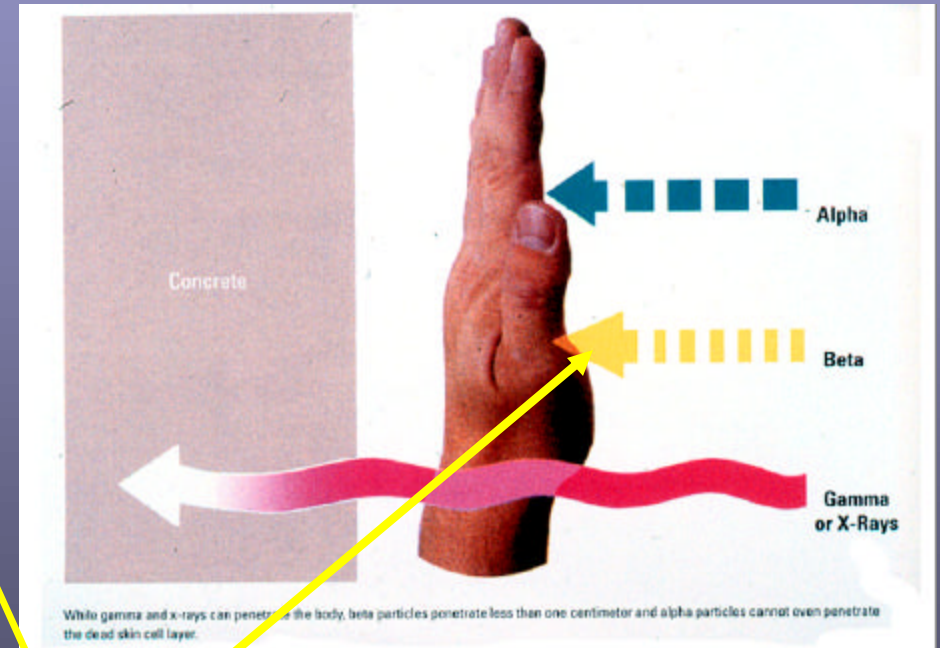
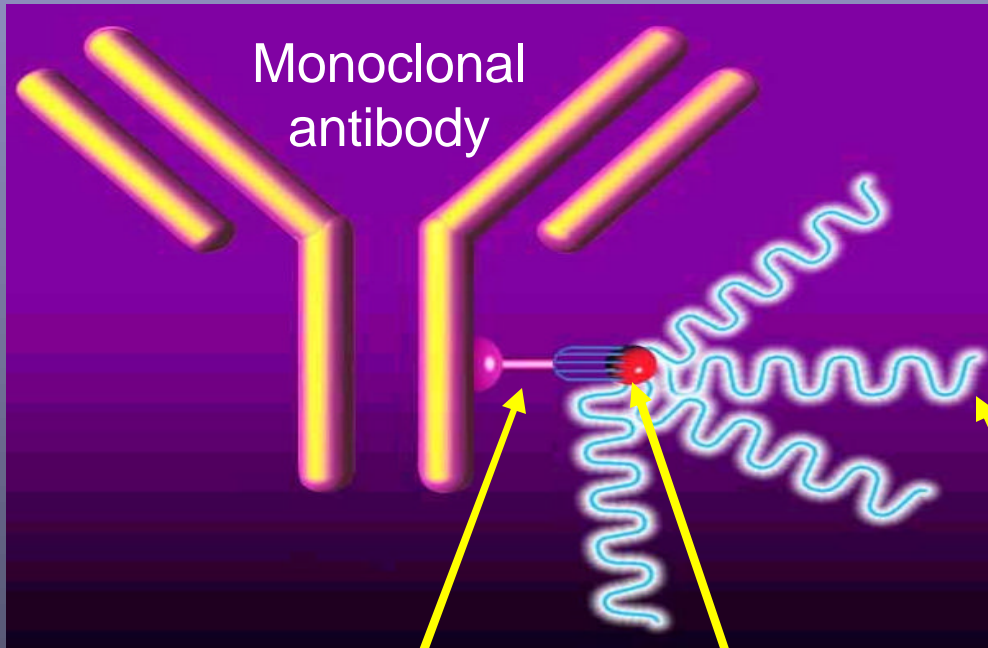


