

# New Horizons in radionuclide therapy

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# Date for you diary

- Interested in Radionuclide imaging and therapy using antibodies and peptides
- IRIST 2008
- Krakow Poland 18-21 June 2008
- [alahub@cm-uj-krakow.pl](mailto:alahub@cm-uj-krakow.pl)

# Where are we now-1

- P-32 bone
- I-131
- Y-90 silicate/colloid
- I-131 Lipiodol
- I-131 mIBG
- Sr-89
- Bone pain\*, brain tumours\*, PCV, TTP
- Hyperthyroidism, DTC
- Radiation synovectomy
- HD\*, HCC
- Neuroblastoma, NET
- Bone pain palliation

# Where are we now-2

- Sm-153 EDTMP
- Re-186 HEDP
- Re-186 colloid
- Ho-166 Chitosan
- Er-169 colloid
- Bone pain palliation
- Bone pain palliation RA
- Synevectomy mid joints
- HCC
- Synevectomy small joint

# Where are we now-3

- I-131 Bexxar
- Y-90 Zevalin
- In-111 octreotide
- Y-90 octreotide/tate/lan
- Re-188 Lipiodol
- Lu-177 octreotide
- NHL
- NHL
- NETs
- NETs
- HCC
- NET

# Where do we go from here

- Need new carriers
  - Antibody
  - Antibody fragments
  - Antibody constructs eg diabodies
  - Peptides
  - Nucleotides
  - Chemical carriers
- All to be based on our knowledge of the molecular basis of disease

# Isotopes used

- Auger/conversion electrons
- Beta emitters
- Alpha emitters
- Sn-177m
- Lu-177
- Cu-67
- Re-188
- Rd 232
- Bs 231

# What is the problem

- At present we can only treat some rare cancers
- No real impact into major cancers such as lung, prostate, breast
- How can we make radionuclide therapy more effective
  - Different targeting
  - Part of combined treatment

# CHT-25 (Basiliximab)

- Chimeric monoclonal antibody derived from a murine monoclonal antibody produced at the Royal Free Hospital (RFT5 2 )
- Constant regions of the heavy and light chains replaced by human constant regions of IgG1
- Binds to 55 kD chain of the IL-2 receptor with high affinity ( $K_a = 1 \times 10^{10} \text{ M}^{-1}$ )

# Patient Selection

- Inclusion criteria
  - Refractory, histologically proven lymphoma
  - **Expression of IL-2R on > 50% of tumour cells**
  - Bi-dimensionally measurable disease
  - Age > 18 years
  - Life expectancy > 3 months
  - WHO PS 0,1,2
  - No anti-lymphoma treatment for 1 month
  - **Stem cell, bone marrow harvest**
  - Satisfactory haematological/ biochemical indices
- Exclusion Criteria
  - **> 25% marrow involvement by lymphoma**
  - Pregnant/ lactating
  - Poor medical risk
  - Hepatitis B,C, HIV
  - **Positive HAMA to CHT-25**

## Administered activity in MBq/m<sup>2</sup> (actual administered activity)

Patient	#1	#2	#3	#4	Cumulative activity
1	370 (663)				370 (663)
2	370 (573)				370 (573)
3	370 (725)	740 (1377)			1110 (2102)
4	740 (1380)	1480 (1868)	2220 (3395)	370 (554)	4810 (7197)
5	740 (1286)	1480 (2220)			2220 (3506)
6	740 (1104)				740 (1104)
7	1480 (2397)	2220 (2560)	2960 (4553)		6660 (10507)
8	740 (1093)				740 (1093)
9	740 (1105)	1480 (2104)	2220 (3239)		4440 (6448)

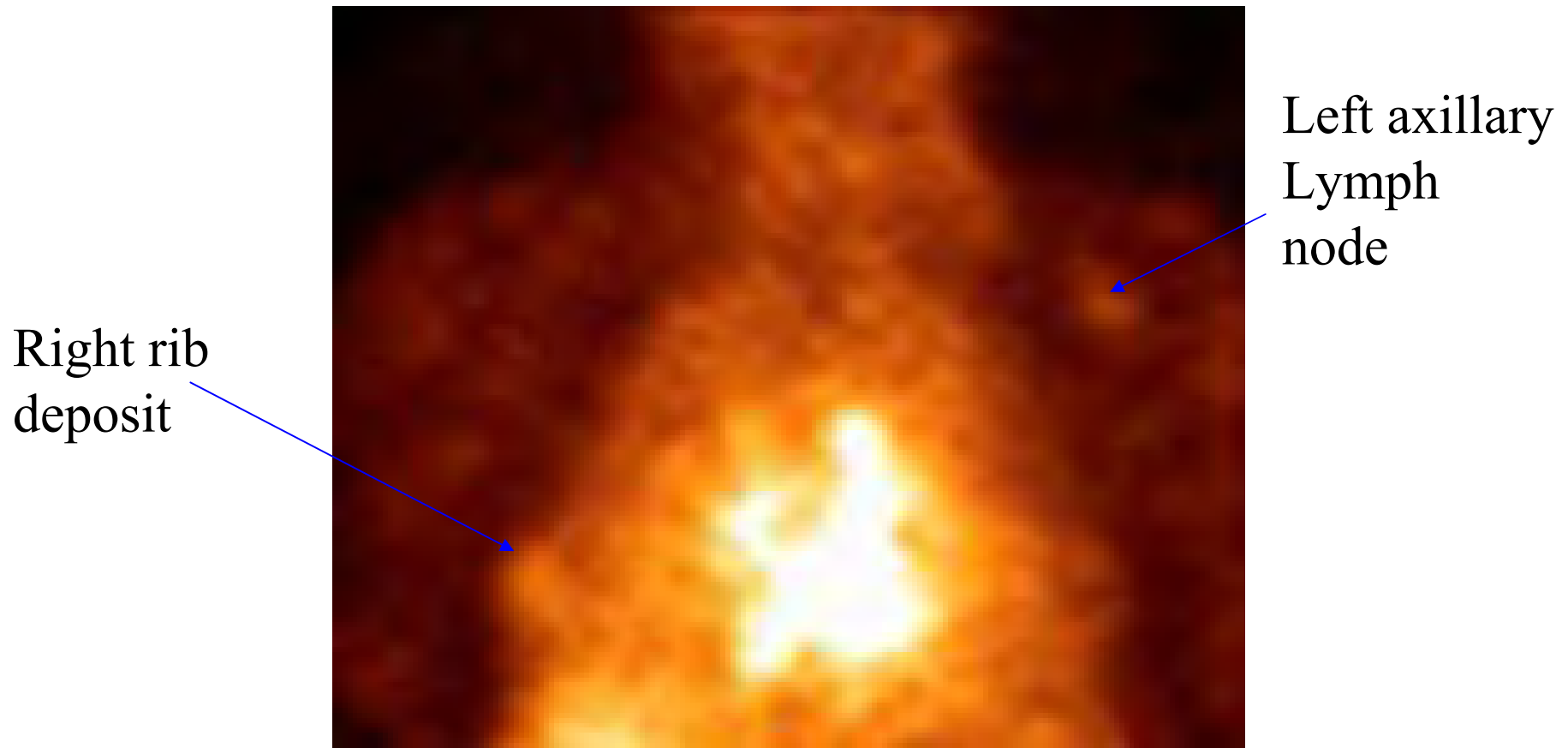
Repeated therapy possible at 1 month if localisation > 3% injected activity/kg + no stem cell rescue required

