Bexxar Dosimetry

George Sgouros, Ph.D.

Russell H. Morgan Dept of Radiology
& Radiological Science

Johns Hopkins University, School of Medicine

Baltimore MD

Clinical Experience with anti-CD-20 Targeted Radioimmunotherapy

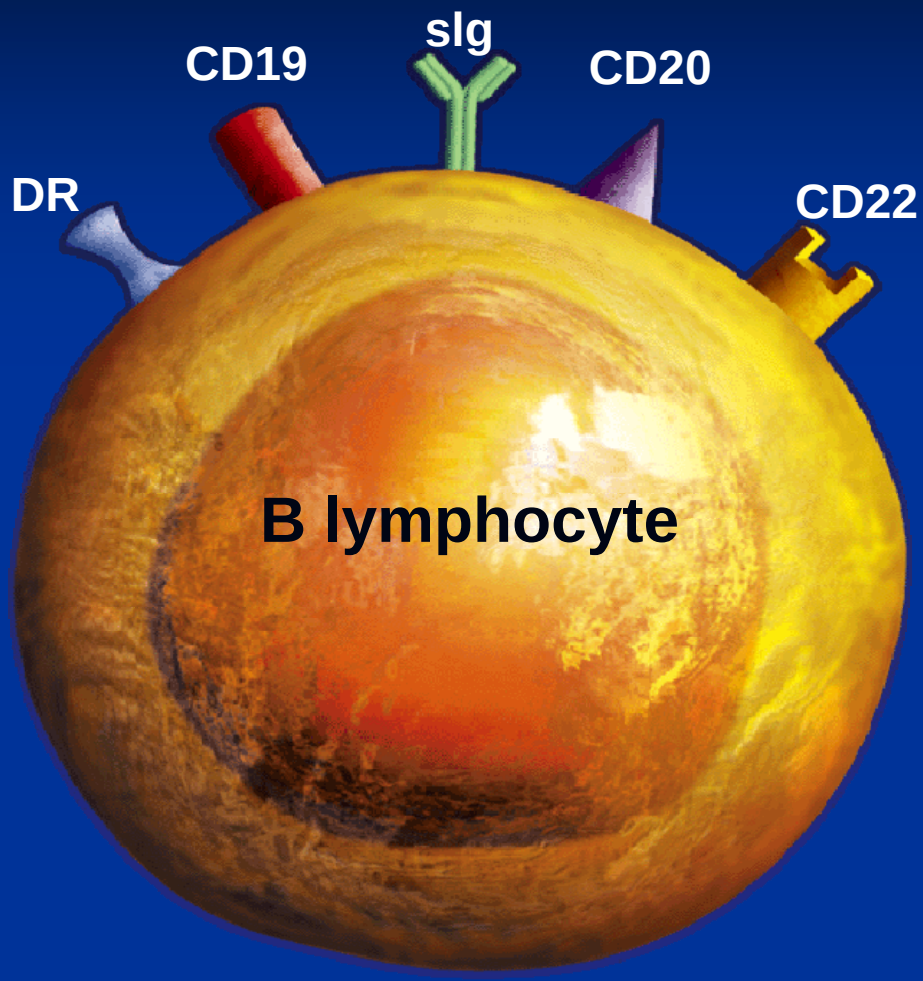
Richard L. Wahl, M.D.
Johns Hopkins University
Division of Nuclear Medicine
Departments of Radiology and Oncology

Follicular NHL

- 2nd most common subtype of NHL[1]
- Accounts for 25 - 40% of all adult lymphomas[1]
  - Common in elderly population[1]
- Involves low grade and intermediate grade subtypes of IWF classifications of NHL

[1]Petry KAJ, et al. In: Grossbard ML (ed). Malignant Lymphoma. Hamilton: DC Decker 2002;96: 94-111.

Immunotherapy Targets on B Cells



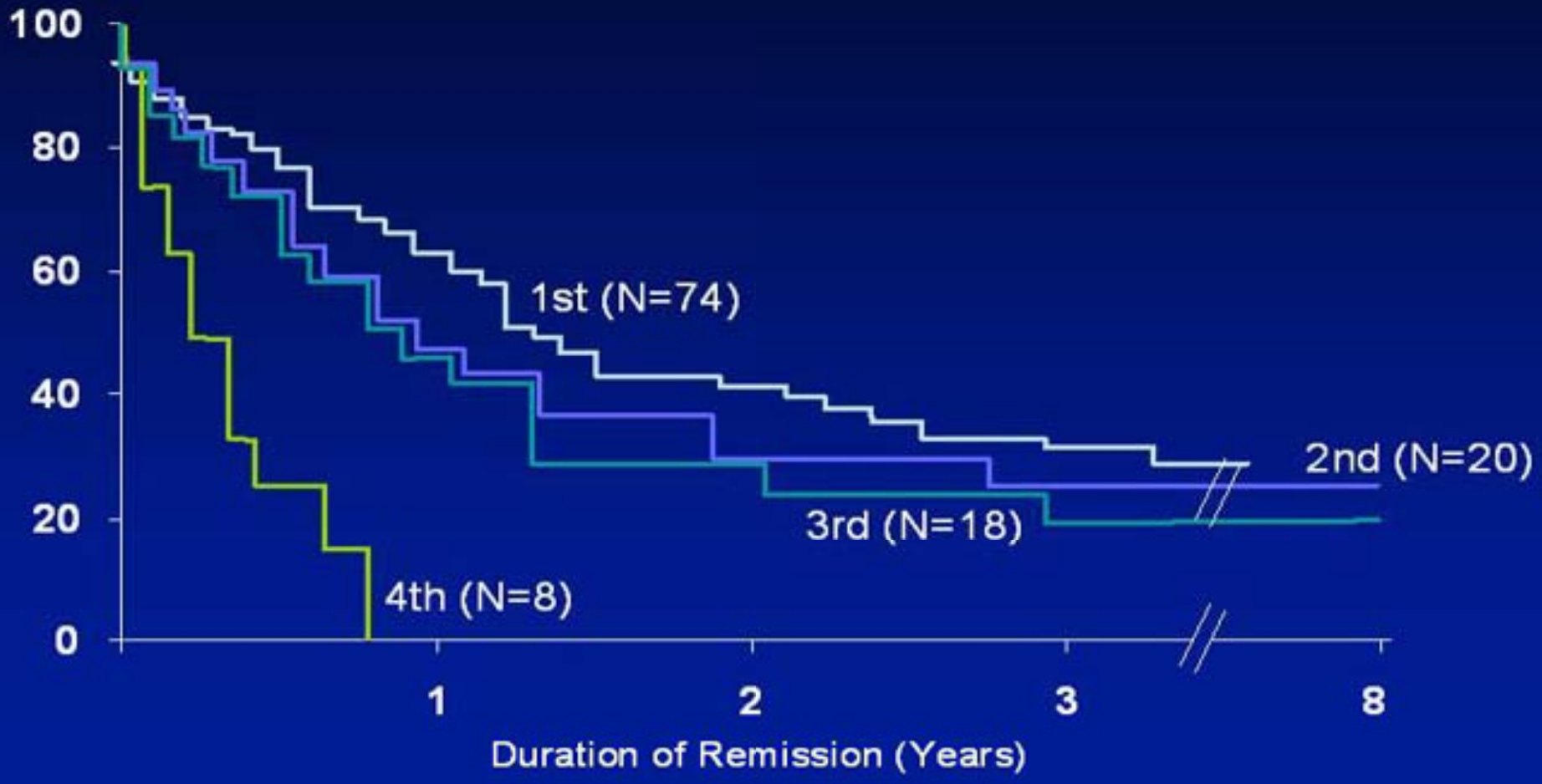
- Surface proteins targeted by immunotherapy
  - Unlabeled monoclonal antibodies (MAbs)
  - Conjugated MAbs
    - Radioisotopes
    - Drugs
    - Toxins

Adapted from Press O, et al. *Cancer J Sci Am.* 1998:4(suppl 2):s19–s26.