# Radioimmunotherapy in the Treatment of Low-Grade B-Cell Lymphoma

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# Radiolabeled Monoclonal Antibodies



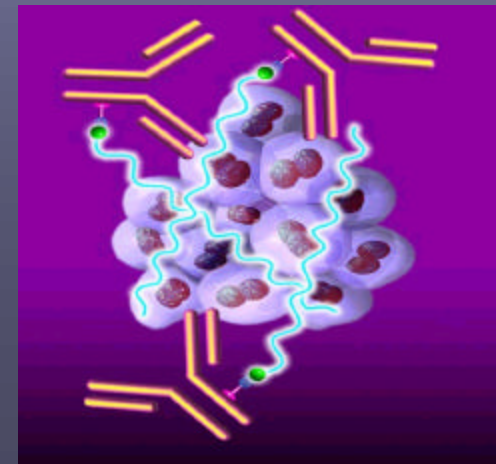
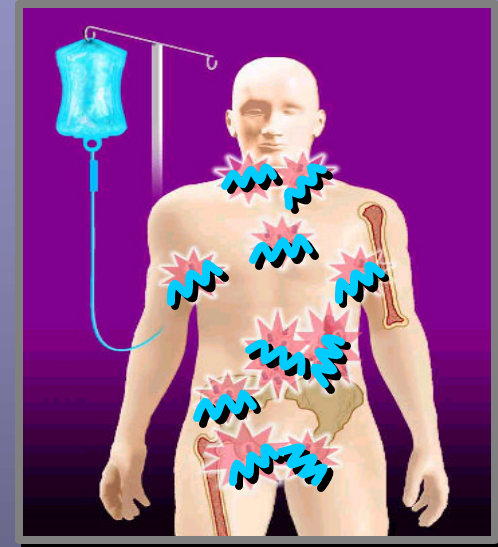
Bond or  
Chelator

Radionuclide

$\beta$  Radiation

# Radiolabeled Monoclonal Antibodies for Radioimmunotherapy

- Proliferating tumor cells are inherently sensitive to radiation
- Treat systemic disease that cannot be defined anatomically but better therapeutic index than TBI
- Continuous rather than intermittent RT
- Crossfire effect—kill tumor cells a few mm from the bound antibody & antigen-negative tumor cells



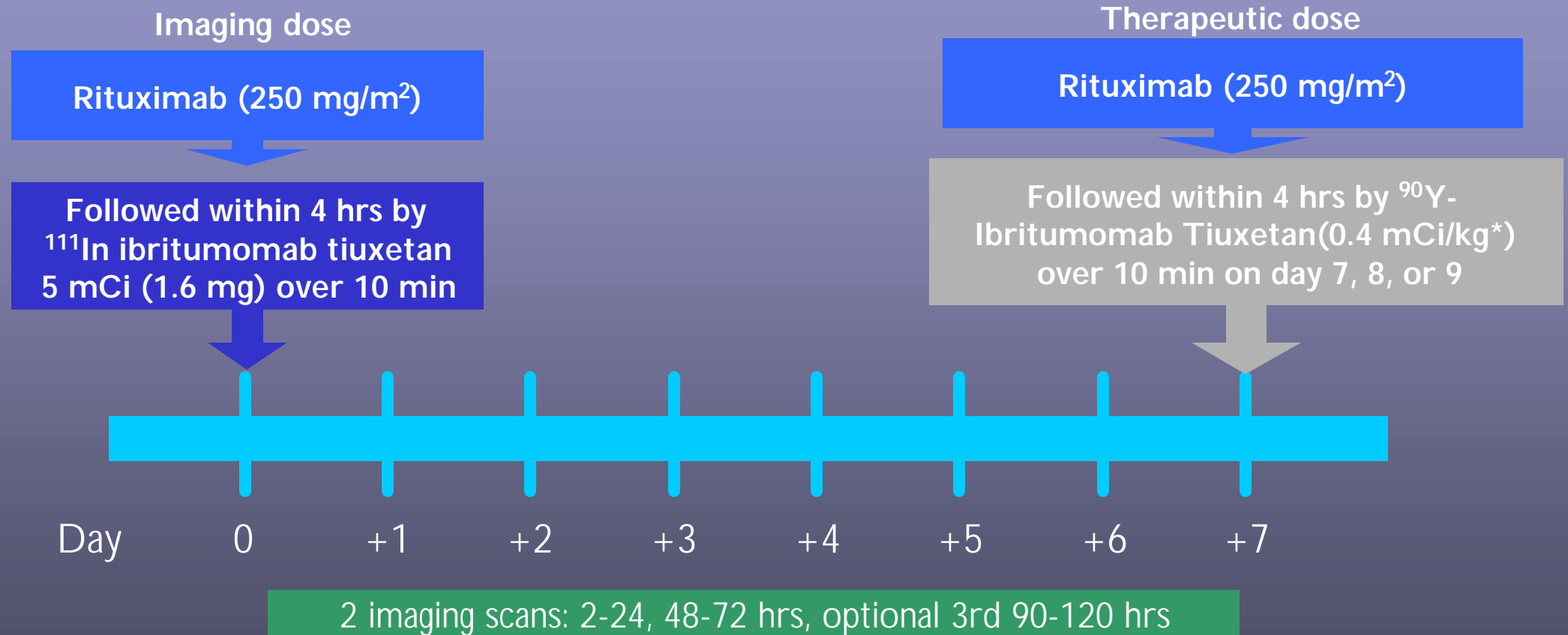
# Bexxar (Tositumomab) and Zevalin (Ibritumomab Tiuxetan)