# Incidence and CTC grade of haematological toxicity in relation to administered activity

Administered activity (MBq per m <sup>2</sup> )	Treatment no.	Haemoglobin	Neutrophils	Lymphocytes	Platelets
370	4	G1(1),G2(2) G3(1)		G1(1),G2(1) <b>G3(2)</b>	G2(1) G3(1)
740	6	G1(1),G2(5)	G2(1)	<b>G3(4)</b>	G1(1) G2(1)
1480	4	G1(1),G2(2)	G1(2),G2(3) <b>G3(4)</b>	G2(1), <b>G3(3)</b>	<b>G3(2)</b> <b>G4(1)</b>
2220	3	G2(2), <b>G4(1)</b>	G2(1), <b>G3(1)</b>	<b>G3(3),G4(1)</b>	<b>G3(1)</b> <b>G4(2)</b>
2960*	1	G2	<b>G4</b>	<b>G3</b>	<b>G3</b>

\*DLT with toxic death due to *pneumocystis* pneumonia

# SPECT image revealing tumour localisation of $^{131}\text{I}$ -CHT25 in patient 07

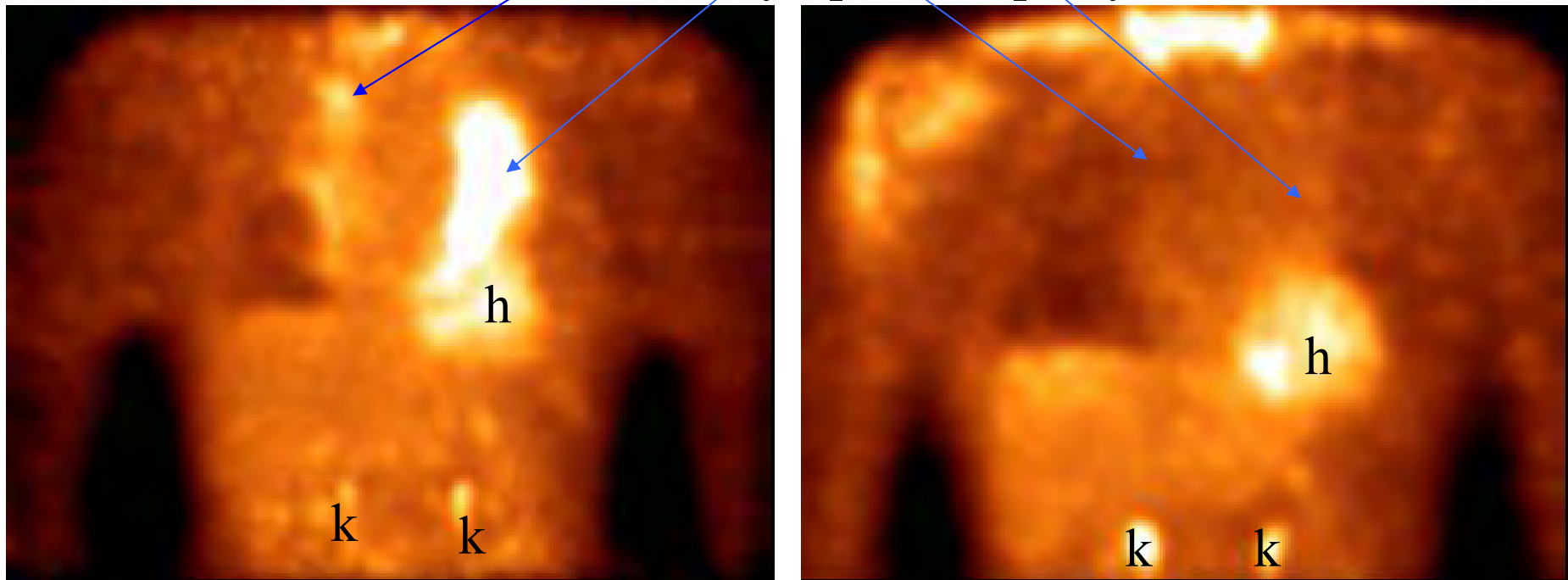


Tumour localisation at  $> 3\%$  injected activity seen in 12/18 therapies

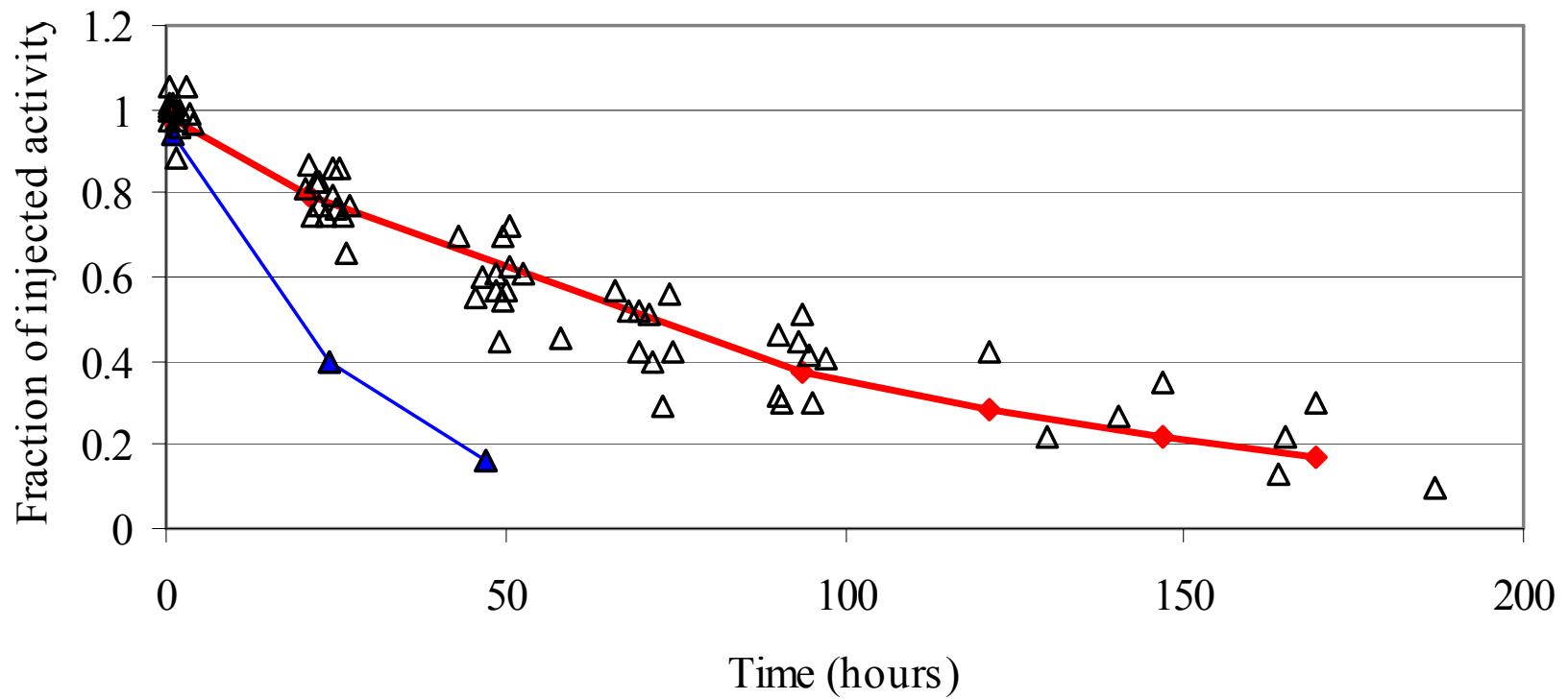
Patient no.	Dose Level (MBq/m <sup>2</sup> )	FDG-PET	CT (WHO criteria)	Comment
1	370	-	-	Clinical progression
2	370	-	PD	
3	370	<b>PR</b>	SD	
	740	-	SD	Clinical progression
4	740	<b>PR</b>	SD	
	1480	CR	SD	
	2220	CR	SD	
	370	<b>PR</b>	SD	
5	740	<b>PR</b>	<b>PR</b>	
	1480	<b>PR</b>	<b>CR</b>	
6	740	SD	SD	
7	1480	-	SD	
	2220	<b>PR</b>	<b>PR</b>	
	2960	-	-	Not available for scanning
8	740	-	PD	Scanned at referring Hospital