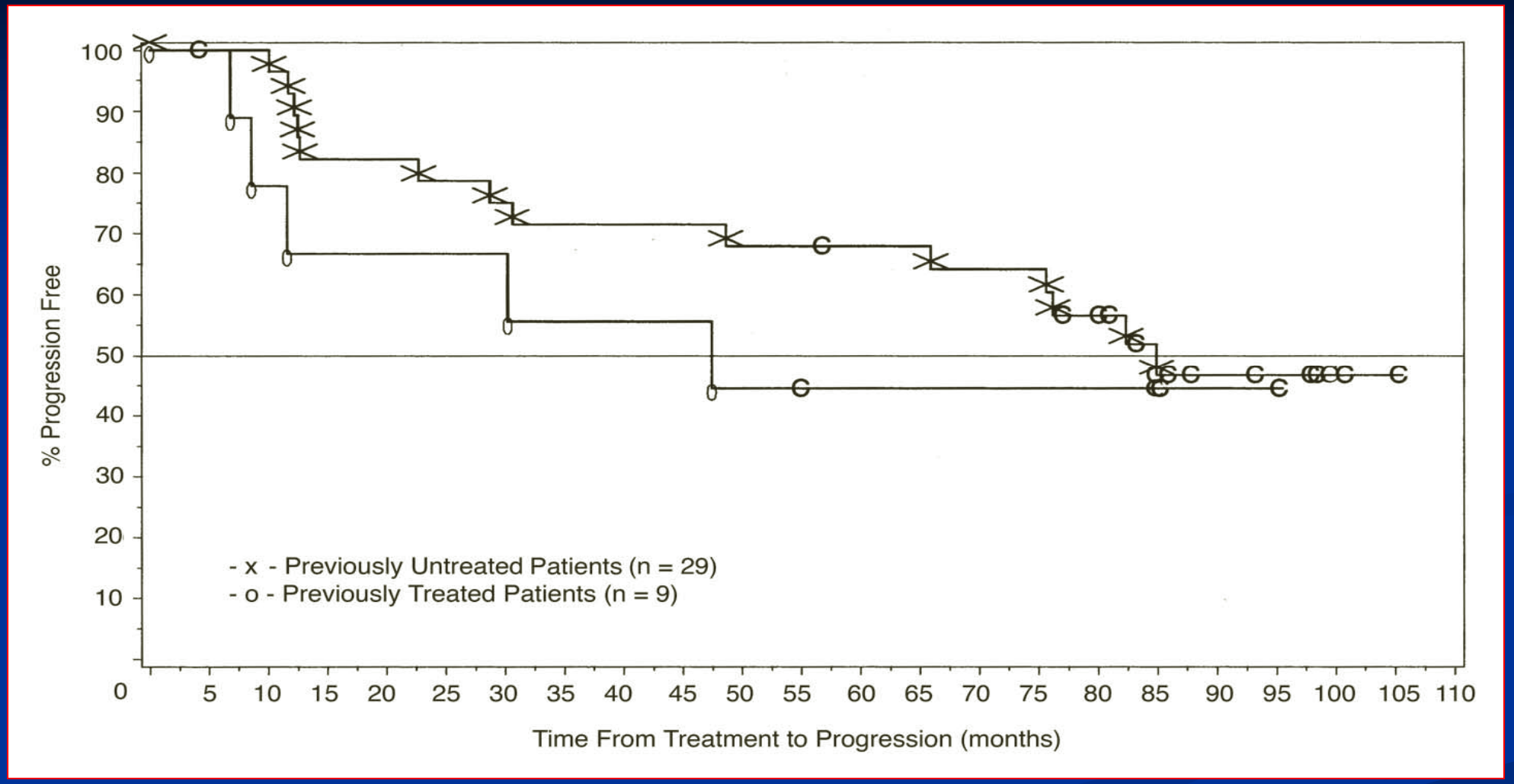
B-Cell Life Cycle CD20 Expression

Seldin DW. J Nuc Technol 2002; 30:109-114.
Stashenko P, et al. J Immunol 1980; 125:1678-85.

Follicular Lymphoma: Duration of Chemotherapy-Induced Remissions



Gallagher CJ, et al. J Clin Oncol 1986; 4:1470-80.

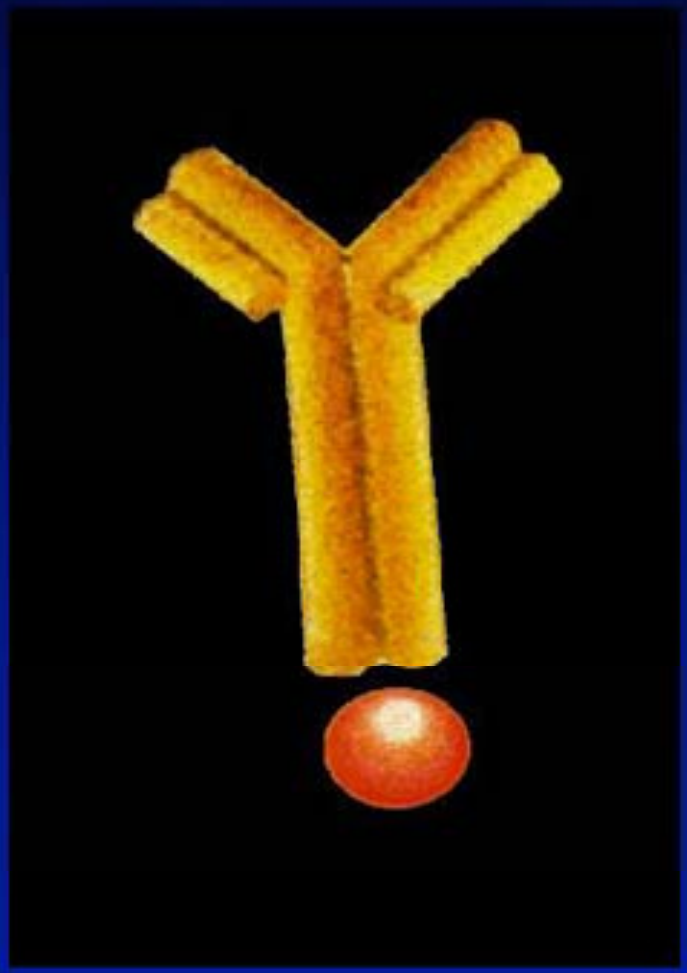


Czuczman et al, J Clin Oncol 22:23, 4659-4664, 2004

Rituximab + CHOP

Iodine I 131 Tositumomab Characteristics and Mechanism Of Action

- **Tositumomab**
  - Murine IgG2a anti-CD20 MAb
  - B-cell specific
  - Induction of apoptosis
  - Complement-dependent cytotoxicity (CDC)
  - Antibody-dependent cellular cytotoxicity (ADCC)
- **Iodine-131 radioisotope**
  - Cytotoxic beta emission
  - Physical half-life of 8 days
  - Short path length
  - Gamma emission allows dosimetry



I-131 Tositumomab Treatment Regimen

Thyroid protective agent: Day –1 continuing through 14 days post-therapeutic dose

Day 0

Dosimetric Dose

450 mg unlabeled tositumomab,
35 mg tositumomab
radiolabeled I 131 (5 mCi)

- Unlabeled dose infused over 1 hour
- Radiolabeled tracer dose infused over 20 minutes

→ Total Body Counts x 3

- Day 0
- Day 2, 3, or 4
- Day 6 or 7

Day 7–14

Therapeutic Dose

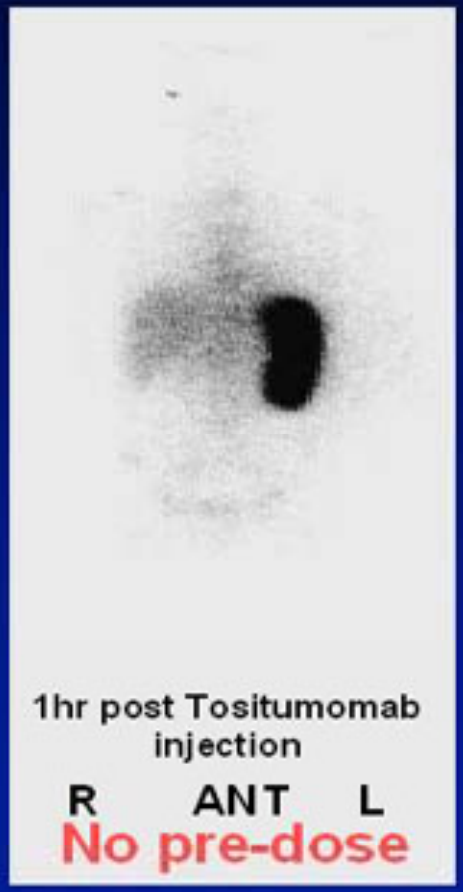
450 mg unlabeled tositumomab,
35 mg tositumomab radiolabeled I 131 to deliver
specific cGy TBD (variable mCi)

