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

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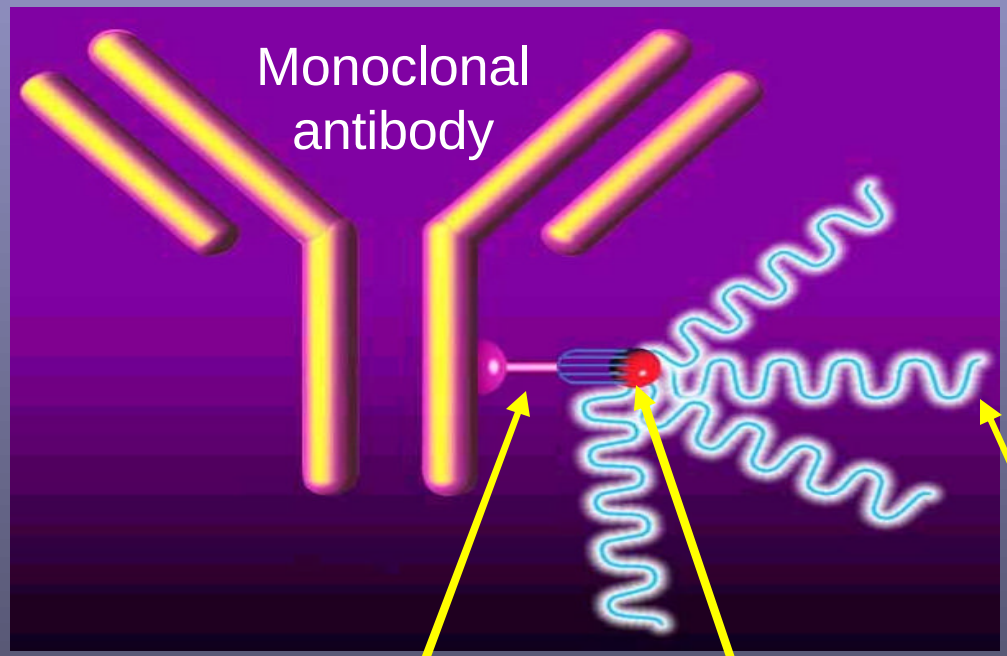
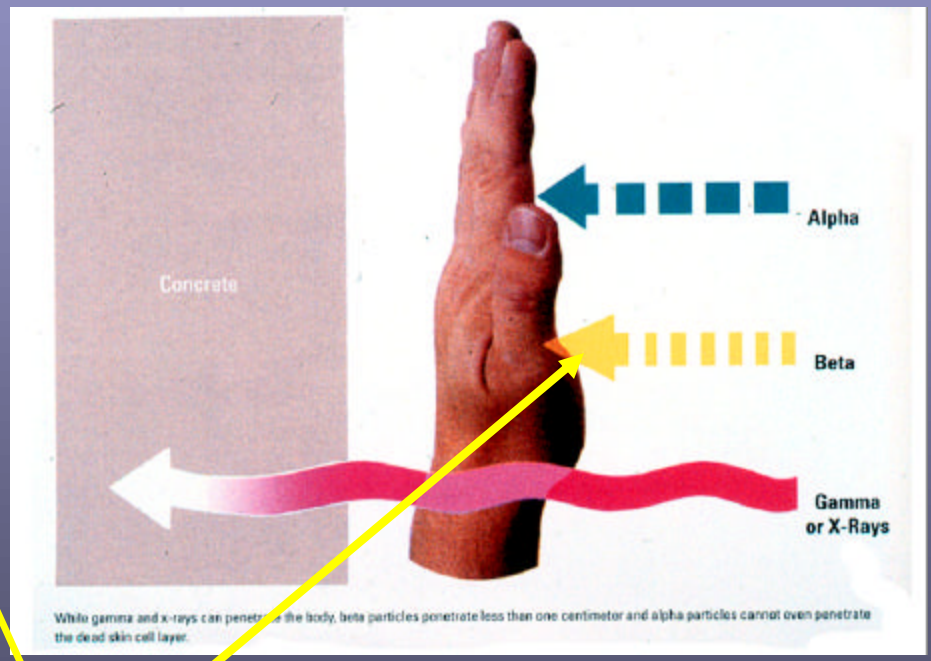
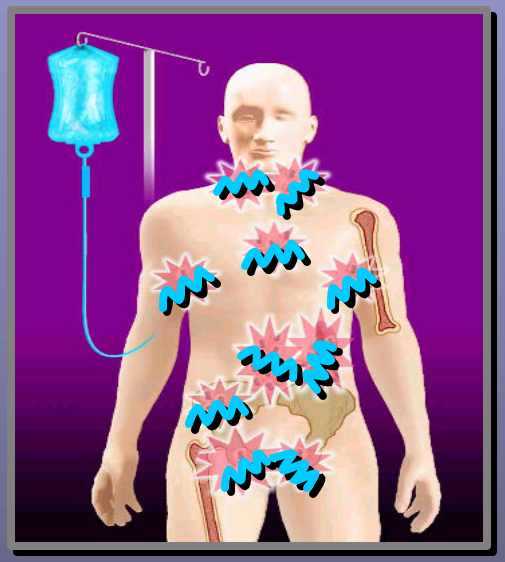
Radiolabeled Monoclonal Antibodies