9	740	SD	SD	
	1480	SD	SD	
	2220	PD	PD	Partial PET response at 1 month

# FDG-PET Response in Hodgkin's disease following 6600 MBq in three fractions (patient 04)

Mediastinal Lymphadenopathy



# CHT-25 Whole Body Clearance Pharmacokinetics



Estimated activity  $T_{1/2}$  66.9 hours

# MIRD absorbed dose estimates

<b>Organ</b>	<b>Absorbed dose mGy/ MBq</b>
Lung	1.85
Heart	1.06
Liver	0.96
Spleen	0.7
Kidneys	0.63
Marrow	1.15

# Phase 1b

- Review of data by CRUK safety committee
- Decided that 1480MBq/m<sup>2</sup> was MTD
- However wished to check if possible to do 10% dose reduction
- Therefore compare 3 patients with 1280v1420MBq/m<sup>2</sup>

# Phase 1B

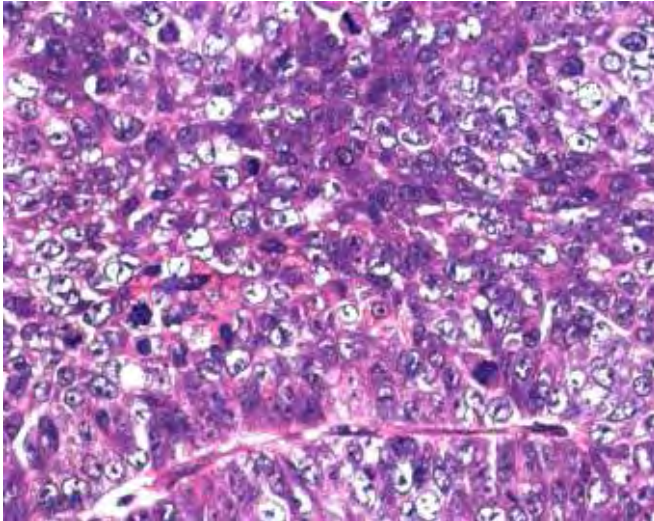
Patient #	Dose level	1 <sup>st</sup> dose response	2 <sup>nd</sup> dose response	Toxicity
10	1280/m <sup>2</sup>	PR	CR	Grade 3 platelets
11	1280/m <sup>2</sup>	PR	CR	Grade 3 platelets
12	1280/m <sup>2</sup>	CR	-	Grade 2 Pt&Leuc

# Overcoming problems in Ca colon

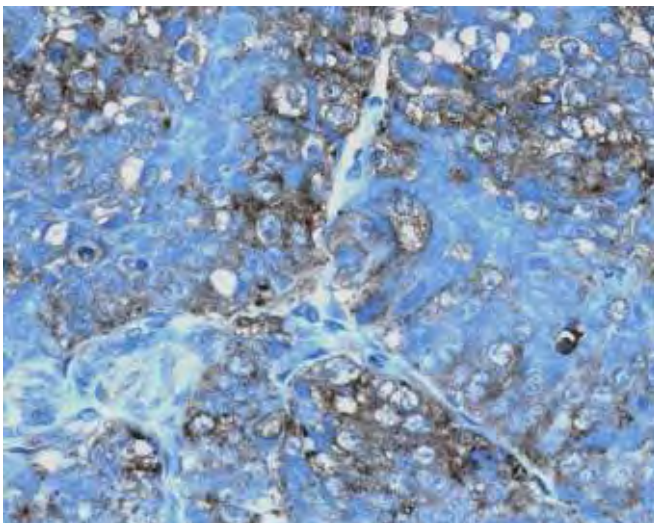
- Need to look at tumour
- Distribution of antigen
- Degree of angiogenesis
- Penetration of antibody in cancer
- Can combination therapies work
- RFH Combratastatin an anti-vEGF and I-131 A5B7 anti-CEA antibody

