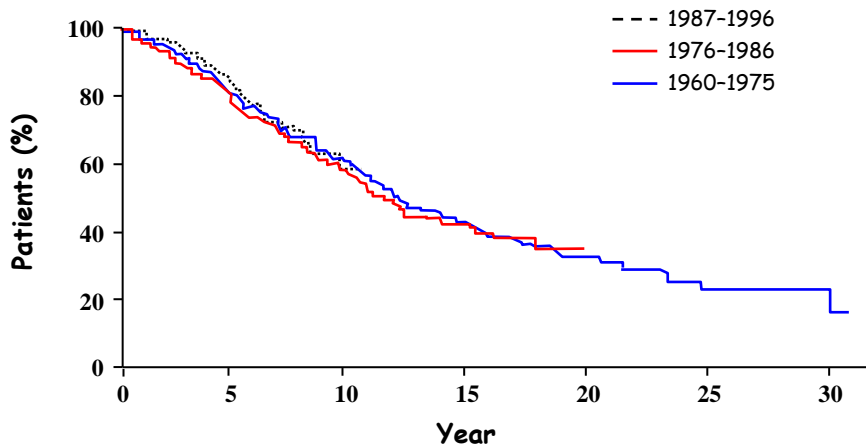
Low grade/slow growing B-cell lymphomas, with a focus on follicular lymphoma.

## Follicular Lymphoma

- FL is the most prevalent indolent lymphoma
  - Represents 35% of adult NHL in United States, 22% worldwide<sup>[1]</sup>
- Outcomes, including OS, improved in recent years largely due to introduction of rituximab<sup>[2-3]</sup>
- Retrospective analysis conducted of patients with stage IV FL (1972-2002) showed improvements in outcomes<sup>[3]</sup>
  - 5-year OS improved from 64% to 95%
  - FFS improved from 29% to 60%
    - Plateau in FFS curve after 8-10 years of treatment

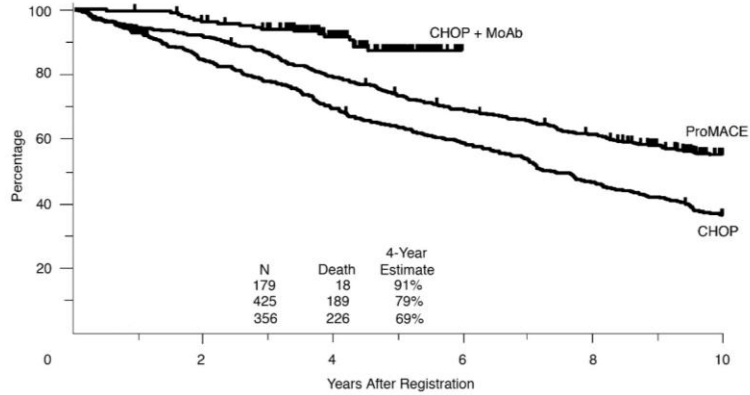
1. Ganti AK, et al. *Oncology*. 2005;19:213-228.  
 2. Fisher RI, et al. *J Clin Oncol*. 2005;23:7565-7573  
 3. Liu Q, et al. *J Clin Oncol*. 2006;24:1582-1589.

### Survival of Patients With Indolent Lymphoma: The Stanford Experience 1960-1996



Adapted from Horning. *Semin Oncol*. 1993;20(suppl 5):75.