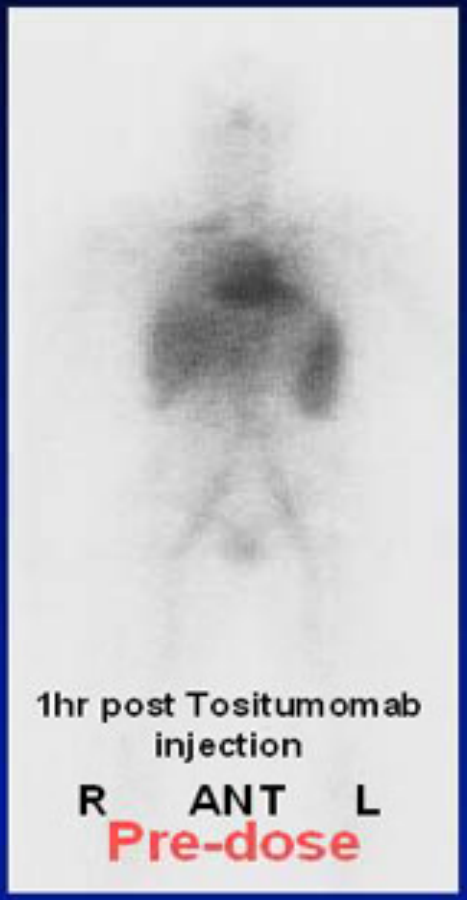
- Unlabeled dose infused over 1 hour
- Radiolabeled therapeutic dose infused over 20 minutes

Purpose of Administering Unlabeled Tositumomab Prior to Iodine I 131 Tositumomab

- To occupy non-tumor CD20 sites on:
  - Circulating B cells
  - Splenic B cells
- To provide a longer residence time of the radioconjugated antibody
- To potentially improve tumor uptake of radioactive antibody

Effect of Unlabeled Antibody Pre-Dose on Distribution



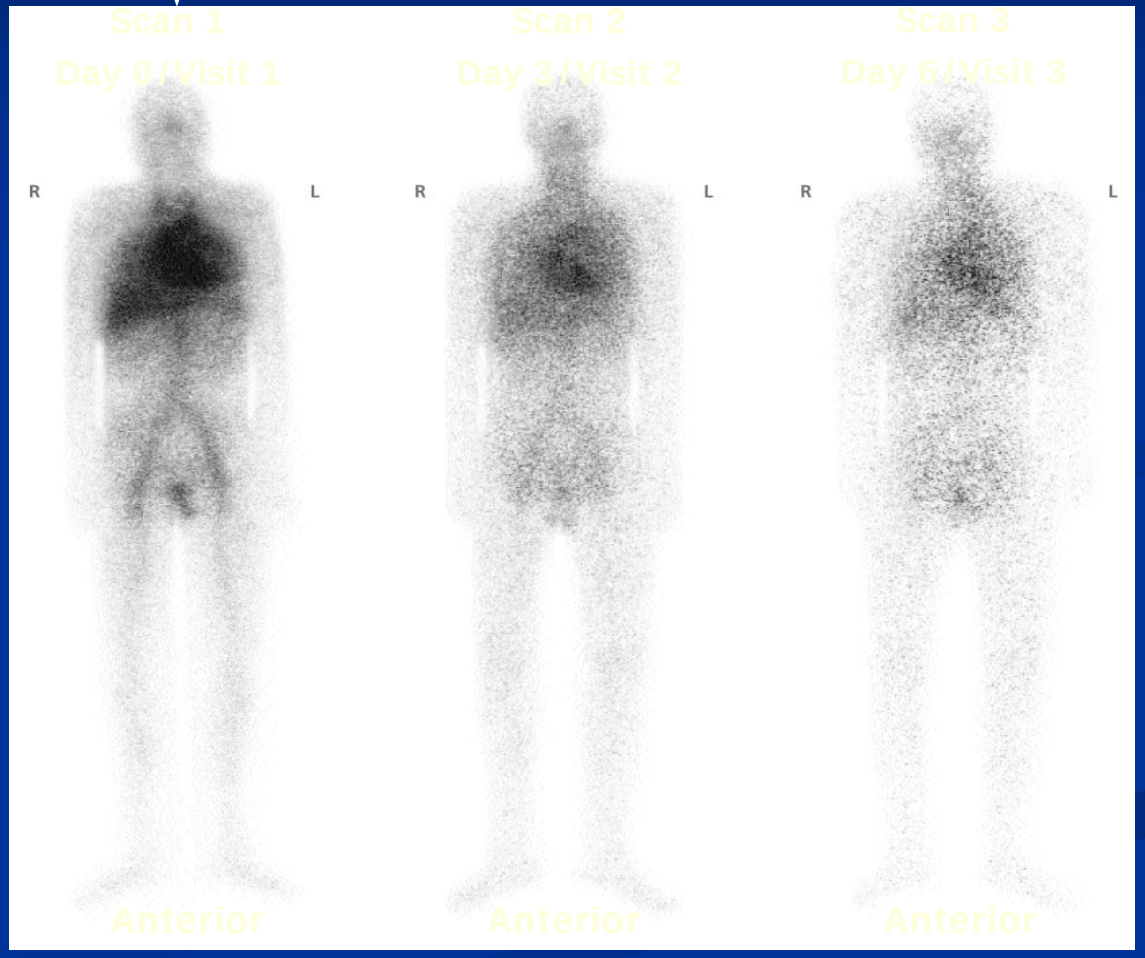


Data on File. Corixa Corporation.

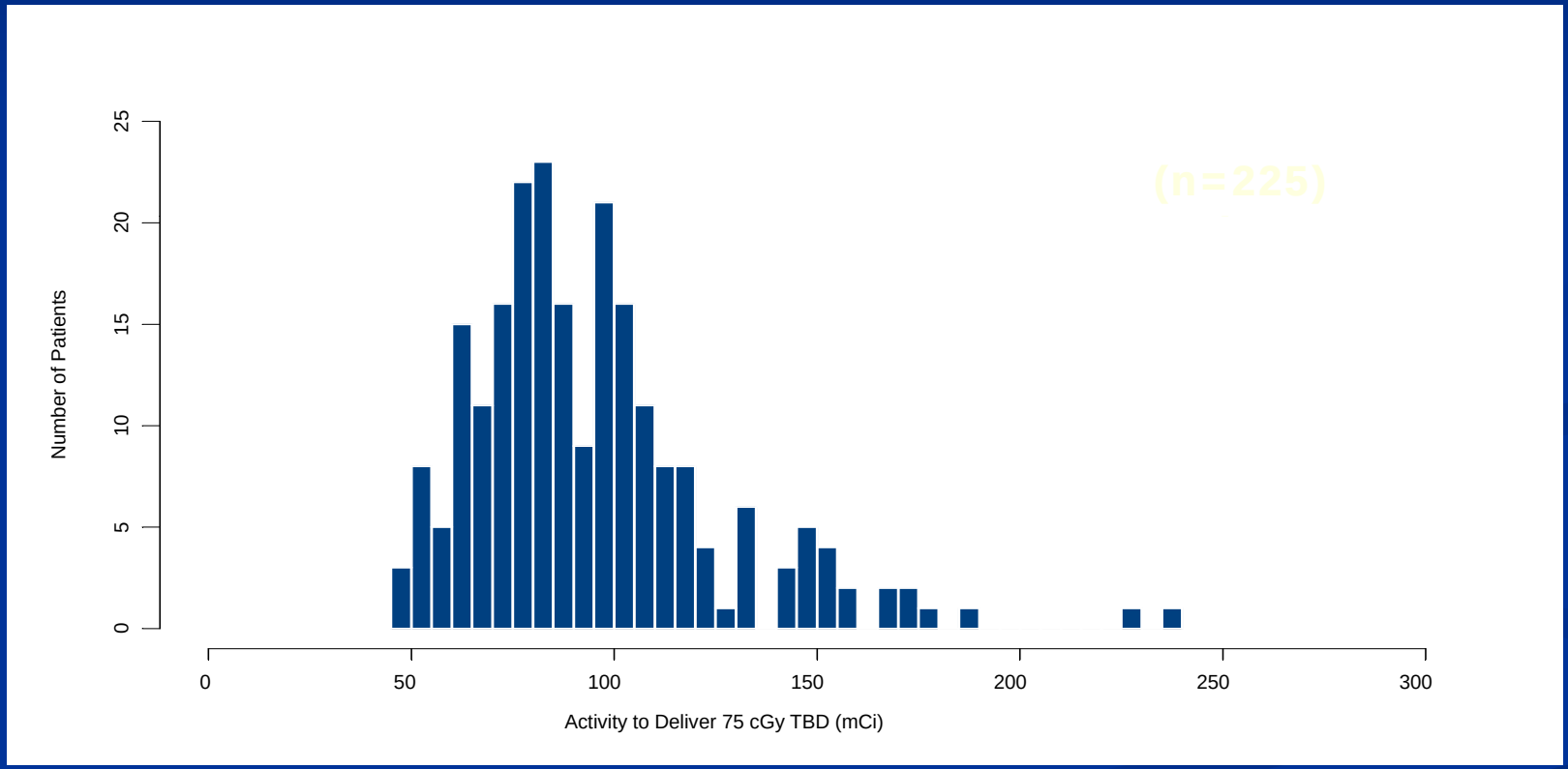
Fundamental Concepts of Radiation Biology