# Effect of Antigen on Antibody Distribution in Tumours

LS174T

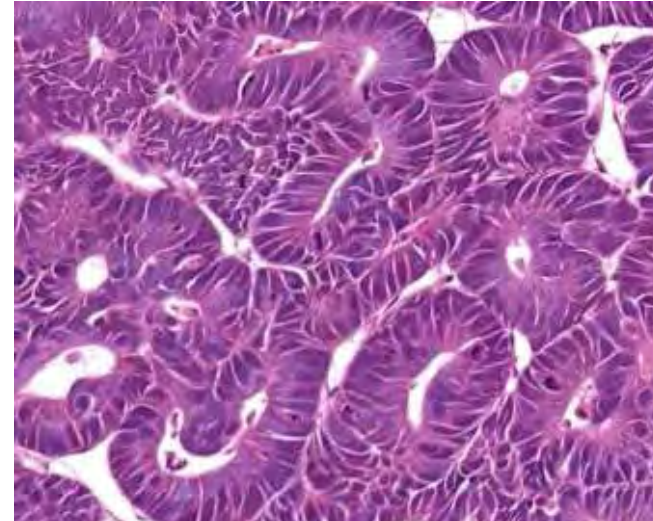


H&E

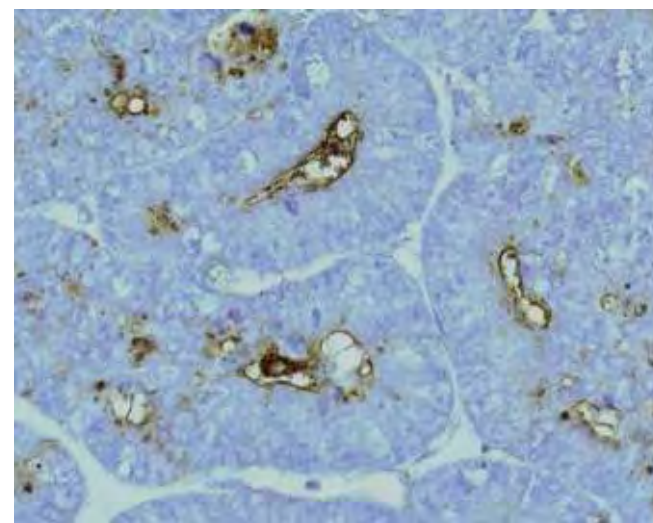


CEA

SW1222



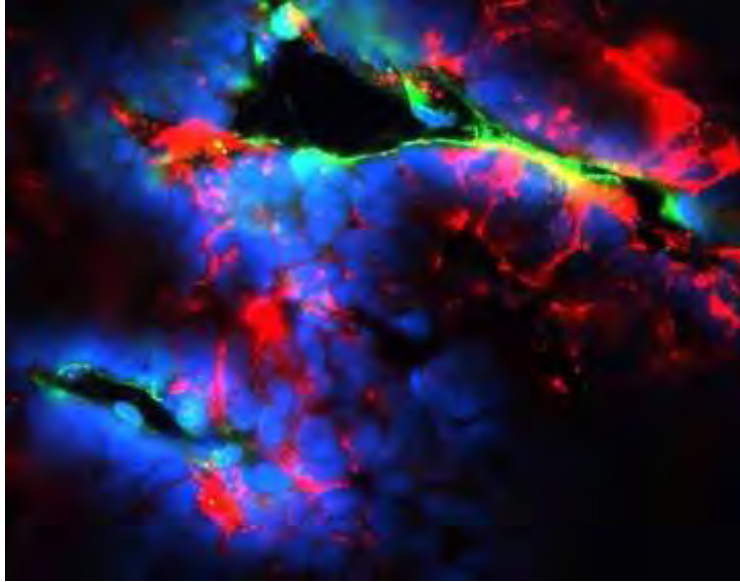
H&E



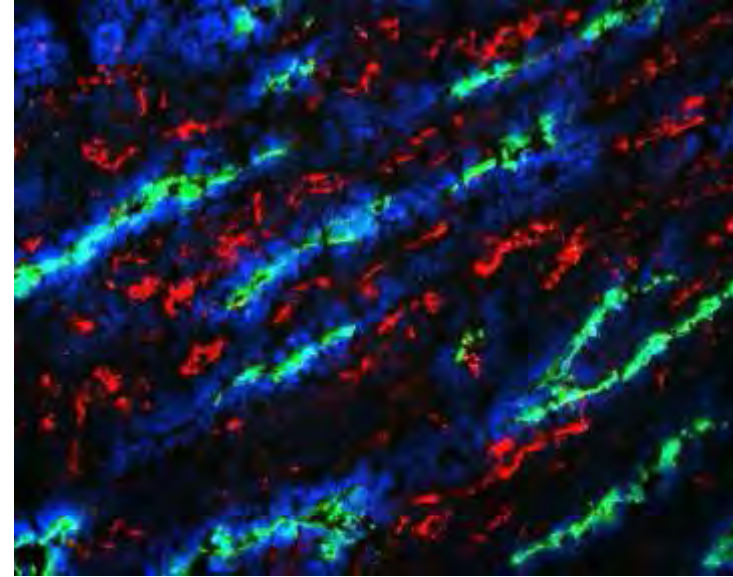
CEA

# Movement of A5B7 over time in SW1222 xenografts

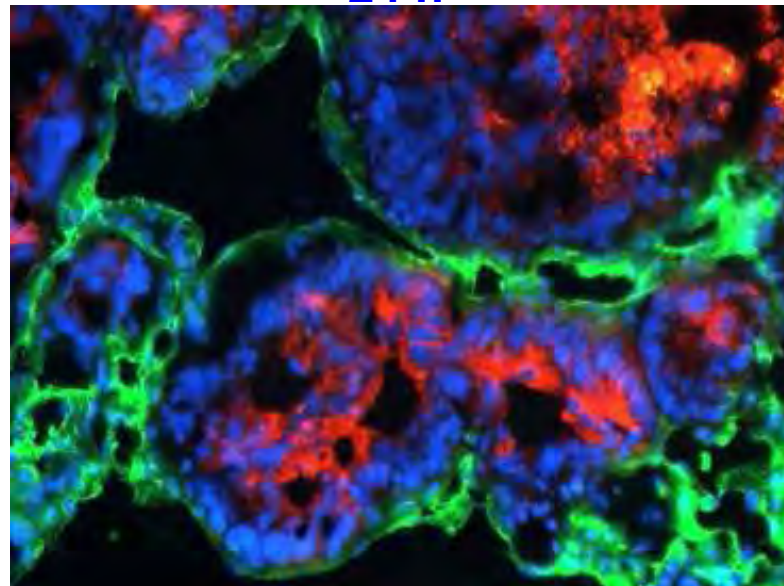
5 min



1- 24 h



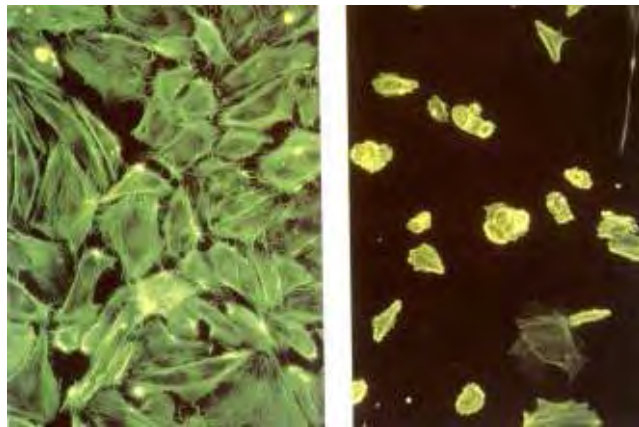
24 h



## Vascular Disrupting Agents eg. Combretastatin CA4-P

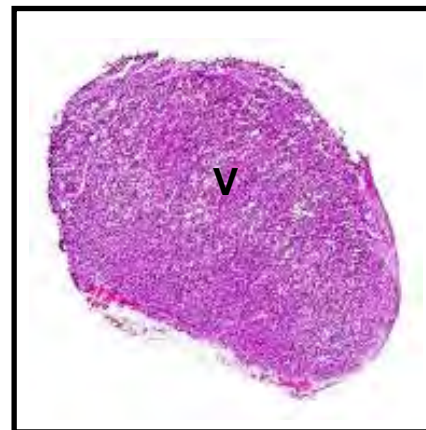
- tubulin binding agent/colchicine binding site
- targets established tumour vessels
- inhibits tumour blood flow
- destroys all but the tumour rim