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

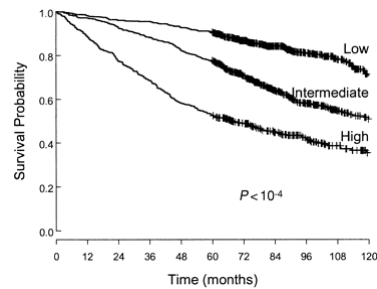


Fisher, R. I. et al. J Clin Oncol; 23:8447-8452 2005

## Follicular Lymphoma International Prognostic Index (FLIPI)

Factor	Adverse prognosis
Age	> 60 years
Ann Arbor Stage	III or IV
Hemoglobin level	<12 g/dL
Number of nodal areas	> 4
Serum LDH level	Above normal

LDH = lactate dehydrogenase



Sokal-Celigny, P. et al. Blood 2004;104:1258-1265

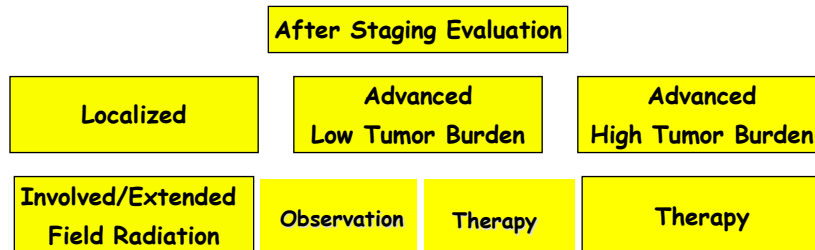
## The Follicular Lymphoma International Prognostic Index 2 (FLIPI2)

- FLIPI2 score used to predict outcomes of therapy based on adding number of risk factors (each factor = 1 point)
  - Longest diameter of largest involved node > 6 cm
  - Hemoglobin < 12 g/dL
  - Bone marrow involvement
  - Age > 60 years
  - $\beta_2$ -microglobulin > ULN

FLIPI Risk Group	Risk Factors, no.	Patients, %	3-Yr PFS, %	5-Yr PFS, %	HR
Low	0-1	20	90.9	79.5	1.00
Intermediate	2	53	69.3	51.2	3.19
High	3-5	27	51.3	18.8	5.76
High vs Int					1.81

Federico M, et al. J Clin Oncol. 2009;27:4555-4562.

## Indolent Lymphoma Common Management Approach

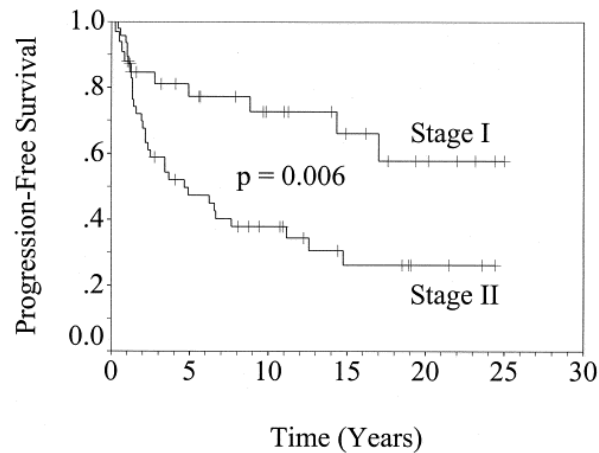


## Therapies for advanced indolent lymphoma

	Remission rate	Durability	Morbidity	Mortality
Watch and wait	0/+	+	0	0
Single agent chemo	+	+	+	+
CVP, CHOP, FND	++	++	++	+
Rituximab	+/**	++	+	0
Radioimmunotherapy	++	+++	++	+
Rituximab-chemo	++	+++	++	+
Auto transplant	+++	+++	+++	++
Allo transplant	+++	+++	+++	+++

Ansell S. Mayo Clin Proc. 2005;80(8):1087-97.