- Maximizing radiation dose to tumor will maximize tumor response
- Higher doses of radiation will result in more toxicity to normal tissues

Normal Biodistribution



Range of mCi Required to Deliver Targeted Total Body Radiation Dose*



*** Patients were prescribed either 65cGy or 75 cGy depending on their platelet count. Data were standardized to 75 cGy.**

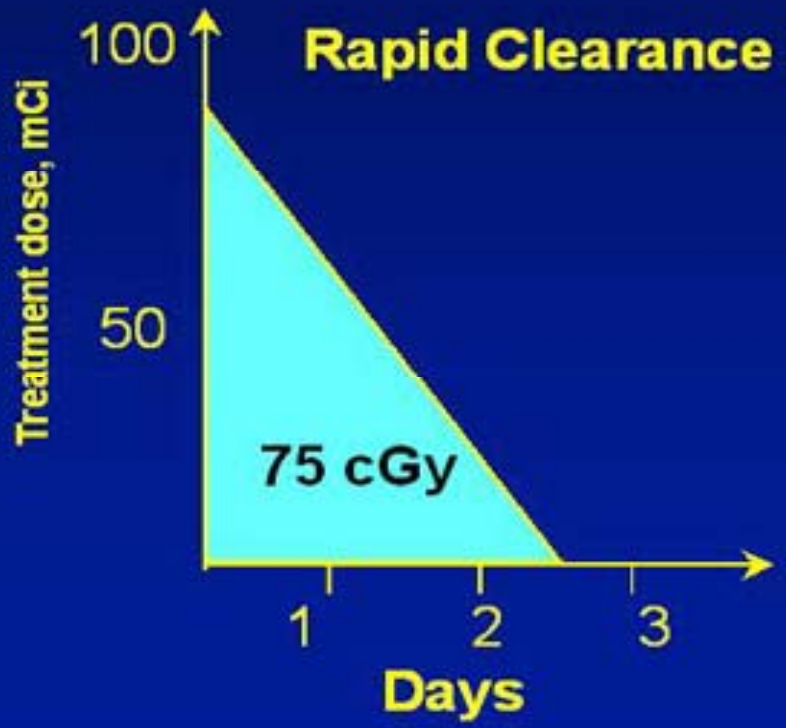
Dosimetry for I-131 Tositumomab

- Dosimetry studies confirmed a 4-fold variation in the clearance rate (or effective half-life) of Iodine I 131 Tositumomab
  - Factors affecting clearance of the antibody include tumor size, splenomegaly, and the amount of bone marrow involvement
- Due to variations in the clearance rate, the administered amount of radioactivity (in mCi) is adjusted individually to ensure that all patients receive the prescribed TBD of 75 cGy
- Using dosimetry with Iodine-131-labeled antibodies enables physicians to directly measure the clearance rate in order to prospectively individualize the therapeutic dose

Wahl R, et al. SNM 2001;42(Suppl):311P (abstract# 1293).

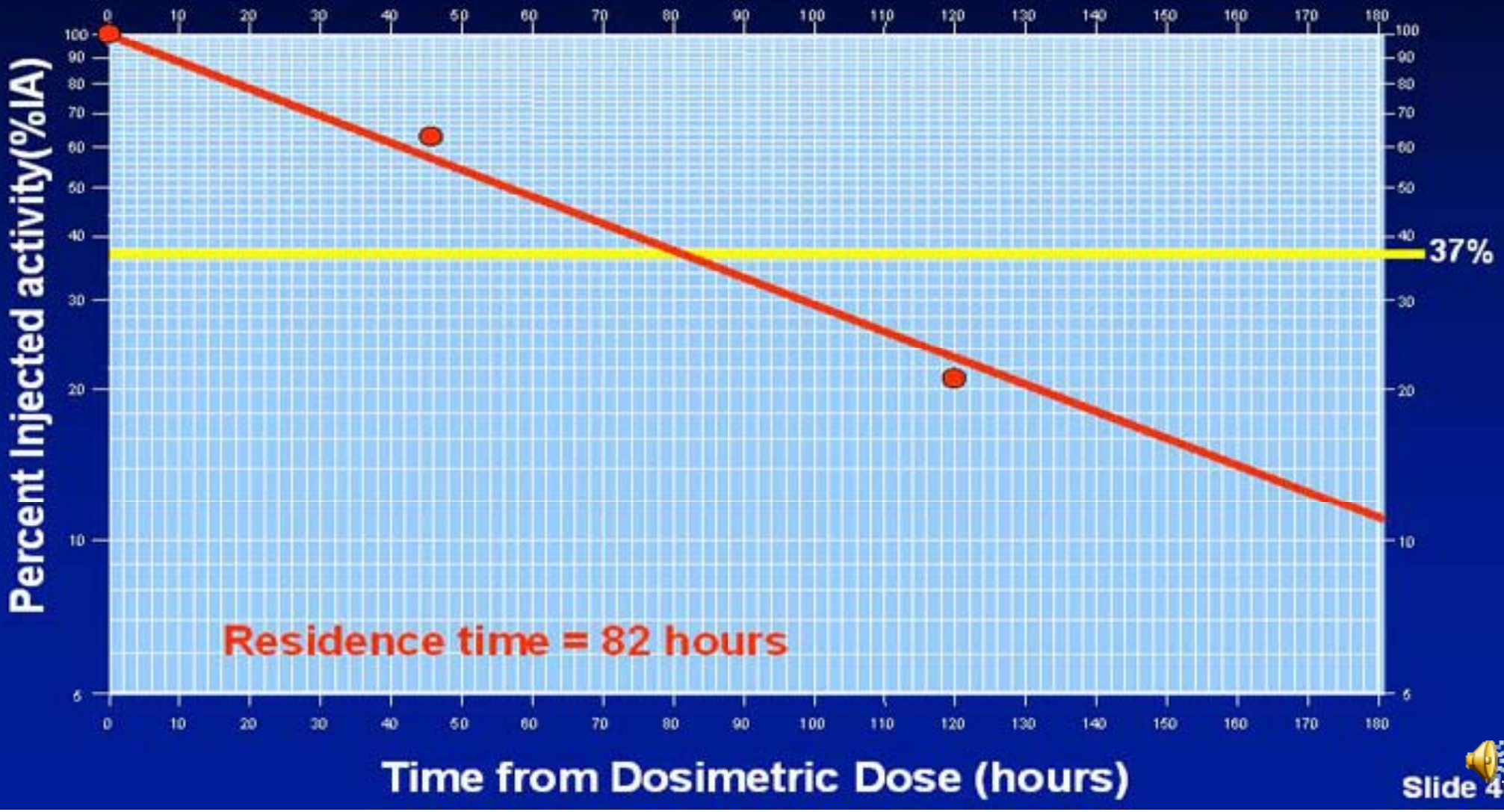
Effect of Clearance Rate on Radiation Exposure (mCi)

Individuals with a rapid clearance rate require a higher dose of radiation (in mCi)



Individuals with a slow clearance rate require a lower dose of radiation (in mCi)

Graphic Estimate of Total Body Residence Time



Activity Hours to Deliver 75 cGy TBD

Mass	Activity Hours	Mass	Activity Hours	Mass	Activity Hours
90.0	9633	94.5	10068	99.0	10500
90.5	9682	95.0	10117	99.5	10548
91.0	9730	95.5	10165	100.0	10595
91.5	9779	96.0	10213	100.5	10643
92.0	9827	96.5	10261	101.0	10690
92.5	9875	97.0	10309	101.5	10738
93.0	9924	97.5	10357	102.0	10785
93.5	9972	98.0	10404	102.5	10833
94.0	10020	98.5	10452	103.0	10880

The Equation Used to Calculate the Therapeutic Dose

$$\text{Therapeutic Dose (mCi)} = \frac{\text{Activity Hours (mCi h)}}{\text{Residence Time (h)}} \times \frac{\text{Desired TBD (cGy)}}{\text{75 cGy*}}$$

* 65 cGy for platelet count $\geq$ 100,000 and < 150,000/mm^3.