- $^{131}\text{I}$  Tositumomab
  - mouse anti CD20
  - direct iodination of tyrosine amino acids on the antibody, subject to dehalogenation
  - $\gamma$  & 1 mm  $\beta$  emission
  - 8.0 day half life
  - thyroid uptake of free  $^{131}\text{I}$
  - urinary excretion
- $^{90}\text{Y}$  Ibritumomab Tiuxetan
  - mouse anti CD20
  - indirect linkage via tiuxetan linker chelated to  $^{90}\text{Y}$  and covalently linked to lysine and arginine amino acids
  - 5 mm  $\beta$  emission length
  - 2.7 day half-life
  - limited urinary excretion

# Regulatory Status of Anti-CD20 Radioimmunotherapy

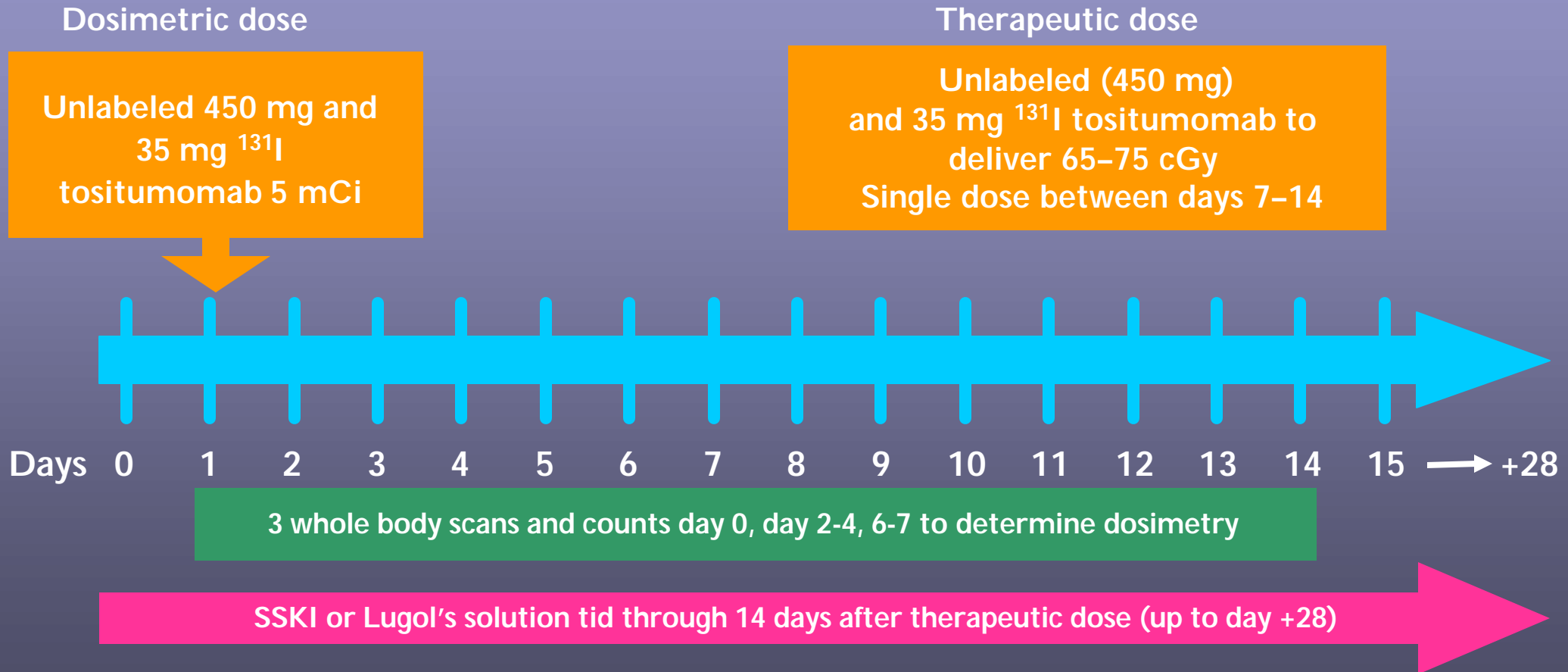
- Y-90 ibritumomab tiuxetan (Zevalin)
  - 2-19-02 FDA approval
    - Indication: treatment of relapsed or refractory low-grade, follicular, or transformed B-cell lymphoma, including patients with rituximab refractory follicular lymphoma
- I-131 tositumomab (Bexxar)
  - 06-30-03 FDA approval
    - Rituximab refractory follicular lymphoma and relapsed after chemotherapy
    - Not indicated for the initial treatment of CD20+ NHL