## Long term outcome of Stage I/II follicular lymphoma treated with Radiotherapy



Wilder RB et al. Int J Radiat Oncol Biol Phys. 2001;51(5):1219-27



## Rituximab for "Low Burden" Untreated Indolent Lymphoma

Number of patients	ORR	CR rate	Reference
50	73%	27%	Colombat et al
60	47%	7%	Hainsworth et al
37	72%	36%	Witzig et al

## Rituximab for "Low Burden" Untreated Follicular Lymphoma - RESORT trial

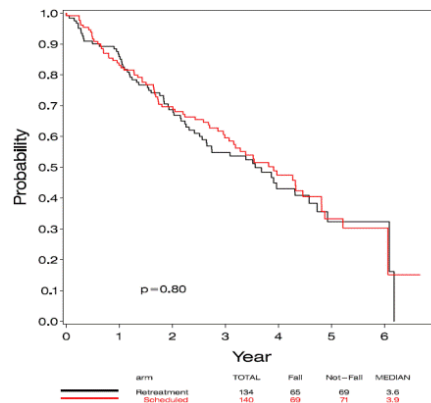
Multicenter study - 384 patients

Randomized between maintenance rituximab (MR) and retreatment rituximab (RR).

Median follow-up of 3.8 yrs

TTTF was and 3.9 yr for MR vs. 3.6 yr for RR (p=NS)

Adverse events and QOL similar

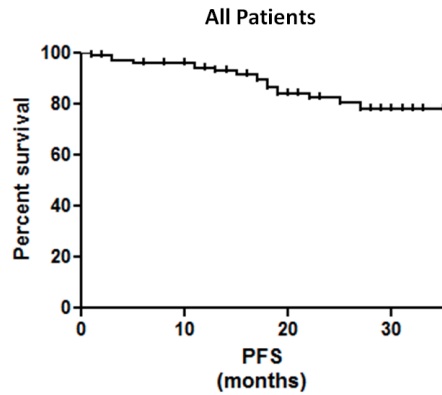


Kahl, et al. ASH 2011, abstract LBA-6.

## Lenalidomide plus Rituximab for untreated "low-burden" Indolent Lymphoma

Lenalidomide + Rituximab - 110 patients (50 follicular)

- ORR 90% - CR 64%
- ORR 98% in Follicular lymphoma - CR 87%
- Median follow up 22 months - estimated 2 year PFS 83%
- AEs - rash, neutropenia, neuropathy, thrombosis



Fowler N, et al. ASH 2012, abstract 901.

## Combination Therapy for Advanced Disease with a greater Tumor Burden

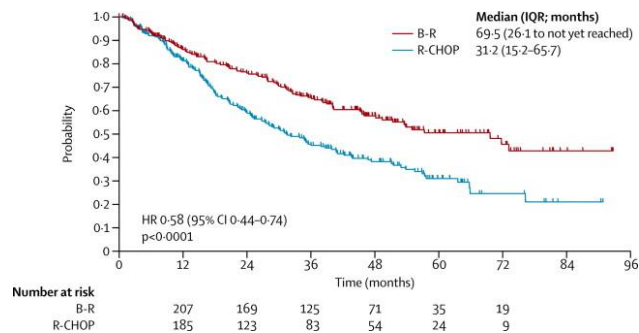
- Which chemotherapy should be combined with rituximab?
  - R-CVP
  - R-CHOP
  - R-FND
  - R-Bendamustine

## Bendamustine plus Rituximab compared to CHOP plus Rituximab in Advanced Untreated Indolent Lymphoma

- STIL study - 549 patients
  - 55% follicular, 18% mantle cell, 17% other
  - R-Bendamustine x 6 vs. R-CHOP x 6
    - ORR equal in both arms - CR rate higher for R-Bendamustine (40% vs. 31%)
    - Prolonged PFS compared to R-CHOP - 55 months vs. 35 months (p=0.0002)
    - R-Bendamustine had fewer AEs
    - No difference in OS

Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

## Bendamustine plus Rituximab compared to CHOP plus Rituximab in Advanced Untreated Indolent Lymphoma



Rummel et al. Lancet. 2013 Apr 6;381(9873):1203-10.