Determination of Maximum Tolerated Total Body Dose (TBD) of BEXXAR

75 cGy was established as Maximum Tolerated TBD

Dose Level (cGy)	Patients With DLT*/ Number Treated
25	0/3
35	0/4
45	0/3
55	0/3
65	0/3
75†	1/6
85	2/3

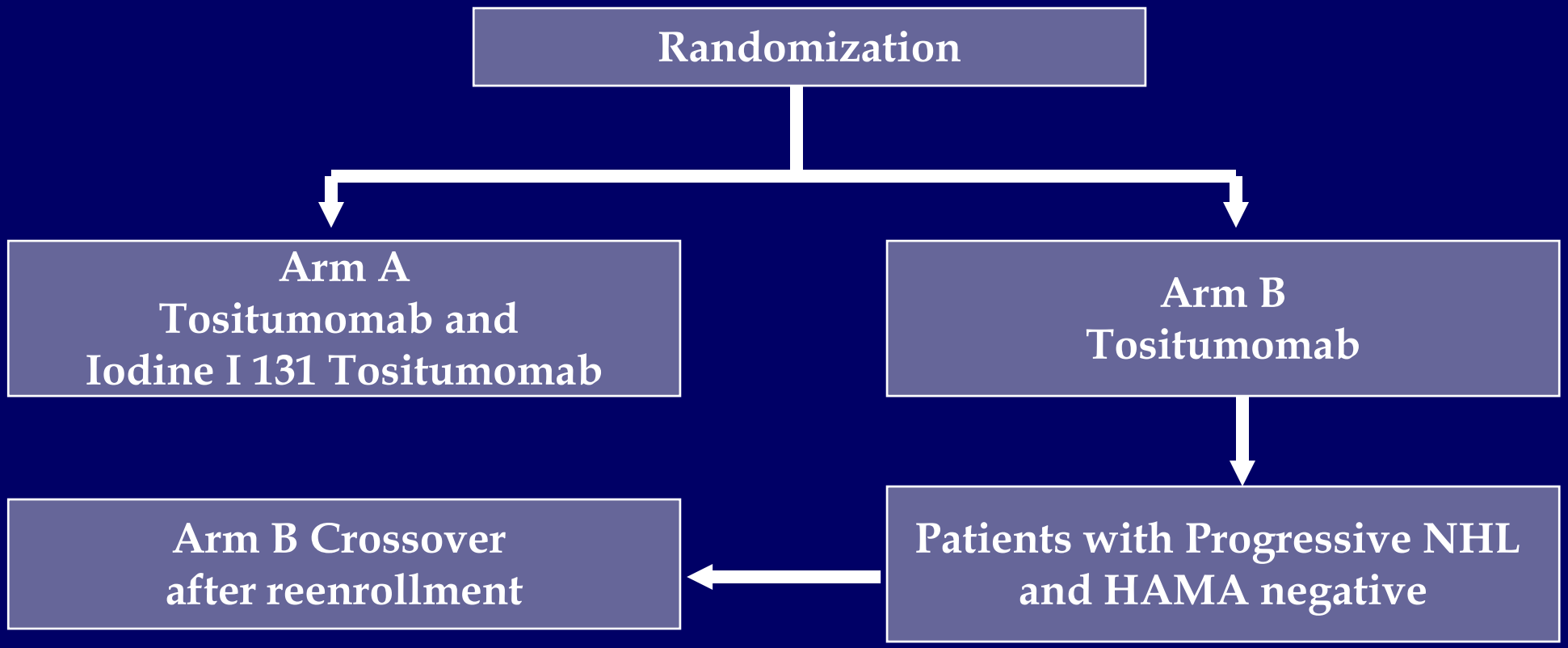
*DLT (Dose-Limiting Toxicity) = Grade 3 hematologic toxicity >2 weeks duration, Grade 4 hematologic toxicity >1 week duration, or Grade 3/4 non-hematologic toxicity.
†75 cGy = MTD.

Data on File. Corixa Corporation.

Summary: I-131 Tositumomab

- Effective treatment for relapsed follicular NHL
- As first line Rx, has 95% response rate
- Complete responses are quite durable
- Major toxicity is hematopoietic
- Explored for retreatment with success in HAMA neg pts.
- High dose RIT is possible with stem cell support and very active
- Recent data suggest I-131 Rituximab has similar anti-tumor activity