# <sup>90</sup>Y Ibritumomab Tiuxetan: Treatment Schema



\*0.4 mCi/kg in patients with a platelet count  $\geq 150,000/\mu\text{L}$  max 32 mCi  
or 0.3 mCi/kg with a platelet count 100,000–149,000/ $\mu\text{L}$ .

# <sup>131</sup>I Tositumomab: Treatment Schema



# Bexxar & Zevalin

- $^{131}\text{I}$  Tositumomab
  - 50-90% of  $^{131}\text{I}$  cleared in urine within 48 hours
  - Scans to determine residence time and rate of clearance
  - Patients received dose based on calculation to deliver 75 cGy of TBI
- $^{90}\text{Y}$  Ibritumomab Tiuxetan
  - 5-10% of  $^{90}\text{Y}$ -chelate cleared in urine, some through bowel
  - Scans to verify expected biodistribution
  - Patients receive fixed dose of 0.4 mCi/kg up to a maximum of 32 mCi

# Bexxar and Zevalin Were Very Active in Phase I Radioimmunotherapy Trials

- Bexxar

- 59 patients
- 50 yrs median age
- 71% low-grade or transformed low-grade
- 25-85 cGy TBI
- **DLT: marrow suppression**
- **MTD 75cGy TBI (65 cGy if low platelets)**
- **71% RR, med dur 9 mos**
- 34% CR, med dur

- Zevalin

- 57 patients
- 60 yrs median age
- 67% low-grade or transformed
- 0.2-0.4 mCi/Kg
- **DLT: marrow suppression**
- **MTD 0.4 mCi/Kg (0.3 mCi/Kg if low platelets)**
- **67% RR, med dur 12 mos**
- 25% CR, med dur 23 mos

# Bexxar and Zevalin Are Active in Patients with Low-grade Lymphoma That Has Recurred After Prior Chemotherapy

- Bexxar<sup>™</sup>

- follicular lymphoma (185 pts)
  - **81% RR**, 38% CR
  - 11 mo median response  
*Vose, ASH 1999*
- transformed (71 pts)
  - **39% RR**, 25% CR
  - 20 mo median duration  
*Zelenetz, ASH 2002*  
(Abst # 1384)
- chemo-resistant (60 pts)
  - **65% vs. 28% RR** [ $p < 0.001$ ]
  - **20% vs. 3% CR** [ $p < 0.001$ ]
  - **6.5 vs. 3.4 mos DR** [ $p < 0.001$ ]  
*Kaminski, J Clin Oncol 2001*