## Bendamustine plus Rituximab compared to R-CHOP or R-CVP in Advanced Untreated Indolent Lymphoma

- BRIGHT study - 447 patients
  - 83% indolent, 17% mantle cell
  - R-Bendamustine x 6- vs. R-CHOP/R-CVP x 6-8
    - CR rate 31% versus 25%
    - CR rate higher for R-Bendamustine in MCL (51% vs. 24%)
    - AEs similar frequency but different
    - No PFS or OS data presented

Flinn et al, ASH 2012, abstract 902

## Ofatumumab added to CHOP in Advanced Untreated Follicular Lymphoma

- Multicenter study - 59 patients
  - Advanced stage. Grades I-III
  - Randomized between ofatumumab 1500mg (group A) or 1000mg (group B) plus CHOP for 6 cycles.
    - ORR 90% and 100% - CR 62%
    - Median follow up 20 months
    - No unexpected toxicities

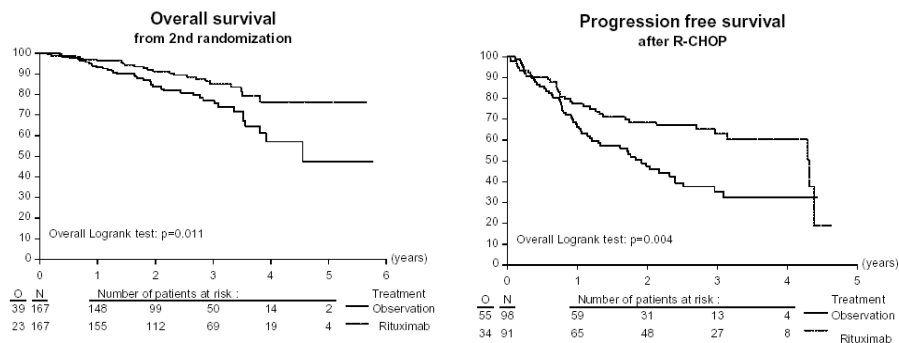
Czuczman et al, Br J Haematol. 2012;157(4):438-45.

## Bortezomib added to R-CVP in Advanced Untreated Follicular Lymphoma

- NCIC study - 94 patients
  - 55% follicular, 18% mantle cell, 17% other
  - R-CVP plus bortezomib 1.3mg/m<sup>2</sup> days 1 and 8 for 8 cycles.
    - ORR 83% - CR 46/94 (49%) PR 32/94 (34%)
    - 59% went on to maintenance rituximab
    - Only 6/95 (6%) had grade 3 or 4 neuropathy

Sehn et al, J Clin Oncol. 2011;29(25):3396-401.

## Rituximab maintenance improves clinical outcome after R-CHOP of relapsed/resistant follicular non-Hodgkin's lymphoma



Van Oers et al. Blood. 2006 108(10):3295-301

## Recurrent Follicular Lymphoma

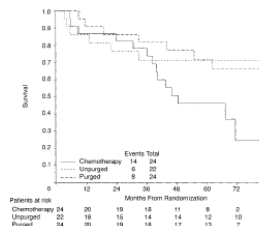
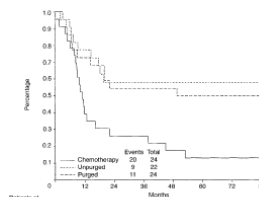
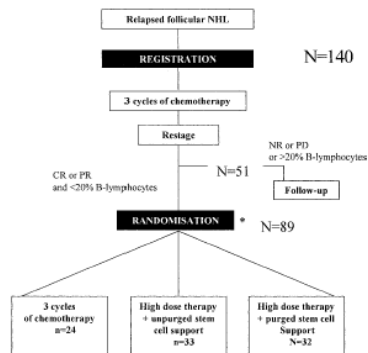
- Conventional strategies
  - Rituximab ± maintenance
  - Chemoimmunotherapy ± maintenance
  - Radioimmunotherapy
  - External-beam radiotherapy
  - Autologous transplant
  - Allogeneic transplant
- Novel strategies
  - Novel monoclonal antibodies
  - Bortezomib
  - Bendamustine
  - Lenalidomide
  - Others

