

## Follicular Lymphoma: Update

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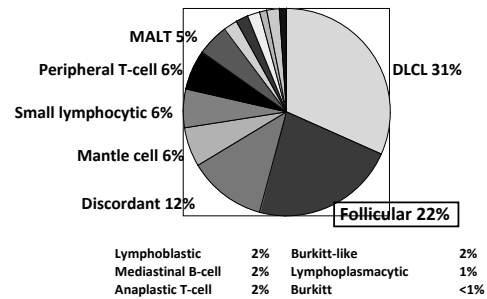
## Financial Disclosure

- I have no significant relationships to disclose

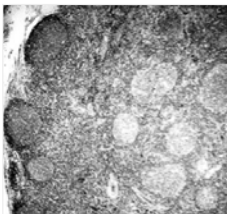
## Follicular Lymphoma Outline

- Background/Characteristics
- Prognostic Scoring
- Frontline therapy/Salvage Therapy
- Novel Agents
- Role of Hematopoietic Stem Cell Transplantation

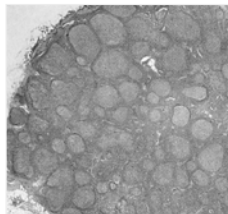
## Non-Hodgkin's Lymphoma



## Lymph Node Architecture



NORMAL



FOLLICULAR  
- back-to-back follicles  
- loss of interfollicular zones  
- attenuation of mantle zones

## Characteristics and Clinical Course

### Follicular lymphoma

- 20% of all newly diagnosed NHL
- 24,000 cases/yr
- Median age: 59 yo
- 50% of patients present as stage IV disease
- Most are asymptomatic at diagnosis
- Sensitive to chemotherapy and radiotherapy
  - Remission usually achieved
  - Continuous pattern of relapses e → shorter remission durations
  - Very treatable...difficult to cure

## Characteristics and Clinical Course Follicular lymphoma

- Median survival ~ 8-12 yrs
- Waxing and waning course
  - Spontaneous regressions
- Histologic transformation
  - Occurs in 30% to 40% of patients
  - Accompanied by new symptoms, rapid progression, elevated LDH, increased activity on PET
  - Generally poor prognosis

## We Are Making Progress!

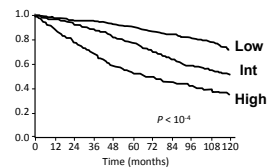
- 10-Yr Survival Trends for Low-Grade Lymphoma in the US

Age Range, Yrs	Survival, %	
	1990-1992	2002-2004
15-44	64	84
45-54	59	81
55-64	54	73
65-74	49	70
75 or older	31	49
Total	52	72

Pulte et al. Arch Int Med. 2008;168:469

## Follicular Lymphoma International Prognostic Index (FLIPI)

- Age > 60 yrs
- Ann Arbor stage III/IV disease
- LDH
- Hemoglobin < 120 g/L
- >4 nodal sites



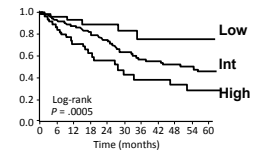
FLIPI Risk Group	Risk Factors, n	5-Yr OS, %	10-Yr OS, %
Low	0-1	91%	71%
Intermediate	2	78%	51%
High	≥ 3	53%	36%

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

## Follicular Lymphoma International Prognostic Index (FLIPI-2)

- FLIPI -2 score → PROGRESSION FREE SURVIVAL

- Age > 60 yrs
- BM involvement
- Hemoglobin < 120 g/L
- Beta-2M
- Nodes >6 cm



FLIPI - 2 Risk Group	Risk Factors, n	3-Yr PFS, %	5-Yr PFS, %
Low	0-1	91%	79%
Intermediate	2	69%	51%
High	≥ 3	51%	20%