- Zevalin<sup>™</sup>

- follicular lymphoma (73 pts)
  - **80% RR**, 30% CR
  - 14 mo median duration of response, 25 mos for CR  
*Witzig, J Clin Oncol 2002*
- transformed
  - **50% RR**  
*Bartlett, ASCO 2002*  
(Abst # 51)
- chemo-resistant (33 pts)
  - **73% RR**  
*Witzig, J Clin Oncol 2002*

# Anti-CD20 RIT is More Effective Than Unconjugated MoAbs in Recurrent Low-grade Lymphoma

(no prior rituximab)

- Bexxar

- WGF A, follicular, & transformed
  - 23% chemo resistant
  - 2 prior chemo median
- Bexxar + tositumomab 450 mg x 2 (42 pts) vs. tositumomab 450 mg x 2 (36 pts)
  - **55% vs 33% RR** ( $p=0.095$ )
  - 17% vs 8% CR ( $p=0.45$ )
  - NR vs 18 mos DR NSD

Davis, ASH 2001 (Abst. #3503)

- Zevalin

- WGF A, follicular, & transformed
  - 48% chemo resistant
  - 2 prior chemo median
- Zevalin + rituximab 250 mg/m<sup>2</sup> x 2 (73 pts) vs. rituximab 375 mg/m<sup>2</sup> x 4 (70 pts)
  - **80% vs. 56% RR** ( $p=0.002$ )
  - 30% vs. 16% CR ( $p=0.04$ )
  - 15.4 vs. 13.8 mos DR NSD
  - 2 yr med dur for CR

Witzig, J Clin Oncol 2002

# Bexxar and Zevalin Are Active in Patients with Follicular Lymphoma Who Are Refractory to Rituximab

(no response or duration < 6 months)

- Bexxar

- 40 patients (35 fit criteria)
- median age 57 yrs
- **4 prior chemo median**
- 28% > 7 cm bulk
- 32% BM involved
- **68% response rate, 30% CR by consensus**
- 14.7 mos median duration of response
- >2 yrs CR duration

Horning, *ASH* 2002 (Abst. #1385)  
FDA update 06-03

- Zevalin

- 54 patients
- median age 54 yrs
- **4 prior chemo med**
- 44% > 7 cm bulk
- 32% BM involved
- **74% response rate, 15% by consensus**
- 6.4 mos median duration of response
- 7.2 mos CR duration