HUVECs



Untreated

After CA4-P

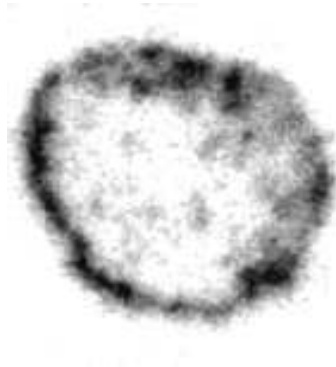


Untreated



24 h post CA4-P

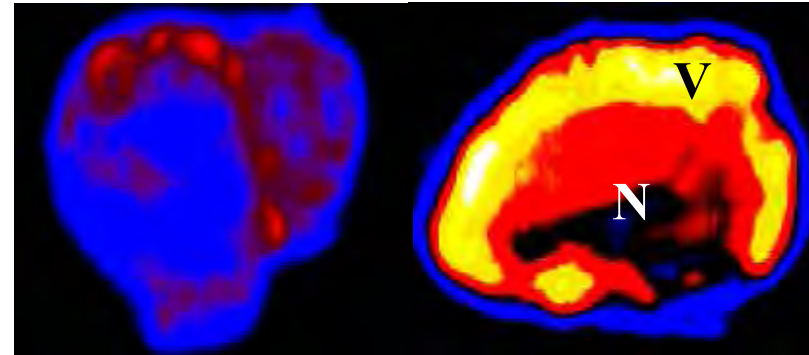
# Basis of Combined Therapies



Antibody