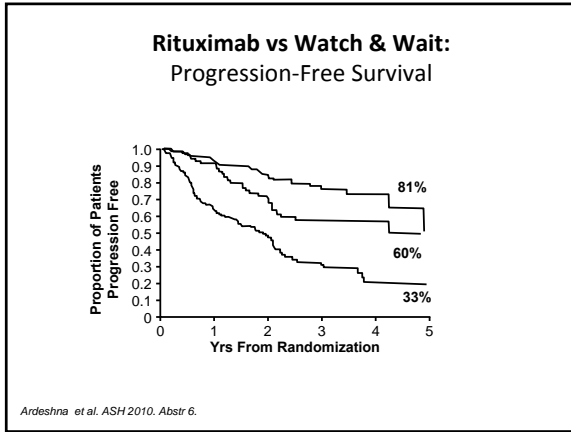
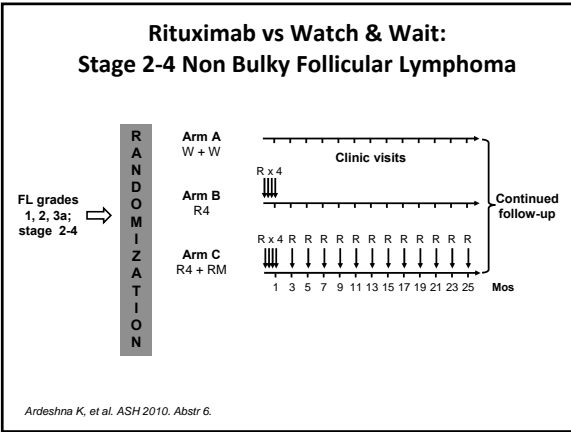
Federica M, et al. J Clin Oncol 2009;27:4555

## Treatment of Follicular NHL: Indications

- Disease-related symptoms
  - Cytopenias
  - Fevers, sweats, weight loss, fatigue
- Enlarging or bulky lymph nodes
- Enlarging liver, spleen
- Bone marrow or organ compromise
- Autoimmune complications (AIHA, ITP)
- Evidence of histologic transformation
- Patient preference

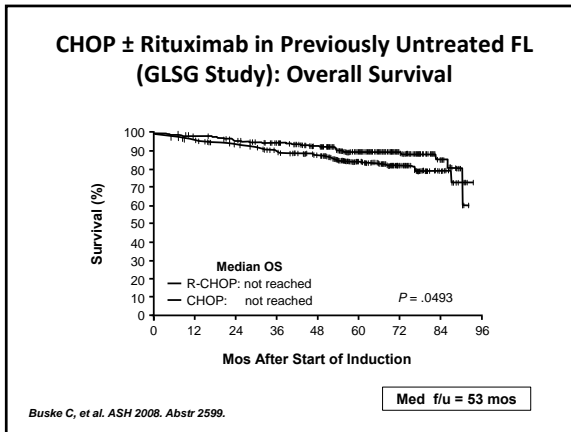
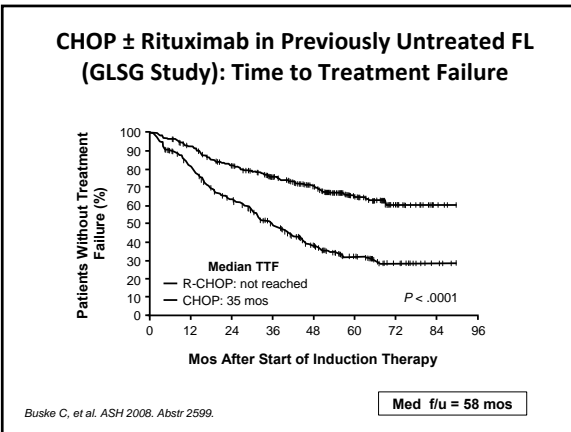
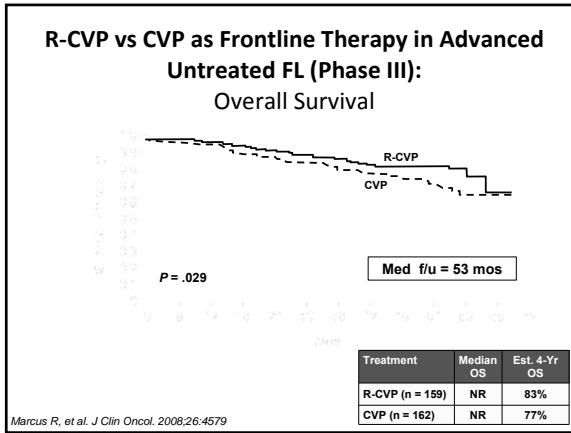
## Follicular NHL Treatment