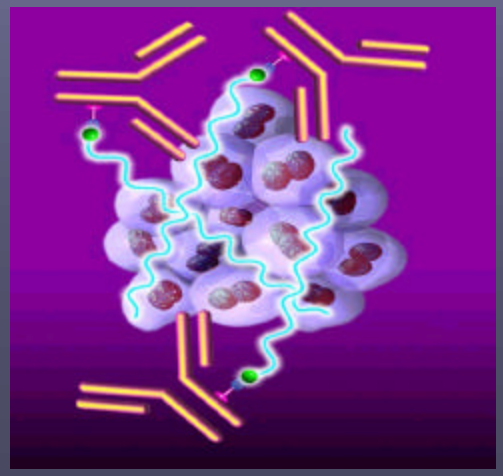




Radiolabeled Monoclonal Antibodies for Radioimmunotherapy

- 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





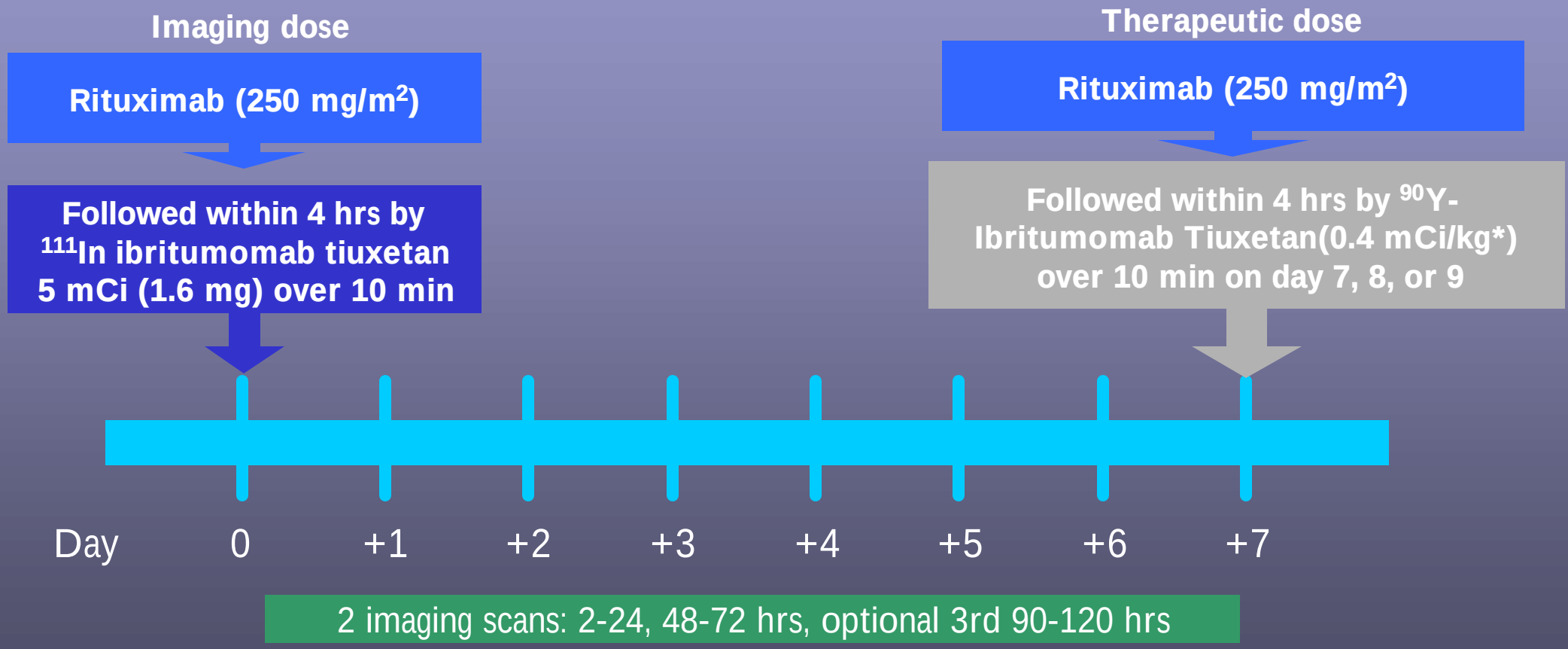
Bexxar (Tositumomab) and Zevalin (Ibritumomab Tiuxetan)