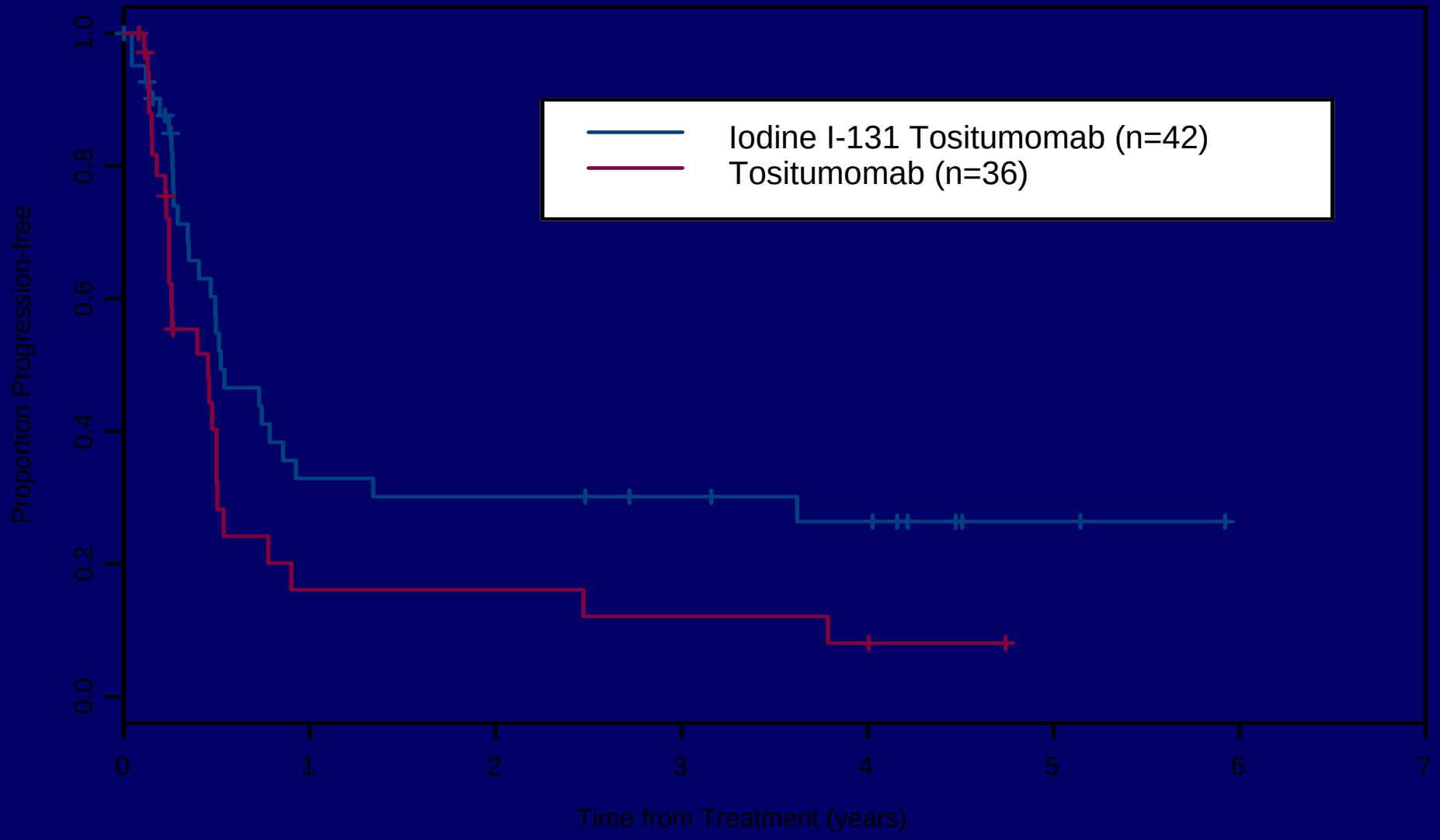
Study Design



Slide 22

s3 increased size of arrows
stewarts, 11/2/2004

MIRROR Panel Assessed Time to Progression or Death Arm A vs. Arm B



Conclusions

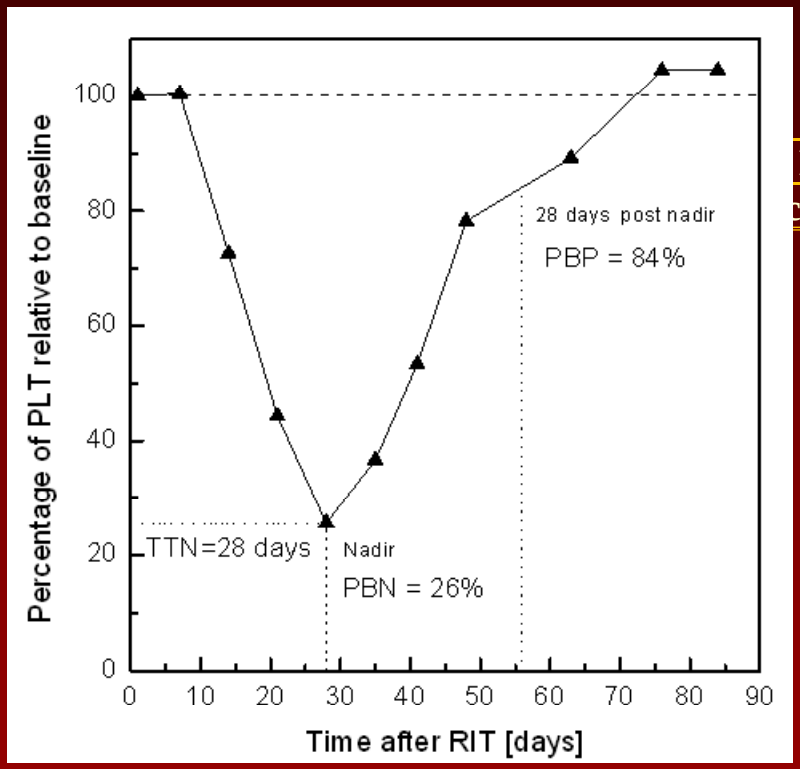
- This study documents that the radionuclide contributes significantly to the action of the radioimmunoconjugate in the BEXXAR therapeutic regimen
- The radionuclide contributes to both the frequency and durability of response
- Toxicity associated with the radionuclide was primarily predictable and manageable myelosuppression
- Low term safety risks: thyroid insufficiency, HAMA seroconversion, possibly MDS are acceptable in light of efficacy results

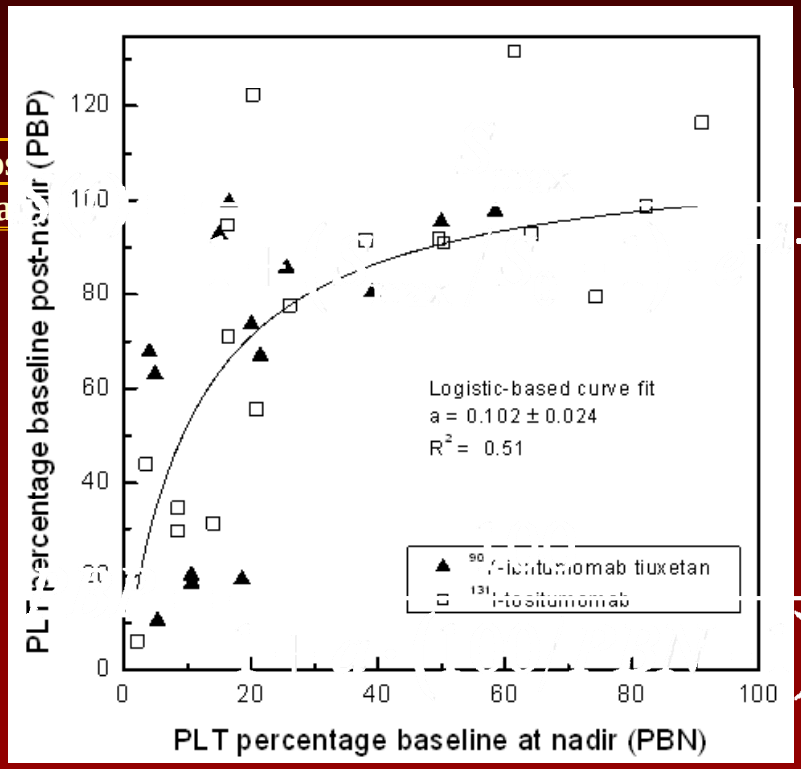
Effect of Chemotherapy: NHL

#	Variable	Characteristics	Mean ± SD or N (%)
1	AGE	Age at RIT	63 ±10 (40-80)
2	NPC	Number of prior chemotherapy regimens at RIT	3.1 ± 1.2 (1-6)
3	TEC	Elapsed time since last chemotherapy (months)	8.9 ± 6.4 (1-25)
4	BMD	Bone marrow dose (Gy)	1.6 ± 0.4 (1.0-2.0)*
			2.1 ± 0.4 (1.2-2.8) †
5	BSL	Baseline at time of RIT	
		Platelets ($\cdot 10^3/mm^3$)	206 ± 100
		Absolute neutrophil count ($1/mm^3$)	3'860 ± 1'880
6	SEX	Male sex	23 (72%)
7	TYP	Type of RIT	
		^{90}Y-ibritumomab tiuxetan	14 (44%)
		^{131}I-tositumomab	18 (56%)
8	DST	Disease stage at RIT	
		III	5 (16%)
		III-IV	27 (84%)
9	PTR	Prior treatment with Rituximab	
		Alone	8 (25%)
		With chemotherapy	23 (72%)
10	RTR	Refractory to Rituximab	14 (44%)
11	BMI	Bone marrow involvement at RIT	7 (22%)
12	PMT	Prior bone marrow transplant	4 (13%)
13	PRT	Prior radiation therapy	7 (22%)
14	PTF	Prior treatment with fludarabine	9 (28%)

- 14 Zevalin, 18 Bexxar (^{90}Y-, ^{131}I-anti-CD20)
- Treated as per dosing guidelines
- BM dose ~ constant
- Identify best predictor of Hematologic toxicity
- 14 variables considered
- Multiple linear regression analysis

Effect of Chemotherapy: NHL





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29	L	H

*** Patient with bone marrow involvement**

Baechler, *et al* SNM '09

SPECT/CT Imaging based Dosimetry in Radionuclide Therapy

Yuni Dewaraja

In collaboration with

Pete Roberson, Jeffrey Fessler, Scott Wilderman, Matthew Schipper, Ken Koral, Anca Avram, Mark Kaminski

University of Michigan

Departments of Radiology, Radiation Oncology, Electrical Engineering & Internal Medicine

This work is supported through grant EB001994 awarded by the National Institute of Health

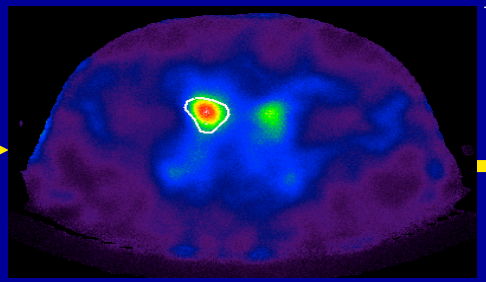
3D Dosimetry coupling SPECT/CT with Monte Carlo