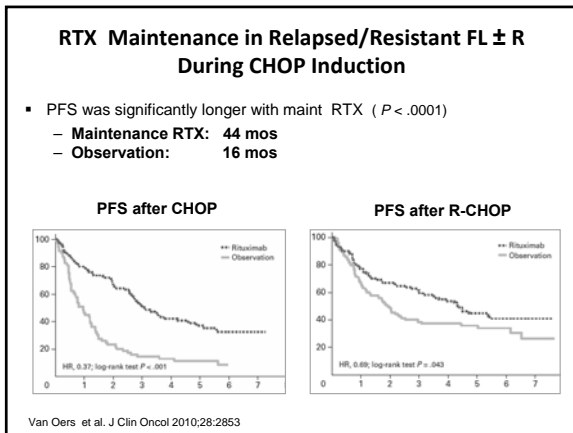
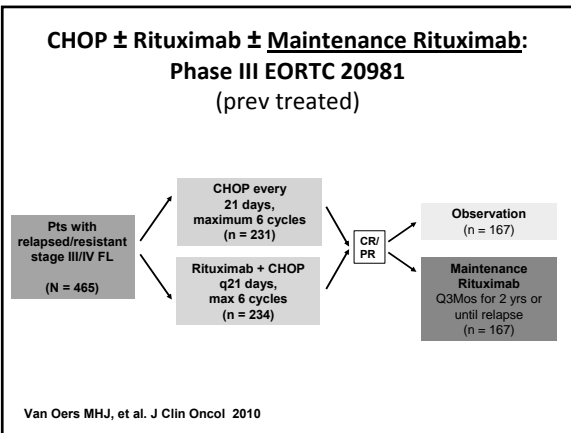
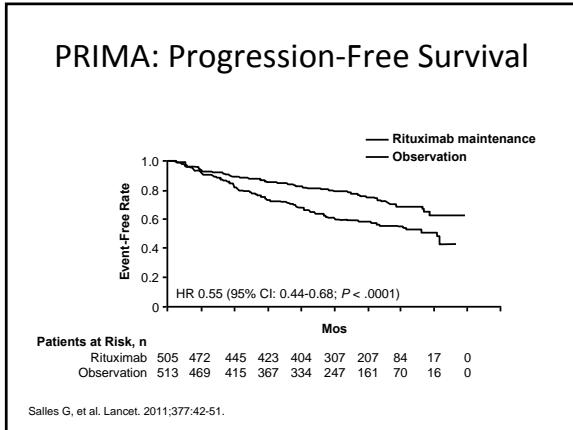
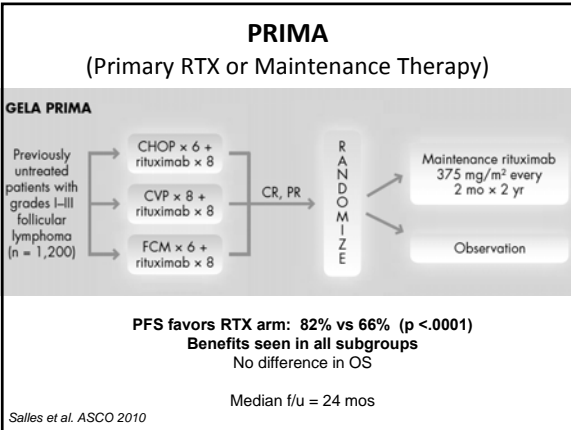
- Initial management
  - Watch and wait \*\*
  - Rituximab (single agent)
  - Chemotherapy (eg, CHOP, CVP, fludarabine) + rituximab
- Localized (stage I/II)
  - IFRT
  - Adding chemotx to localized early stage disease does not appear to improve OS



### Frontline Therapy: Advanced Disease

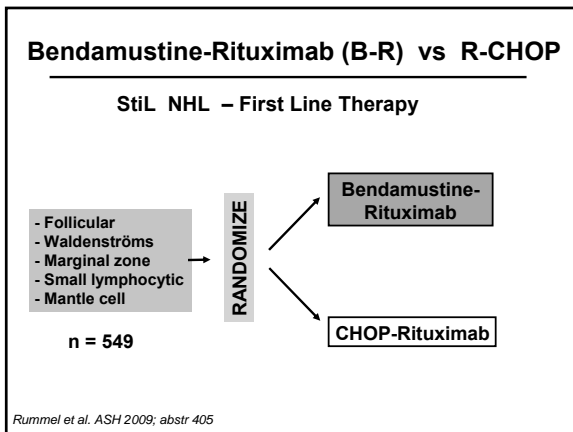
What is the best therapy for advanced disease or when treatment IS indicated?