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

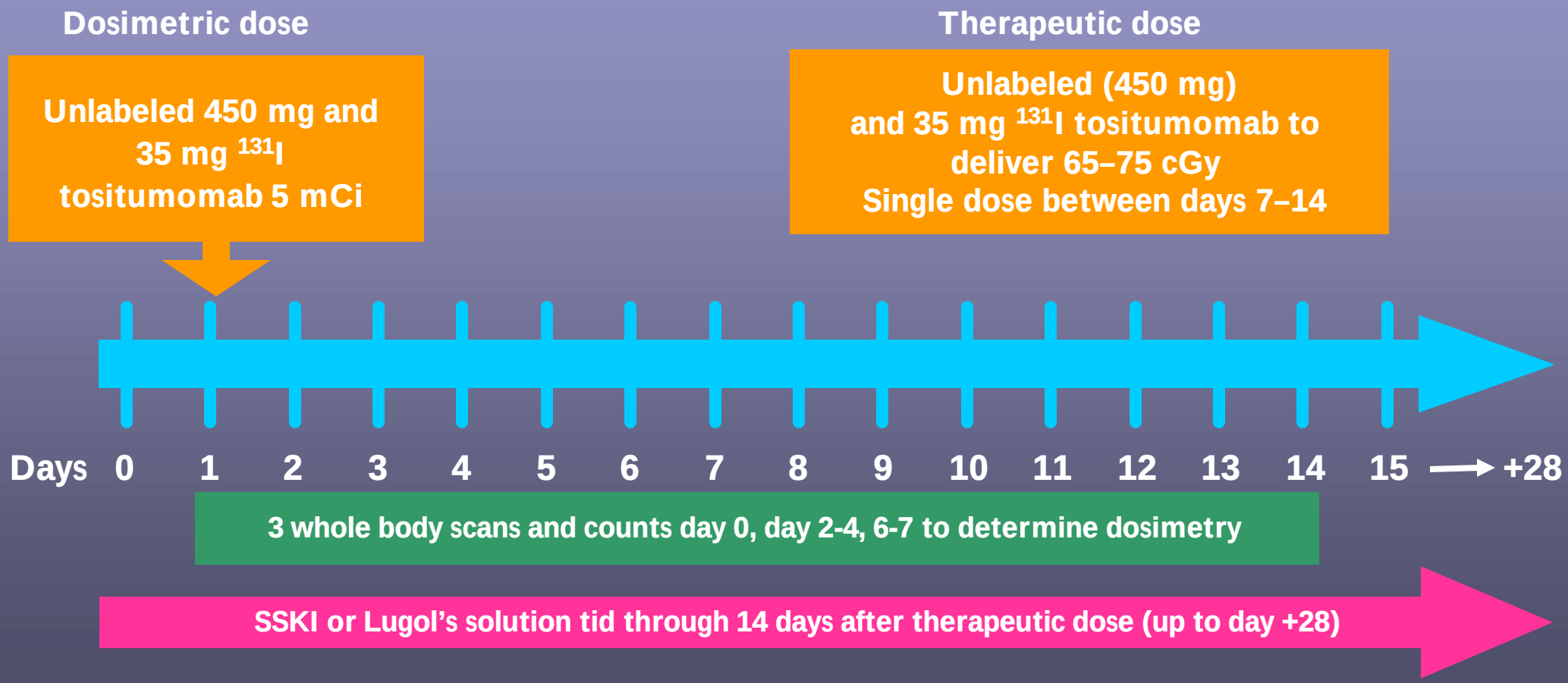
^{90}Y Ibritumomab Tiuxetan: Treatment Schema