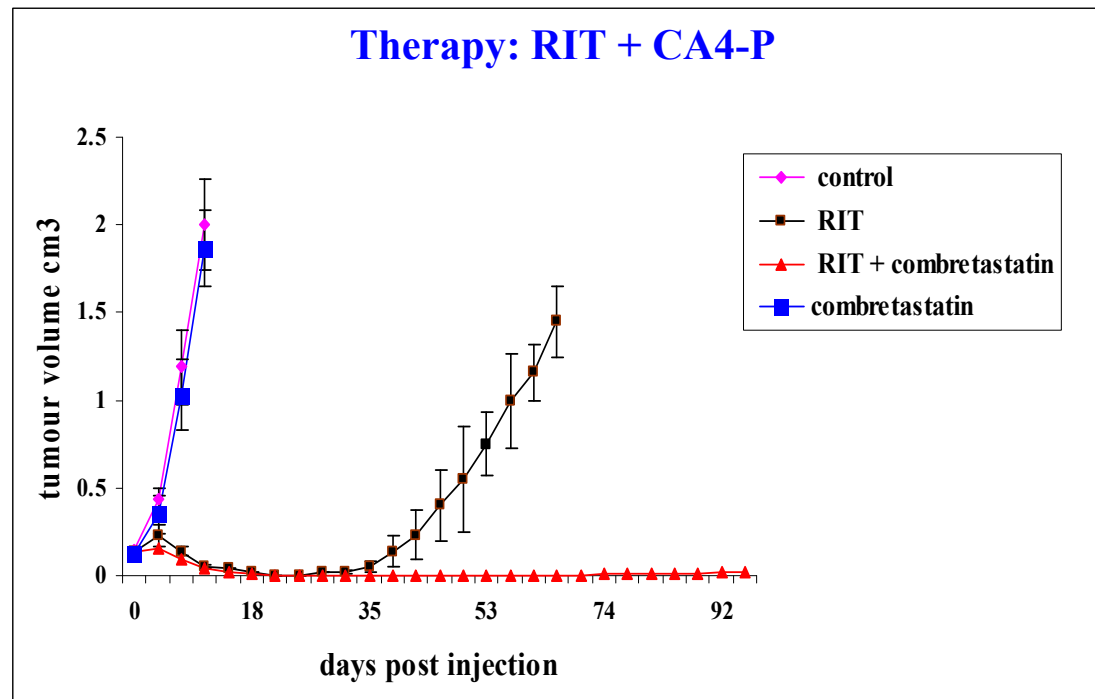


Combretastatin 24h

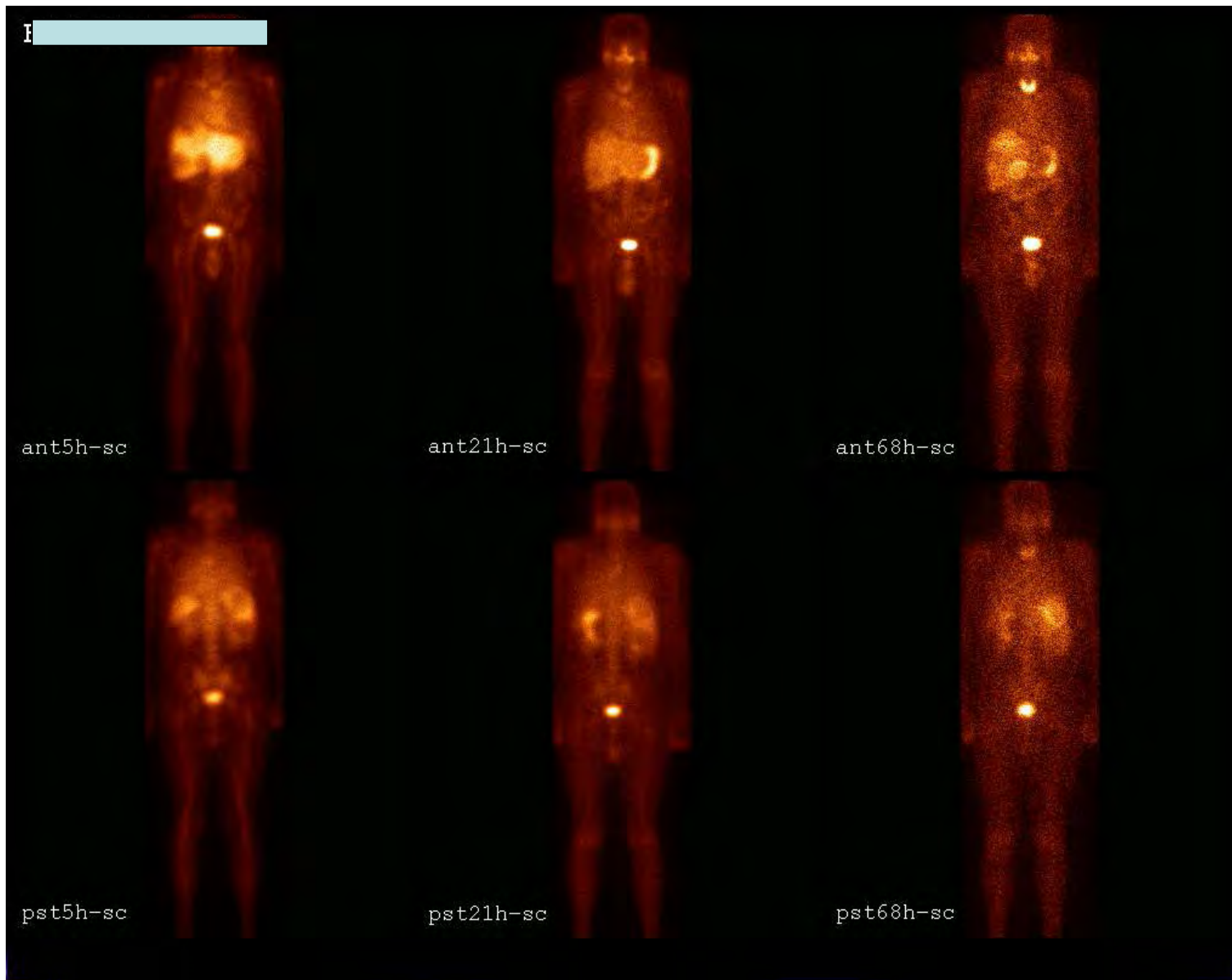


PI of antibody alone  
(25% ID/G)

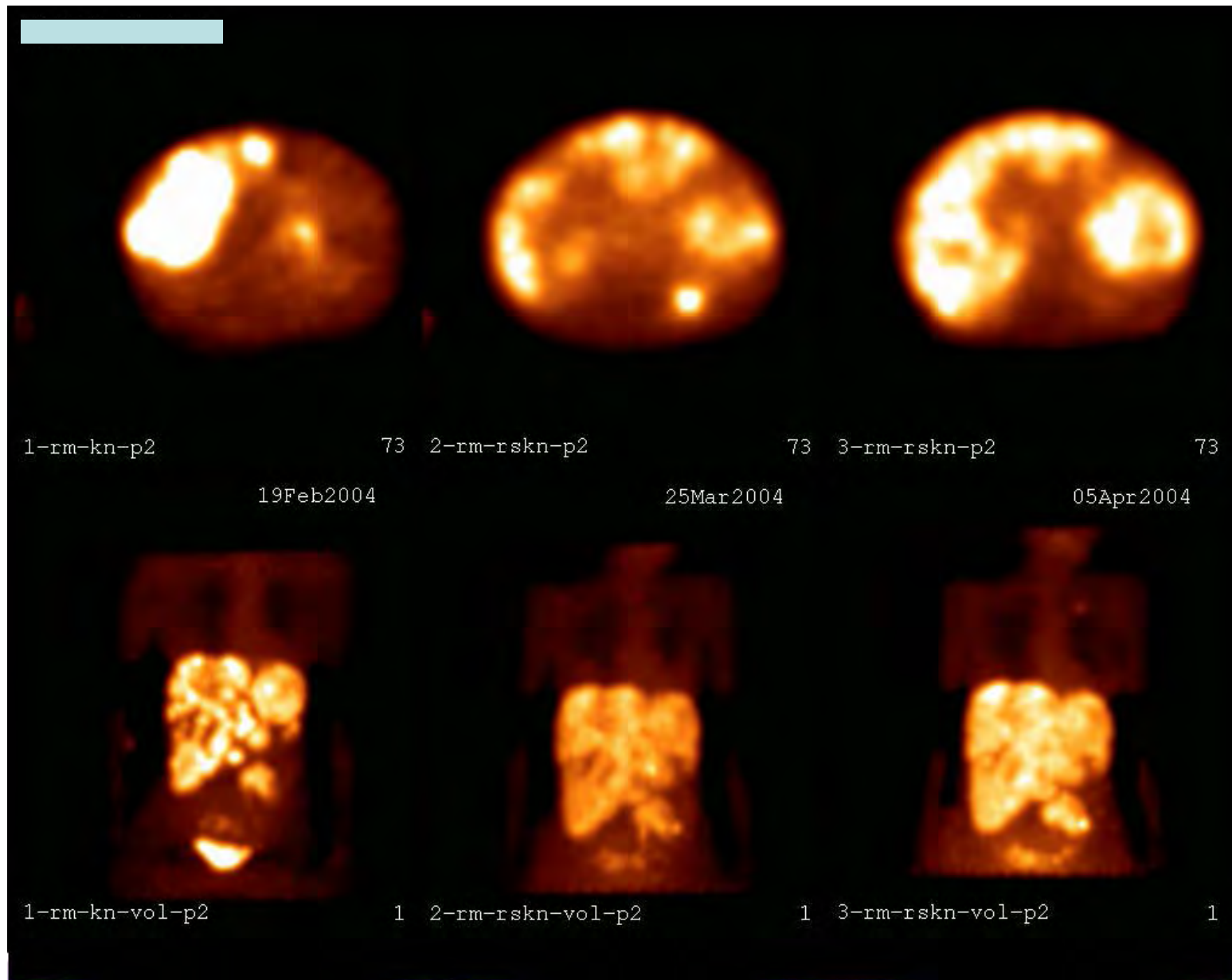
Combined  
(42% ID/G)