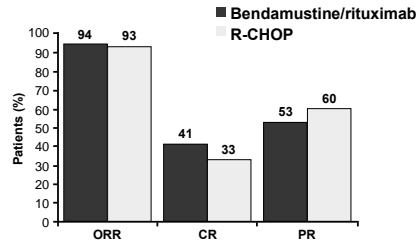


## Bendamustine

- Developed in early 1960s in East Germany
  - > 20,000 patients
  - Extensive clinical and safety data
  - NHL, CLL, multiple myeloma, Hodgkin's disease and solid tumors
- "Bifunctional" molecule with alkylator and antimetabolite properties
- Bendamustine + RTX → activity in relapsed indolent lymphomas

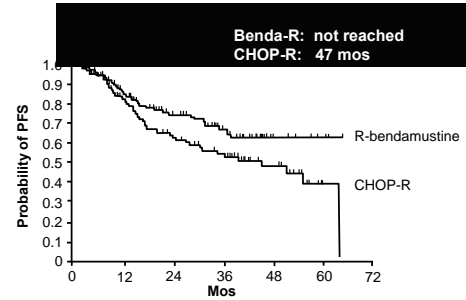


### First-line Benda-R vs R-CHOP in Indolent Lymphomas and MCL



Rummel et al. ASH 2009; abstr 405

### StiL: PFS for Follicular Lymphoma



Rummel MJ, ASH 2009. Abstr 405.

### Bendamustine-R vs CHOP-R

- > B-R significantly improved PFS and CR rates compared to CHOP-R in patients with FL, MCL and Waldenström's
- > B-R showed better tolerability profile
  - no alopecia
  - less hematotoxicity, infections, and neuropathy

Rummel et al. ASH 2009; abstr 405

### Bendamustine in Refractory/Relapsed NHL

Study Investigator	N	NHL Grade	ORR, %	CR, %	Dose, mg/m <sup>2</sup> ; Schedule
Bremer <sup>[1]</sup>	61	Indolent	82	15	50-60; Days 1-5
Heider <sup>[2]</sup>	58	Indolent	73	11	120; Days 1-2
Weidmann <sup>[3]</sup>	18	Aggressive	44	17	120; Days 1-2
Friedberg <sup>[4]</sup>	76	Indolent, MCL, transformed	77	34	120; Days 1-2
Kahl <sup>[5]</sup>	100	Indolent, MCL	75	14	120; Days 1-2

1. Bremer K. J Cancer Res Clin Oncol. 2002;11:603. 2. Heider A, et al. Anticancer Drugs. 2001;12:725. 3. Weidmann E, et al. Ann Oncol. 2002;13:1285-1289. 4. Friedberg JW, et al. J Clin Oncol. 2008;26:204. 5. Kahl B, et al. ASH 2007. Abstr 1351.

### Follicular NHL

What is the role of radio-immunotherapy?

Frontline or Relapsed Disease?

### <sup>131</sup>I-Tositumomab After Progression on Rituximab

N = 40 FL patients

- Refractory to prior chemotherapy: 22 (56%)
- Rituximab nonresponders: 24 (60%)
- Median # of prior regimens: 4

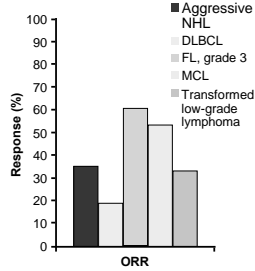
- Responses
  - ORR: 65%
  - CR: 38%

Responses were **not** significantly associated with previous rituximab response

Horning SJ, et al. J Clin Oncol. 2005;23:712-719.