CT data

Integrated imaging

CT-based attenuation corr, scatter corr, VOI definition

Monte Carlo Dosimetry: DPM Code

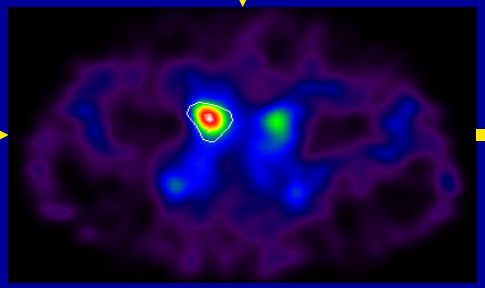


Dose map

Dose-rate map

SPECT projection

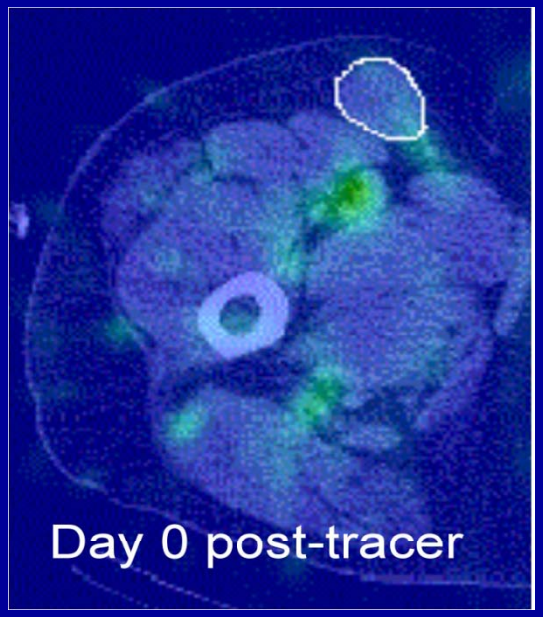
Dead time

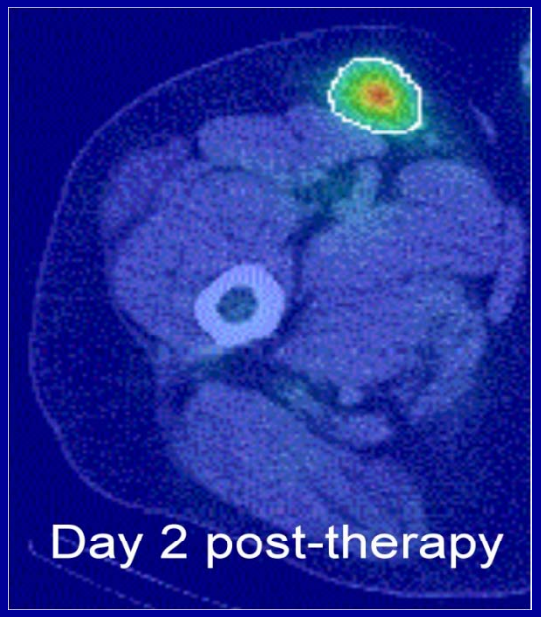


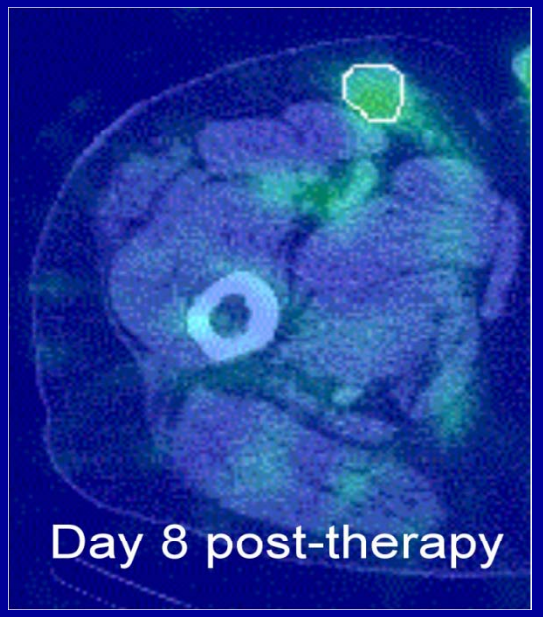
Reconstruction & quantification

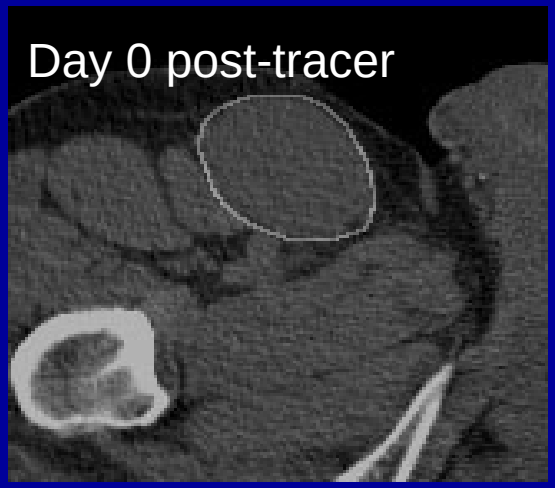
Dewaraja, et al. JNM 2010

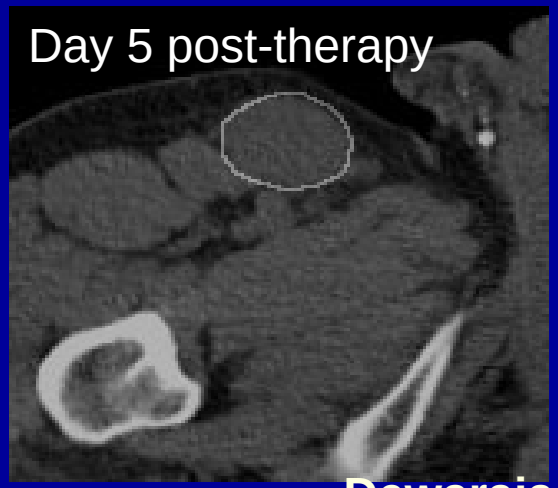
Patient Results: Initial tumor regression











Dewaraja, et al. JNM 2010

Patient results: SPECT/CT images

Day 0 post-tracer

Day 5 post-therapy

Day 8 post-therapy

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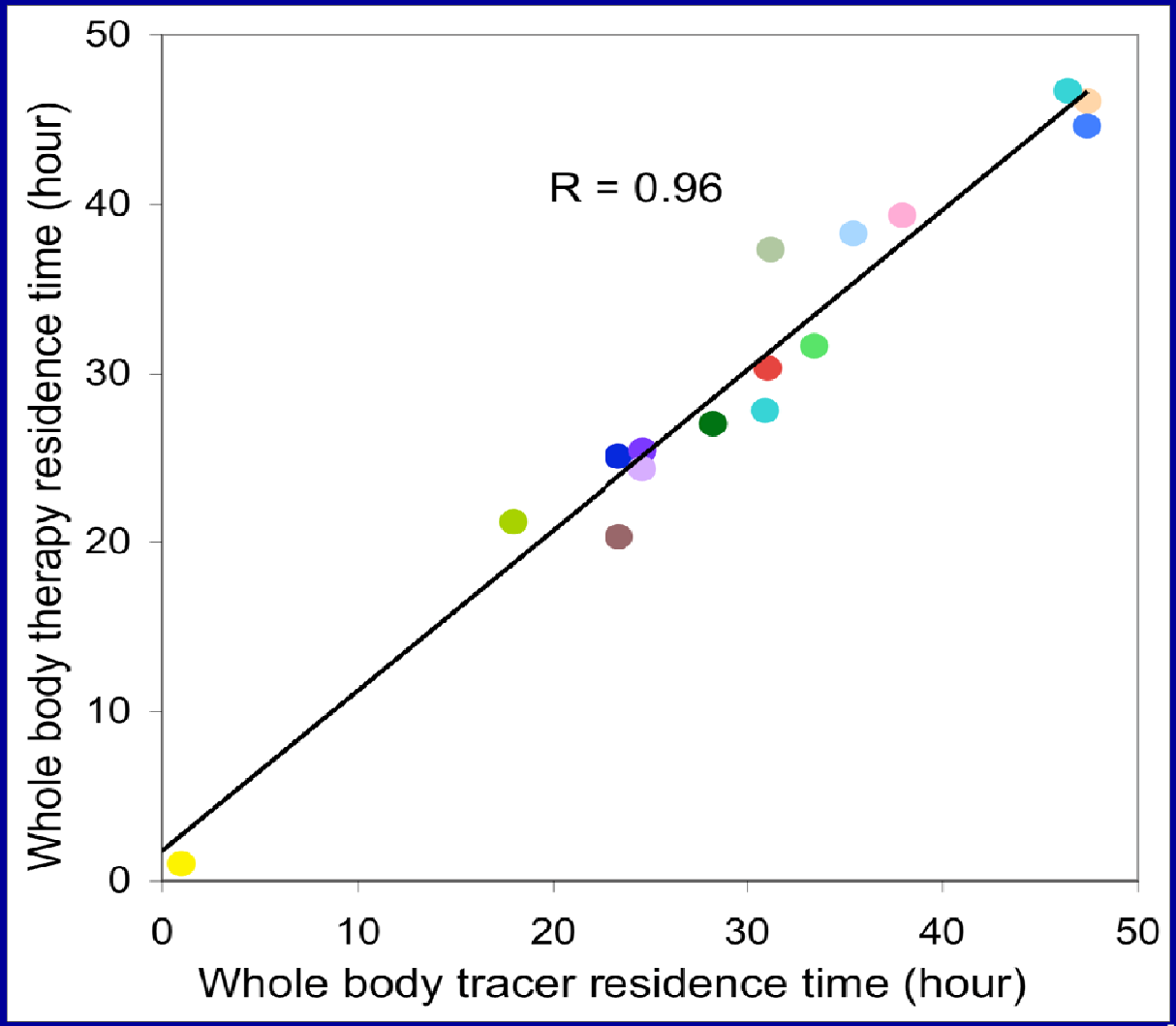
Tracer-therapy correlation: whole-body (SPECT FOV)