Witzig, *J Clin Oncol* 2002  
IDEC update 02-03

# RIT is Effective Against Bulky Disease

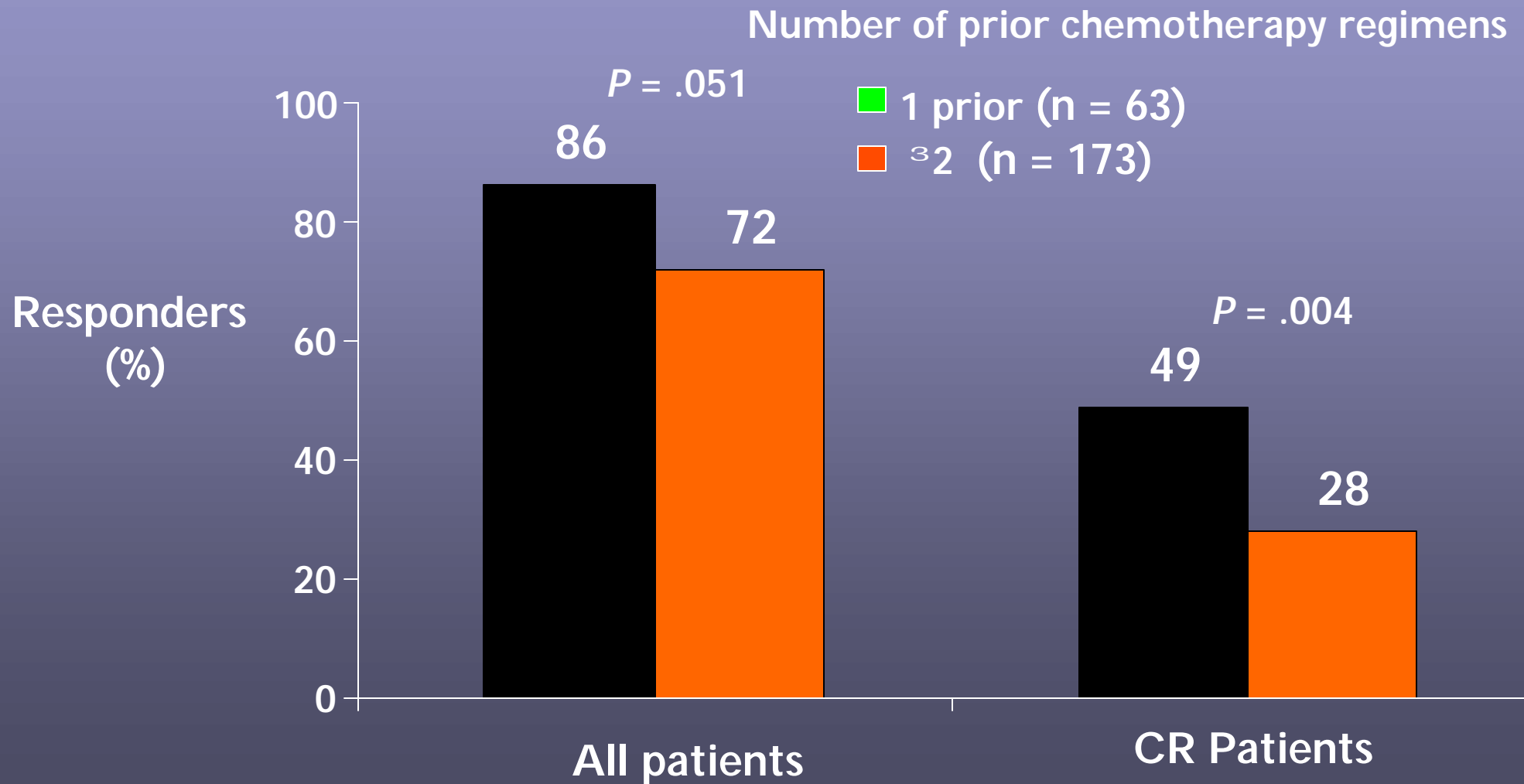
- 117 patients, relapsed/refractory NHL, 3 institutions, treated with Bexxar
  - 63 < 5 cm max: RR 71%, CR 41%
  - 54 > 5 cm max: RR 63%, CR 21%
    - 9/11 CR continuing median F/U 2 yrs

Kaminski, et al., ASCO 2002 (Abst. #17)

- 54 patients, follicular lymphoma, treated with Zevalin
  - 14 2-5 cm max: RR 100%
  - 40 > 5 cm max: RR 65%

Flinn, et al., ASCO 2001 (Abst. #1141)

# Higher Responses with <sup>90</sup>Y Ibritumomab Tiuxetan if Fewer Prior Chemo Regimens



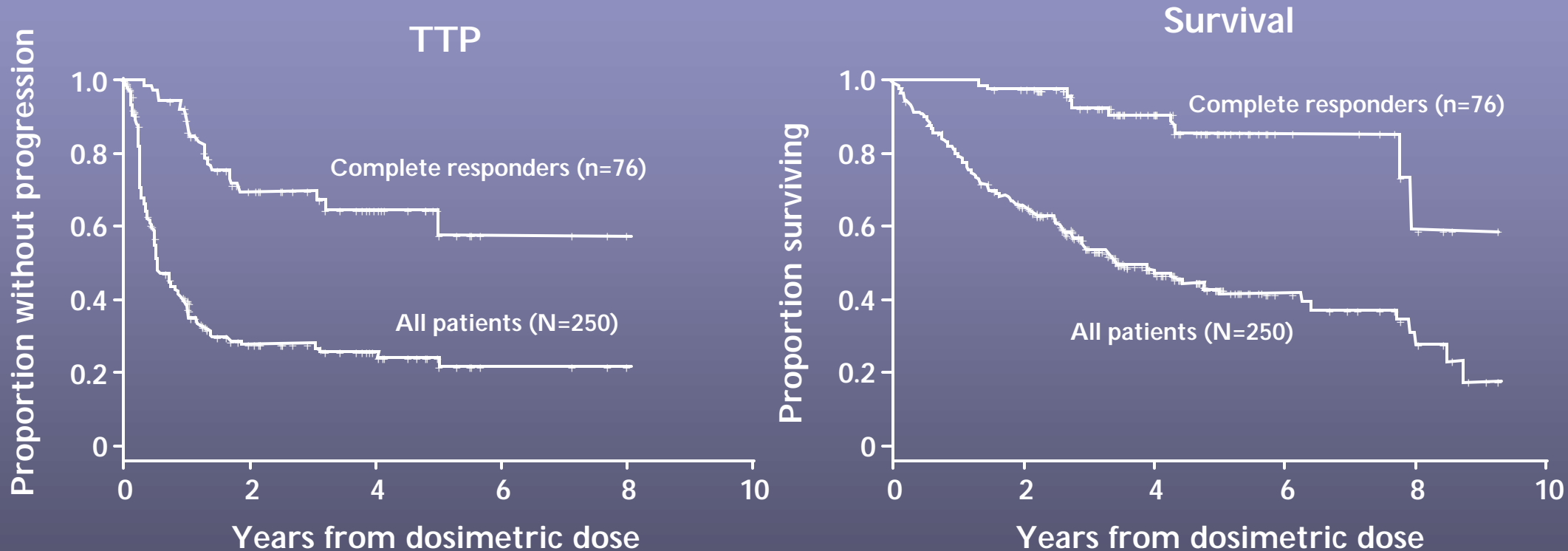
# Presence of Too Much Rituximab May Reduce Efficacy of Anti-CD20 RIT