## Lenalidomide

- **Thalidomide derivative**
  - Does not cause significant somnolence, constipation or neuropathy
  - myelosuppression
- **Efficacy as monotherapy** demonstrated in phase II study
- Relapsed/refractory NHL (N = 49)

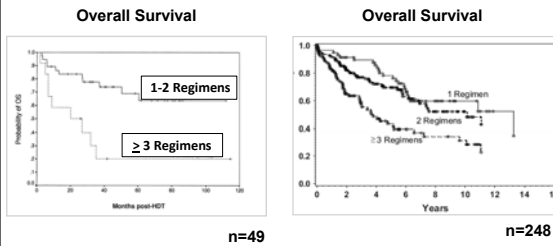


Wiernik PH, et al. *J Clin Oncol*. 2008;26:4952

## Follicular NHL

*What is the role of hematopoietic cell transplantation?*

### Effect of # Prior Regimens: Autologous SCT



*Biol BMT* 2001;7:294

*Biol BMT* 2008;14:36

### Follicular NHL: Randomized Trials of Chemo vs Autologous SCT as Consolidation Therapy

	n	Regimen	PFS	OS	Follow-up	2° Cancers
German GSLG 2004	240	Flu/Mel	33% 64% <i>p</i> <.0001	NR	52 m	1% 6%
French GOELAMS 2009	166	Flu/Cy/Rit	39% 64% <i>p</i> =.004	80% 76%	108 m	1% 14%
French GELA 2006	401	Flu/Cy	28% 38% <i>p</i> =.11	71% 76%	92 m	7% 14%

■ conventional chemo arm  
■ transplant arm

No difference in OS;  
Late cancers are problematic

Lenz et al. *Blood* 2004;104:2667  
Gyan et al. *Blood* 2009;113:395  
Sehban et al. *Blood* 2006;108:2540

### Allogeneic SCT for Follicular NHL: Reduced Intensity PROSPECTIVE Trials

	n	Median Age (range)	Regimen	PFS	OS	TRM	Follow-up
GELTAMO 2010	37	50	Flu/Mel	57%	54%	24%	52 m
MD Anderson 2008	47	53	Flu/Cy/Rit	83%	85%	15%	60 m
CALGB 2007	23	53	Flu/Cy	71%	76%	7%	31 m
U.K. Consortium 2004	41	51	Flu/Mel/Alemtuz	65%	73%	11%	36 m

Khoury et al. *Blood* 2008;111:5530 Morris et al. *Blood* 2004;104:3865  
Shea et al. *Blood* 2007;110:150a Pinana et al. *Haematologica* 2010;95:1176

CTN #0701

**Non-Myeloablative Allogeneic HSCT for Patients with Relapsed Follicular NHL Beyond CR1 or PR1**

Intergroup Phase II Trial:  
CALGB, SWOG, ECOG

Protocol Chair: Ginna Laport

Marcie Tomblyn (DCC) Hillard Lazarus (ECOG)  
Tom Shea (CALGB) Brent Logan (CIBMTR)  
Auypporn Nademanee (SWOG) Chitra Hosing (MD Anderson)  
Shelly Carter (EMMES) Cathy Gurgol (EMMES)

## Considerations Regarding Initial Therapy

- **Patients with low tumor burden**
  - Watchful waiting
  - Single-agent antibody therapy
  - R-CVP
  - R-CHOP
  - R-Bendamustine
  - R-FND
- **Patients with high tumor burden**
  - R-CVP
  - R-CHOP
  - R-Bendamustine
  - R-FND

NCCN guidelines: non-Hodgkin's lymphomas, v.2011.

## Recurrent FL: Recommended Treatment

- **Conventional strategies**
  - Rituximab ± maintenance
  - Chemoimmunotherapy ± maintenance
  - Radioimmunotherapy
  - External-beam XRT
  - Autologous SCT
  - Allogeneic SCT
- **Novel strategies**
  - Novel monoclonal antibodies
  - Bortezomib
  - Bendamustine
  - Lenalidomide
  - Others
- **Clinical trial**

NCCN guidelines: non-Hodgkin's lymphomas, 2011

## Follicular NHL: Summary

### Relapsed/Refractory Disease

- Numerous choices...need to individualize based on age and co-morbidities
- RTX + chemotherapy with RTX maintenance
- Role of lenalidomide, bortezomib being explored
- **Autologous HSCT**
  - NO role as first line therapy
  - May prolong OS in less heavily treated patients
- **Allogeneic HSCT**
  - Less relapse seen compared to autologous SCT
  - Myeloablative regimens have high TRM
  - Reduced intensity regimens appears promising