*0.4 mCi/kg in patients with a platelet count ≥150,000/μL max 32 mCi or 0.3 mCi/kg with a platelet count 100,000–149,000/μL.

Wiseman, et al., *Eur J Nucl Med.* 2000;27:766–777

^{131}I Tositumomab: Treatment Schema



Vose, et al., *Blood* 1999;94:89a.

Bexxar & Zevalin

- ^{131}I Tositumomab
  - 50-90% of ^{131}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}Y Ibritumomab Tiuxetan
  - 5-10% of ^{90}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

Kaminski, *J Clin Oncol* 1996.

- **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

Witzig, *J Clin Oncol* 1999

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

- **Bexxar™**
  - **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™**
  - **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^2 x 2 (73 pts) vs. rituximab 375 mg/m^2 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

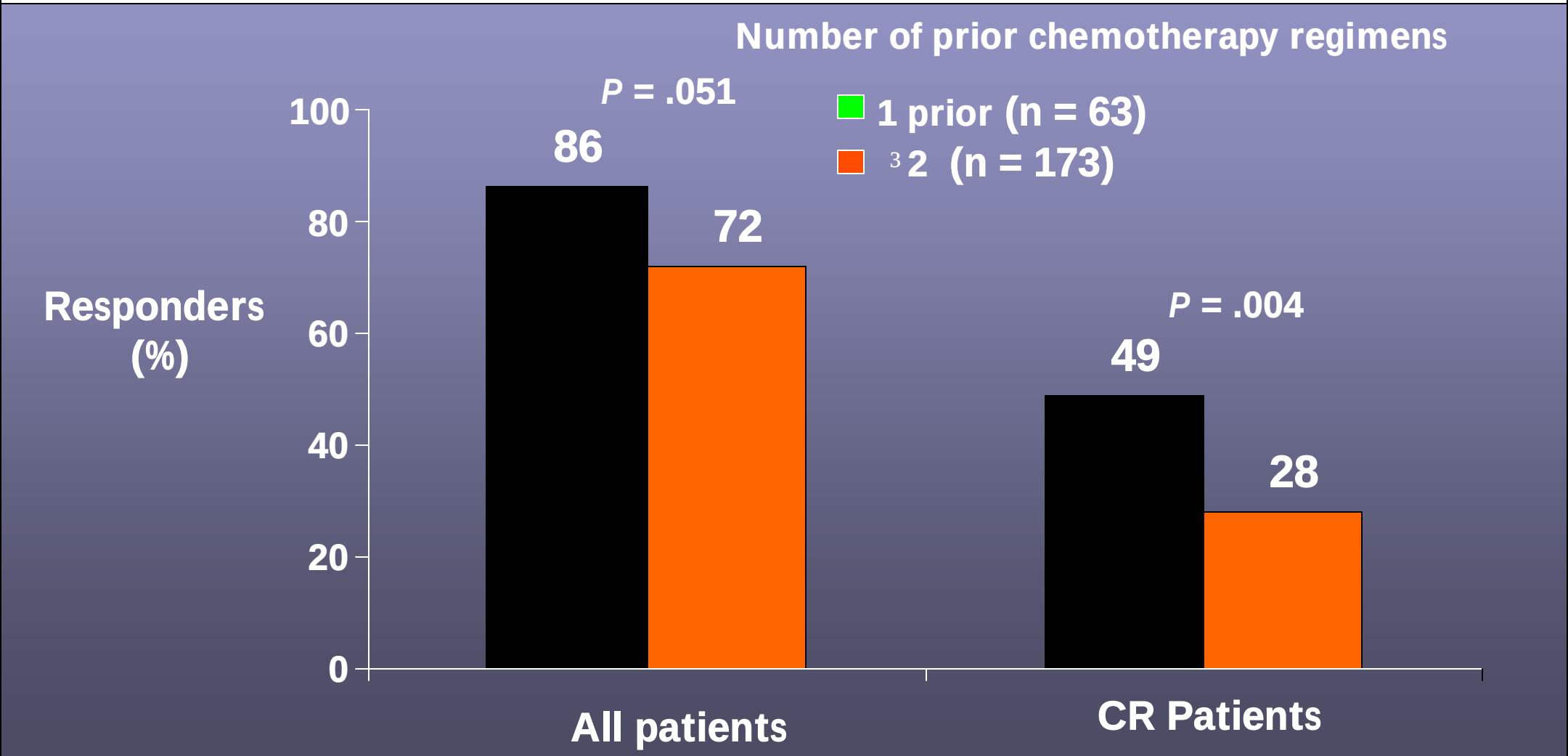
- **117 patients, relapsed/refractory NHL, 3 institutions, treated with Bexxar**
  - **63 < 5 cm max: RR 71%, CR 41%**
  - **54 > 5 cm max: RR 63%, CR 21%**
    - **9/11 CR continuing median F/U 2 yrs**