# 04DB SPECT Images A5B7 Uptake



# 03JW PET Images



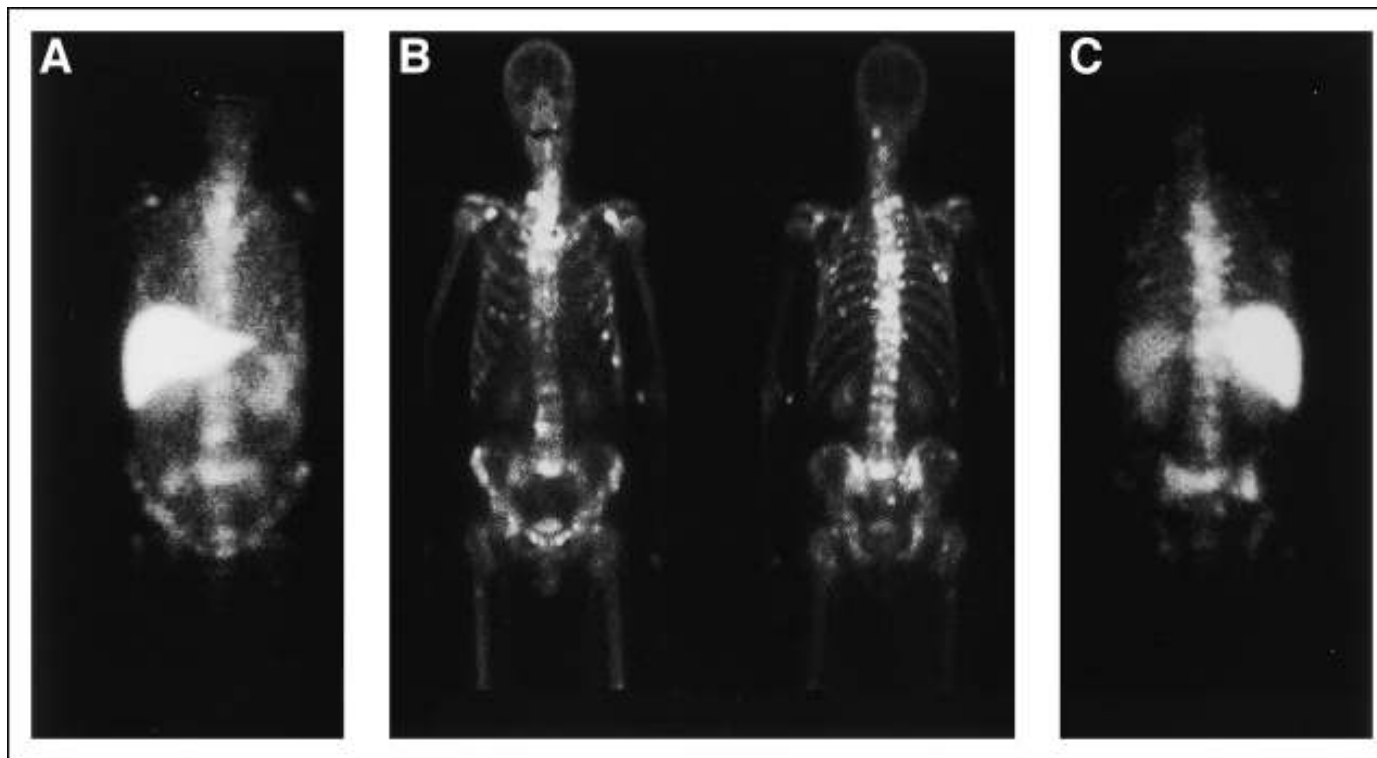
# RIT in Cancer of the Prostate

- Best target looks to be not PSA which is released into blood and occurs of dead cells but Prostate specific Membrane antigen-PSMA
- Anti-PSMA antibodies developed
- Binds to external domain of PSMA
- Radiolabelled by metals eg In-111, Y-90 and Lu-177 via DOTA

# Phase I trials of Y-90 J591

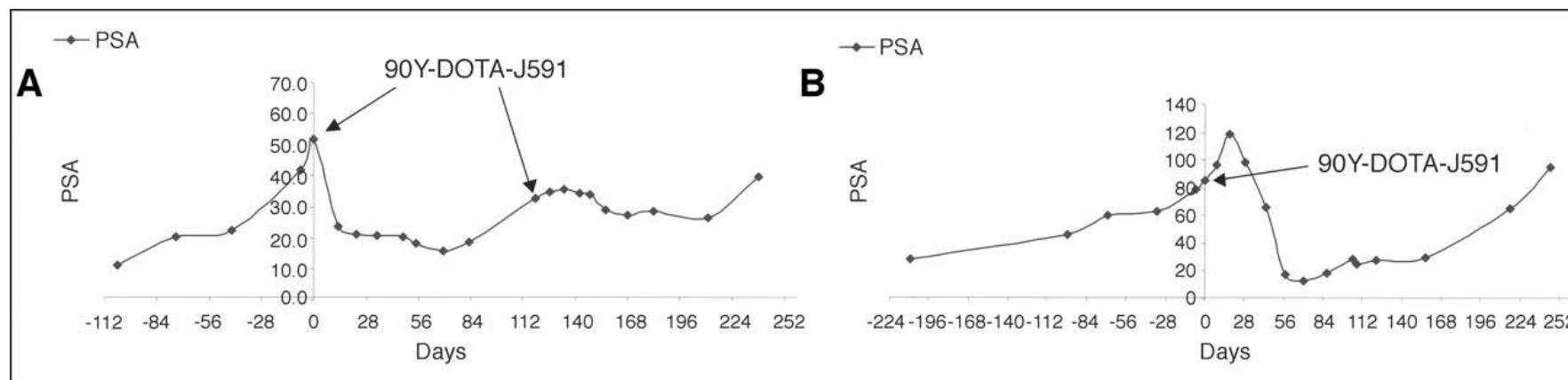
- Milowsky et al JCO 2004
- J Clin Oncol 2004 2522
- Looked at hormone resistant prostate cancer
- Dose escalation trial 185-3700 MBq per m<sup>2</sup>
- Pre-imaging with In-111 J591
- Used CT and PSA to monitor treatment