- Pre-existing rituximab levels and CD20 binding alters pharmacokinetics and dosimetry for Y90 ibritiumomab tiuxetan
- Absence of circulating CD20+ lymphocytes is a surrogate for persisting rituximab effect and usually persistent serum levels of rituximab
- In rituximab “refractory” trial, absence of circulating B cells was associated with lower response rate 47% vs. 88% ( $p=.003$ )

# RIT as Initial Therapy

- 76 patients accrued 1996-1999
  - Follicular lymphoma, no prior therapy
  - Median age 49 years
  - 75 cGy TBI based on dosimetry
- Median follow-up 3.6 years
  - 95% OR, 74% CR; 62% 5 yr PFS
  - 55/57 (97%) still in CR 2.5 to 5.5 yrs
  - Myelosuppression, hypothyroidism
  - 63% HAMA
- “The  $^{131}\text{I}$  tositumomab therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive NHL”

# Complete Responses Can Be Very Durable After Anti-CD20 Radioimmunotherapy



<sup>131</sup>I-tositiumomab: relapsed/refractory low-grade or transformed NHL, 56% RR with 30% CR  
Median TTP 13 mos and OS > 3 yrs for all; median TTP & OR not reached for CR

# Toxicity of Radiolabeled Anti-CD20 MoAbs in Radioimmunotherapy

- Acute: Infusion related toxicity associated with removal of circulating CD20+ cells during 1st Rx
- Subacute: Bone marrow suppression
  - nadir 7-9 weeks, resolved by 9-12 weeks
  - Grade III-IV cytopenia in > 50% of patients
  - best predicted by extent of BM infiltration
- Long-term: radiation damage
  - Myelodysplasia/Acute Leukemia
  - I-131: hypothyroidism
  - I-131: stomach, lung, kidney, bladder CA

# Zevalin Hematologic Toxicity Increases With Marrow Involvement

	% Marrow Involvement			<i>P</i> values
	0-5%	6-20%	>20%	
Grade 4 nadir	n = 214	n = 103	n = 32	
Hemoglobin	3%	2%	13%	.76, .04
ANC <500 mm <sup>3</sup>	24%	37%	53%	.04, .01
Plts <10,000 m <sup>3</sup>	7%	13%	25%	.04, .05

ANC = absolute neutrophil count

\*% of patients experiencing grade 4 toxicity, only 11 with 1-5%

*P* value: Fisher's exact test, 2-tailed for 0 vs. 1-20 and 1-20 vs. >20

# Hematologic Toxicity Correlates With Extent of Prior Treatment

- 349 patients in 5 clinical trials
  - 254 patients, no prior fludarabine; 95 patients prior
- Fludarabine-treated patients
  - More likely to have grade 3 or 4 neutropenia ( $P = .05$ ), thrombocytopenia ( $P = .025$ ), or anemia ( $P < .001$ )
  - Significantly longer median duration of grade 3 or 4 thrombocytopenia (28 vs. 22 days,  $P = .029$ )
- Fludarabine treated group
  - Longer time from diagnosis to treatment with  $^{90}\text{Y}$  ibritumomab tiuxetan (4.5 vs. 3.3 years,  $P = .005$ )
  - More prior chemotherapy regimens (4 vs. 2 regimens,  $P < .001$ )
  - Lower pretreatment platelet ( $P = .001$ ) and Hgb ( $P = .02$ )