[http://www.nccn.org/professionals/physician\\_gls/PDF/nhl.pdf](http://www.nccn.org/professionals/physician_gls/PDF/nhl.pdf)

## Autologous Transplant for relapsed follicular lymphoma

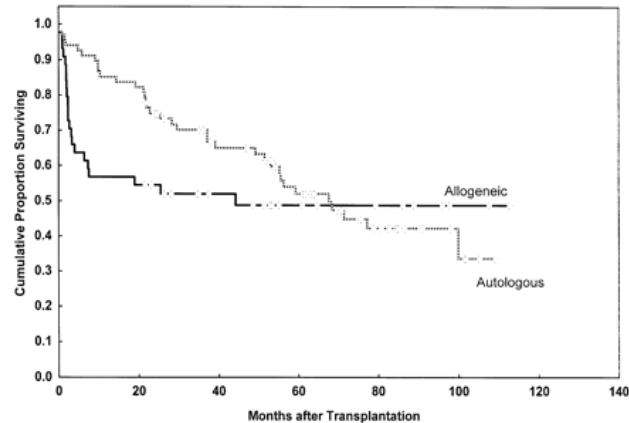
65% first relapse

28% second relapse



Schouten et al. JCO. 2003 21:3918-27

## Indolent lymphoma - autologous vs. allogeneic transplant



Hosing et al, Ann Oncol. 2003;14(5):737-44

## GA101 (obinutumumab) for Relapsed Follicular Lymphoma

22 patients Phase 1 trial -  
 200-2000mg weekly x 4, then maintenance q 3 months x 8 doses  
 86% had previous rituximab  
 32% response rate - 6 PRs, 1 CR

Sehn et al. Blood. 2012;119(22):5118-25.

21 patients Phase 1 trial -  
 50-2000mg q 3 weeks x 8 doses  
 95% had prior rituximab  
 ORR - 43% (5 CRs, 4 PRs)

Salles et al. Blood. 2012;119(22):5126-32.

Phase 2 trial - GA101 versus rituximab  
 175 pts (149 follicular and 26 non-follicular indolent NHL)  
 ORR - 43.2% (32/74) v 38.7% (29/75)  
 No appreciable differences in safety

Sehn et al. ASH 2011, abstract 269

## Other antibody approaches for Relapsed Follicular Lymphoma

### Ocaratuzumab (AME-133v) -

Phase 1 trial - 23 patients received IV ocaratuzumab up to 375 mg/m<sup>2</sup> weekly for 4 doses. 95% had previous rituximab  
 ORR - 5 of 23 (22%)  
 Median PFS was 25.4 weeks

Forero-Torres et al. Clin Cancer Res. 2012;18(5):1395-403

### Milatumuzumab (Anti-CD74 Antibody) and Veltuzumab -

18 patients  
 veltuzumab 200 at mg/m<sup>2</sup> weekly combined with escalating doses of milatumuzumab at 8, 16, and 20 mg/kg twice on weeks 1-4, 12, 20, 28, and 36.  
 Partial responses were observed in 3 pts (2 with grade 3 follicular NHL refractory to rituximab)  
 Stable disease was observed in 10 pts; 6 pts had SD of a median duration of 6 months (range 2.5-10 months)

Christian et al. ASH. 2011;abstract 3707

## Bendamustine in Rituximab-Refractory Indolent B-Cell NHL

- Multicenter - Bendamustine 120 mg/m<sup>2</sup> Days 1 + 2 every 21 days
- ORR
  - Patients with ≥ 1 dose of bendamustine (n = 100): 75%
  - Patients with ≥ PR to last regimen (n = 51): 88%
  - Patients with no response to last regimen (n = 36): 64%
- Response rates did not significantly differ by histology

Histology	No. of Patients	ORR	CR	CRu	PR	SD	PD	Unknown
Follicular	62	74	15	5	55	15	10	2
Small lymphocytic	21	71	5	0	67	19	5	5
Lymphoplasmacytic	1	100	0	0	100	0	0	0
Lymph node marginal zone	9	78	11	0	67	22	0	0
Extralymph node marginal zone	7	86	43	0	43	14	0	0
Total	100	75*	14	3	58	16	7	2

- Median DOR: 9.2 mo
- Median PFS: 9.3 mo

Kahl B, et al. Cancer. 2010 Jan 1;116(1):106-14.