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 ^{90}Y Ibritumomab Tiuxetan if Fewer Prior Chemo Regimens



Emmanouilides, et al., *Proc Am Soc Clin Oncol.* 2003;22:595. (Abst. #2392)

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)

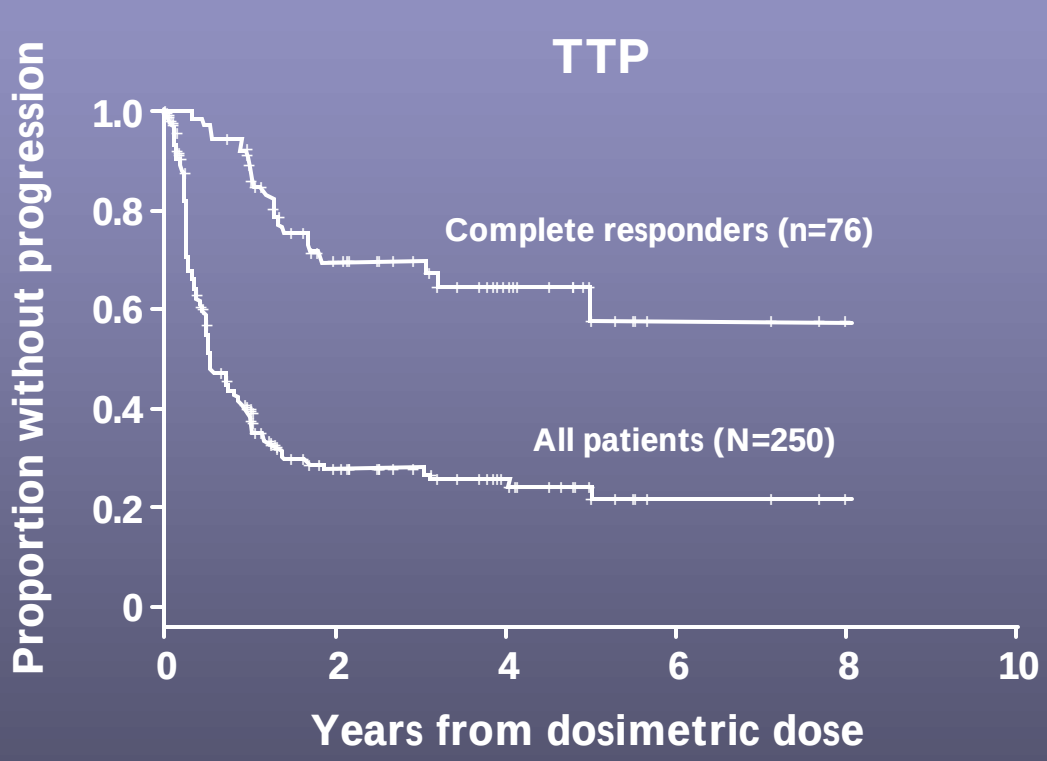
Witzig, et al., *J Clin Oncol* 2002

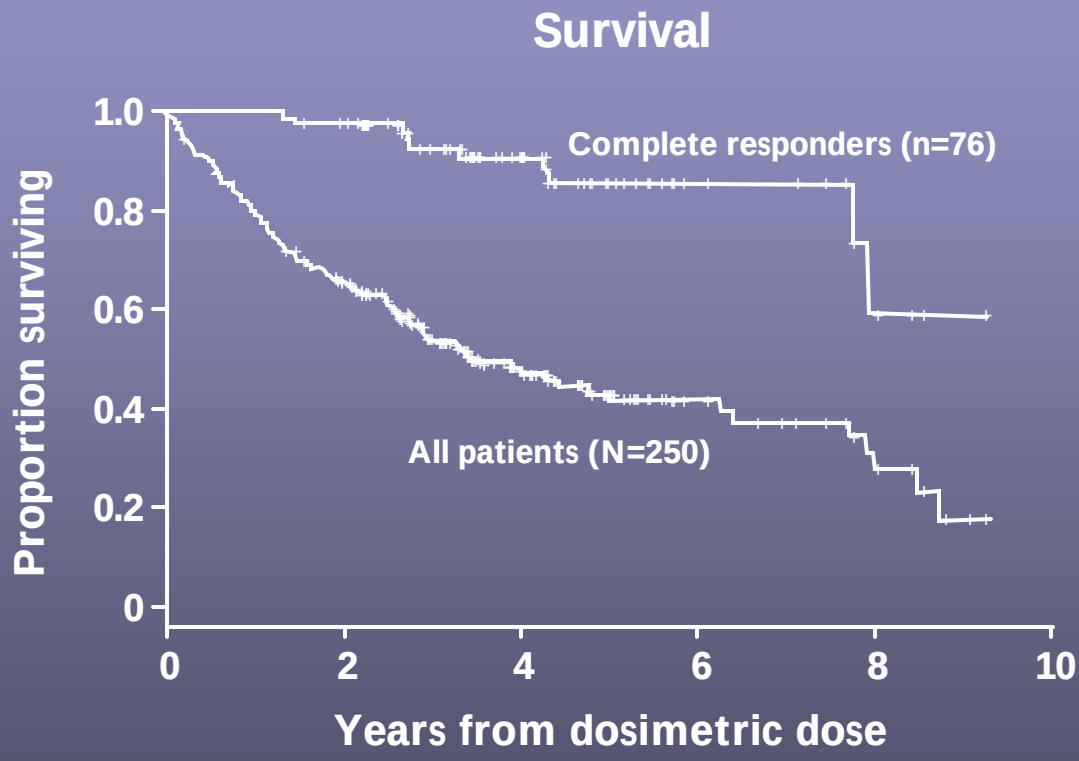
RIT as Initial Therapy

- 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}I tositumomab therapeutic regimen is not indicated for the initial treatment of patients with CD20 positive NHL"

Kaminski, et al., *ASH* 2002 (Abst. #1381)

Complete Responses Can Be Very Durable After Anti-CD20 Radioimmunotherapy





^{131}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

Kaminski, et al., *Blood.* 2002;100(suppl 1):356a. (Abst. #1382), (updated from presentation).

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

Holm, et al., Cancer risk after iodine-131 therapy for hyperthyroidism. *JNCCI* 83:1072, 1991

Zevalin Hematologic Toxicity Increases With Marrow Involvement

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

Witzig, et al., *J Clin Oncol* August 2002, ASH2002

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}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 ($P = .02$)

Witzig, et al., *J Clin Oncol* 21:1263, 2003

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/U1.5 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

Kaminiski, *ASCO* 2003 (Abst. #2313)
Czuczman, *ASH* 2002 (Abst. #1386)

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)

Ansell, et al., *J Clin Oncol* 20:3885-3890, 2002

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

Schilder, *ASCO* 2003 (Abst. #1064)
Saleh, *ASCO* 2002 (Abst. #30)

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 $> 1500/mm^3$
- Platelet count $>150{,}000/mm^3$ (lower dose if 100k-149k)
- Peripheral blood lymphocytes $<5000/mm^3$
- 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 I^{131}
- "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