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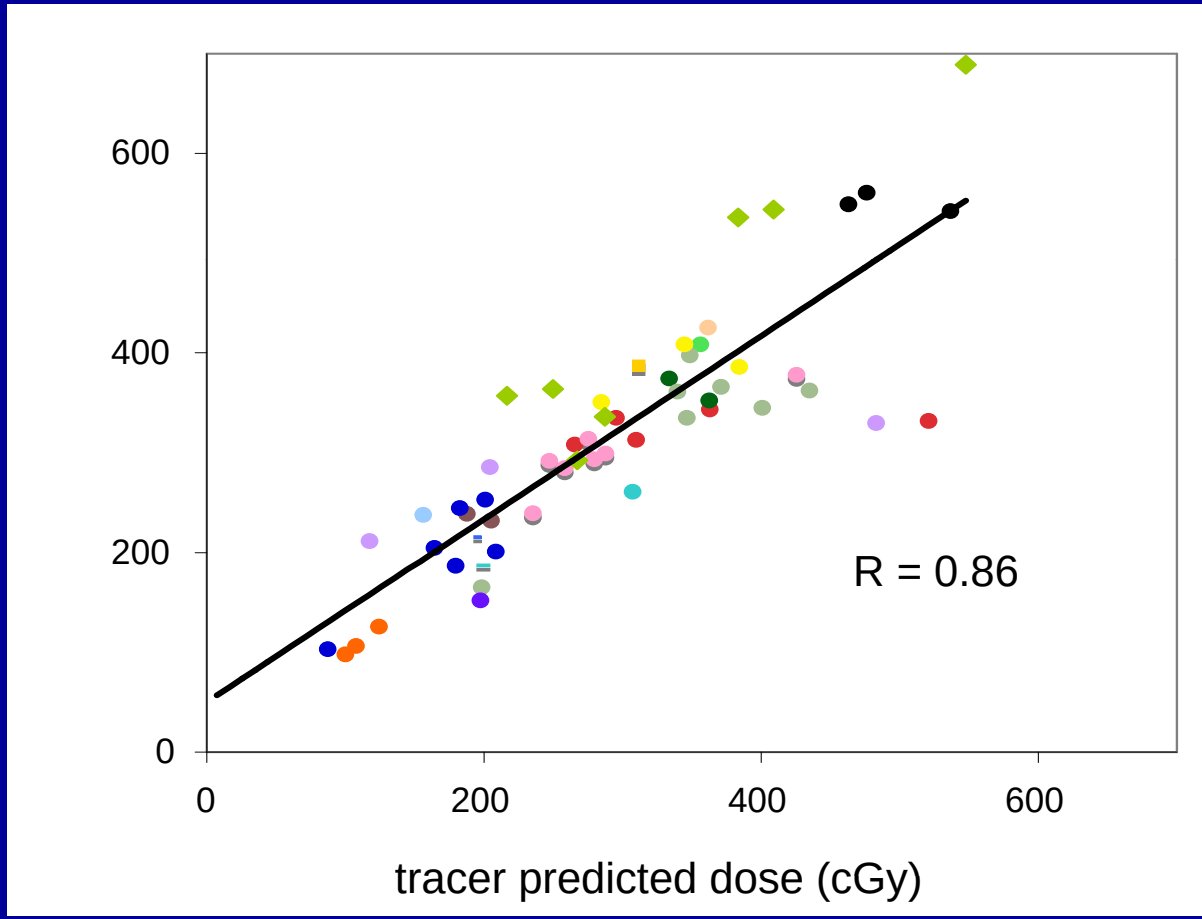
Tracer-therapy correlation: tumor

- High correlation between tracer predicted and therapy delivered mean tumor absorbed dose



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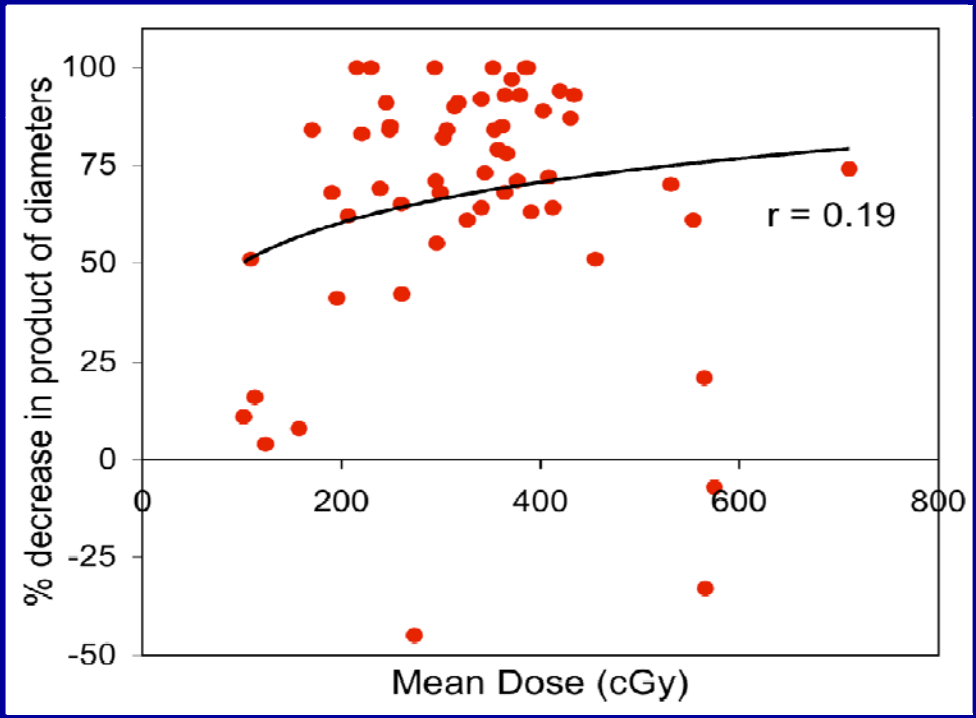
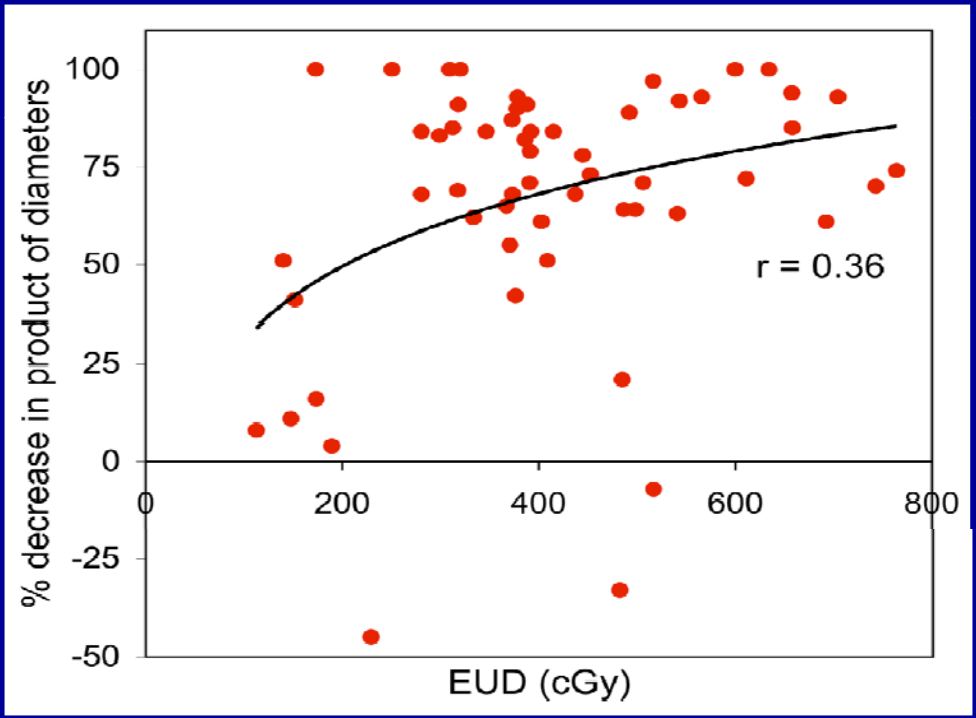
Tumor dose-response





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