## GA101(obinutumumab) plus CHOP or FC in Relapsed Follicular Lymphoma

- Relapsed follicular lymphoma (n=56) - CHOP x 6-8 q 21 day cycles (n=28) or fludarabine/cyclophosphamide x 4-6 q 28 day cycles (n=28).
- ORR at the end of induction was 96.4% in the G-CHOP group (39.3% CR) and 92.9% in the G-FC group (50.0% CR)
- Response rates to G-CHOP compared favorably with historical response rates to R-CHOP.
- G-CHOP could be delivered at 3-weekly intervals in most patients. G-FC in a more heavily pretreated population showed worse tolerability.

Radford et al, ASH 2011, abstract 270

## Lenalidomide in Relapsed/Refractory Indolent NHL: Phase II Results

43 patients - follicular and other indolent lymphomas

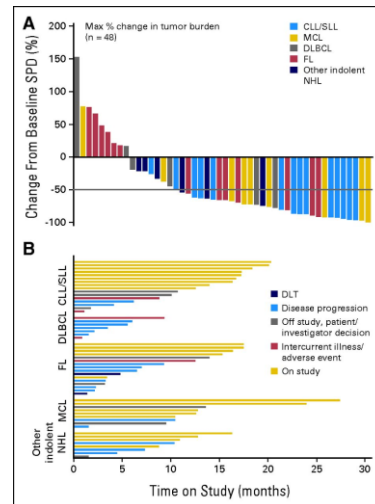
Response*	% of Patients	AE* (Grade 3/4)	% of Patients
ORR	23	Neutropenia	46
CR	7	Thrombocytopenia	19
PR	16	Febrile Neutropenia	2
SD	37	Anemia	9
PD	40	Asthenia	5

- Median PFS 4.4 months
- Median DOR > 16.5 months
- 7/10 responses ongoing at 15-28 months

Witzig et al. J Clin Onc 2009;27:5404.

## Btk inhibitor in Relapsed Lymphoma

- Btk downstream of BCR signalling
- PCI-32765 - oral inhibitor given daily. Phase 1 study
- 56 patients (16 FL, 16 SLL, 7 DLBCL, 9 MCL, 4 Marginal zone lymphoma, 4 Waldenstrom macroglobulinemia)
- ORR 54% (MCL -7/9, SLL - 11/16, FL - 6/16, DLBCL - 4/7, WM - 3/4, MZL - 1/4.
- Well tolerated



Advani et al, J Clin Oncol. 2013;31(1):88-94.

## Summary: Current Treatment Options for Low-grade Lymphoma

- Early stage follicular lymphoma - consider radiotherapy.
- More extensive disease and asymptomatic - "watch and wait" or rituximab alone or a clinical trial.
- Extensive disease, symptomatic or poor prognostic features - R-chemo possibly followed by rituximab maintenance or a clinical trial.

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## Question and Answer Session

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The Leukemia & Lymphoma Society's (LLS) Co-Pay Assistance Program offers financial assistance to qualified lymphoma patients to help with treatment-related expenses and insurance premiums. Patients may apply online or over the phone with a Co-Pay Specialist.

- **WEBSITE:** [www.LLS.org/copay](http://www.LLS.org/copay)
- **TOLL-FREE PHONE:** (877) LLS-COPAY

For more information about slow-growing lymphomas and other LLS programs, please contact an LLS Information Specialist.

- **TOLL-FREE PHONE:** (800) 955-4572
- **EMAIL:** [infocenter@LLS.org](mailto:infocenter@LLS.org)