# MDS & AML in Lymphoma

- MDS or AML
  - Estimated at 1 - 8% during > 10 yrs follow-up, and 0.5 - 5% per year in NHL patients who have not undergone ABMT
  - Observed rates of 8 - 12% during 5 - 6 years of follow-up post ABMT in patients with follicular lymphoma

Pederson-Bjergaard, *J Ann Intern Med* 103:195-200,1985

Kantarjian, *J Semin Oncol* 14:435-443,1987

Pederson-Bjergaard, *J Haematologica* 83:481-482, 1998

Peterson, *J Clin Oncol* 21:5-15, 2002

Freedman, et al., *Blood* 1999

Apostolidis, et al., *J Clin Oncol* 2000

# RIT Does Not Appear to Increase the Frequency or Rate of MDS & AML

- Bexxar

- median F/U 1.5 yrs: MDS/AML Dx post RIT
  - Follicular lymphoma subset
  - 19/620 (3.1%) of all patients
  - 1.7% per yr from Rx with RIT

- Zevalin

- median F/U 3-4 yrs: MDS/AML Dx post RIT
  - Vast majority indolent lymphoma
  - 10/770 (1.3%) of all patients
  - 0.62% per yr from Rx with RIT
  - 0.21% per yr from Dx of NHL

# Subsequent Chemotherapy Regimens Are Well-tolerated After Radioimmunotherapy

- 58 patients (Mayo Clinic) who had disease progression after previous treatment with Y-90 ibritumomab tiuxetan
  - Median of 2 prior therapies before RIT: 54 CHOP, 35 CVP, 24 rituximab, 20 chlorambucil, 11 fludarabine
  - 1-7 subsequent chemo regimens, median 2
    - Grade IV toxicity: 25% ↓ platelets, 33% ↓ ANC
    - 1/3 required CSF and/or hospitalized for febrile neutropenia and/or bleeding
    - similar to contemporary cohort controls without RIT
  - 8 had autologous stem cell transplants (7 PBSC)

# Chemotherapy, Radiation Therapy and Rituximab Can Be Effective After Radioimmunotherapy

- 153/521 (29%) patients received other treatment after Zevalin
- Response data for 100/153 patients : 1st subsequent therapy after Zevalin
  - 60/100 (60%) overall response rate
  - 20/25 (80%) RR to focal radiation therapy
  - 25/49 (53%) RR to chemotherapy
  - 15/26 (58%) RR to rituximab

# Clinical Criteria for Radioimmunotherapy in Lymphoma

- Relapsed low-grade, follicular, and/or transformed low grade B-cell lymphoma
- Normocellular marrow
- Bone marrow involvement <25%
- ANC > 1500/mm<sup>3</sup>
- Platelet count >150,000/mm<sup>3</sup> (lower dose if 100k-149k)
- Peripheral blood lymphocytes <5000/mm<sup>3</sup>
- No human anti-mouse antibodies (HAMA)
- No prior radioimmunotherapy (preferred)
- No prior stem cell transplant (preferred)

# Practical Advantages of Zevalin Over Bexxar

- Y90 emits only beta radiation:
  - no requirement for shielding or isolation
  - no requirement for relative isolation from family & friends
- No risk of hypothyroidism, no need for SSKI to protect thyroid from  $^{131}\text{I}$
- “Cold” rituximab is a standard agent with proven safety and efficacy, and reimbursement that can be given by hematologist/oncologist; tositumomab is not approved as a separate product
- Rate of HAMA is lower (1% vs. 10%) because receive about 1000 mg of mouse protein with tositumomab compared to 25-50 mg mouse protein with rituximab

# Summary

- Anti-CD20 radioimmunotherapy is a new effective therapy for low-grade and relapsed B cell lymphoma
- One course of therapy is as effective as multiple course of chemotherapy
- Patient selection is important to maximize benefit and minimize toxicity