**Fig 1. Anterior and posterior (B) views of bone scan flanked by the respective indium-111 (111In)-J591 images (A, C)**



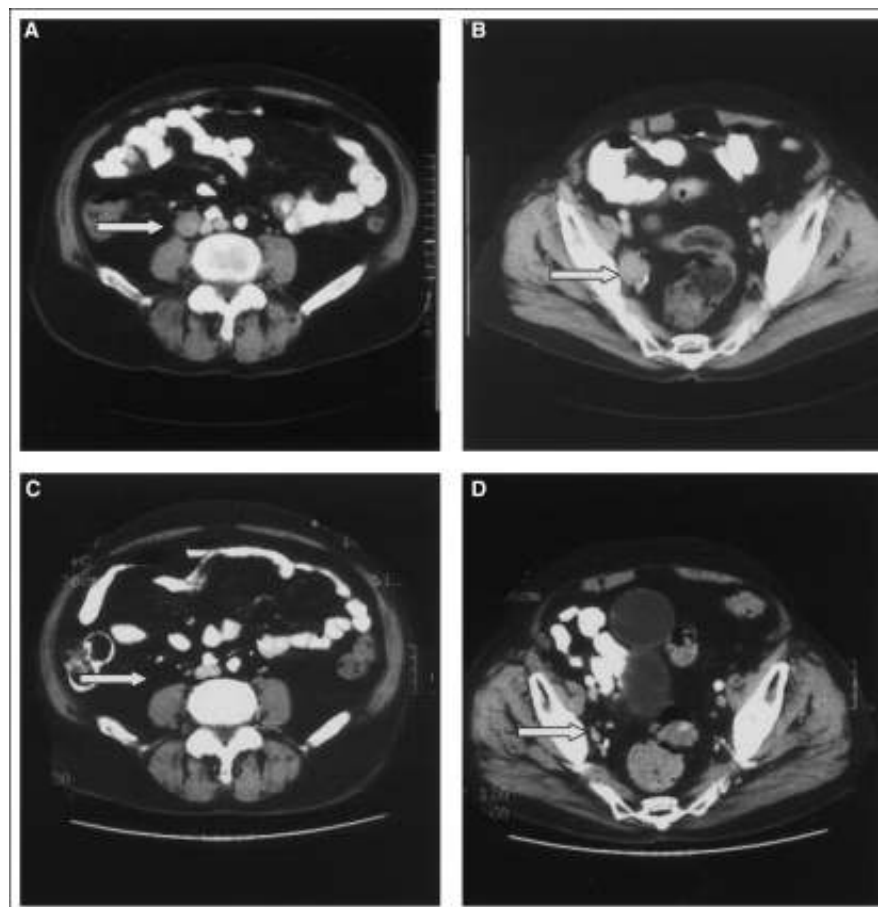
Milowsky, M. I. et al. J Clin Oncol; 22:2522-2531 2004

**Fig 2. Prostate-specific antigen (PSA) graphs for two patients at the 20 mCi/m2 dose level, demonstrating 70% (A) and 85% (B) declines in PSA lasting 8 and 8.6 months, respectively**



Milowsky, M. I. et al. J Clin Oncol; 22:2522-2531 2004

**Fig 3. Pretreatment (A,B) and 9-week posttreatment (C,D) computed tomography scans of the pelvis, revealing a partial response in lymphadenopathy seen in a patient with an 85% prostate-specific antigen decline treated at the 20 mCi/m<sup>2</sup> dose level**



**Milowsky, M. I. et al. J Clin Oncol; 22:2522-2531 2004**



# Three di-ScFv Forms

Di-scFv format chosen for anti-cancer modules



**diabody**

**Non-covalent**



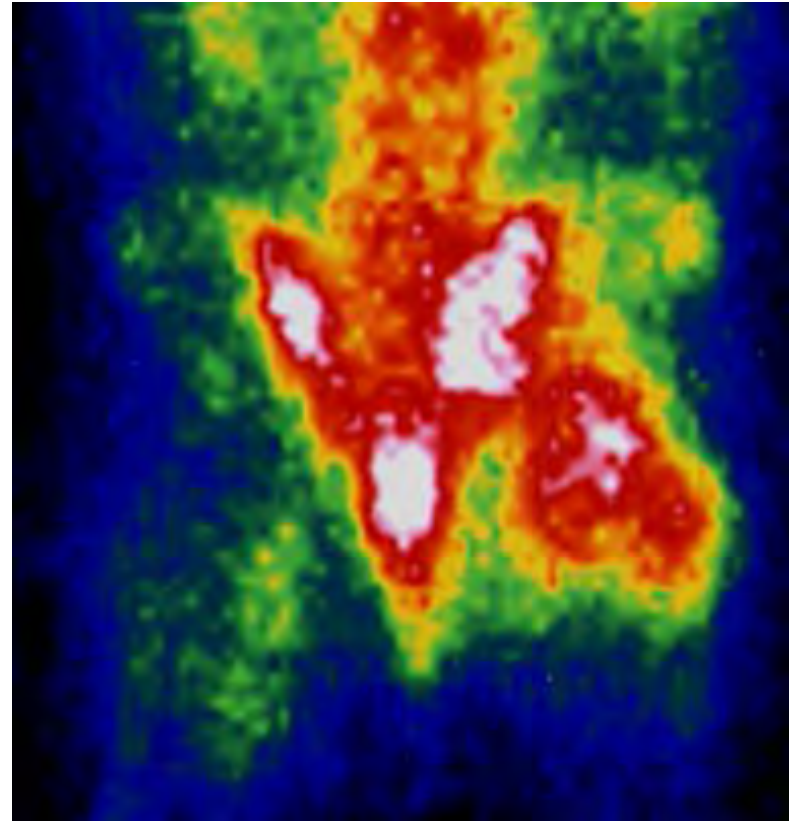
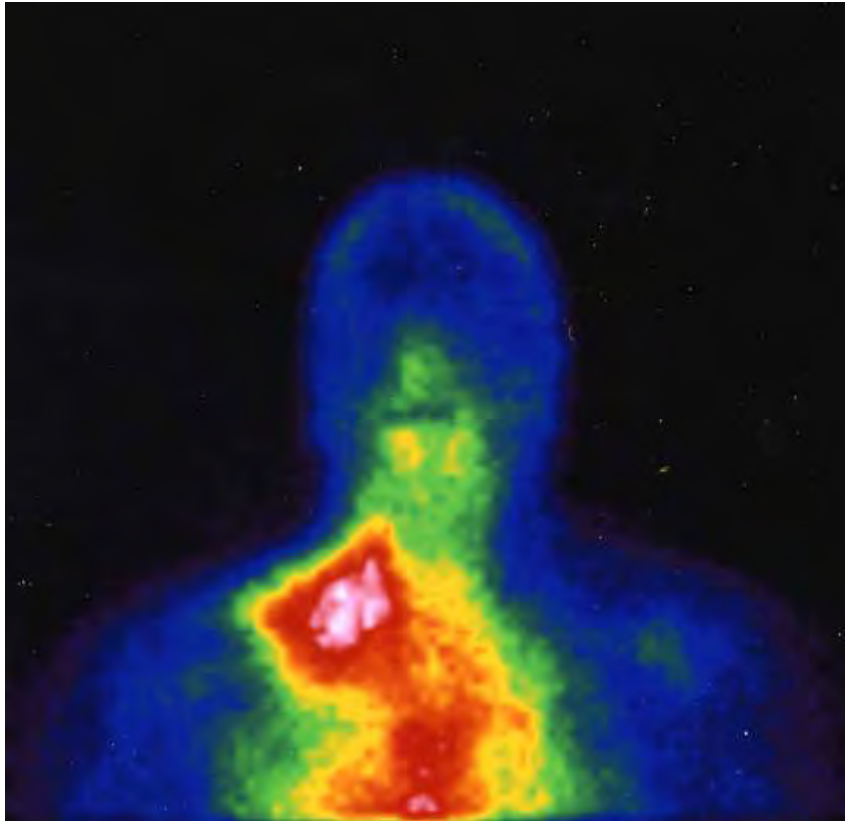
**sc(Fv')<sub>2</sub>**



**di-scFv or sc(Fv)<sub>2</sub>**



# MAb Targeting Muc1 Aberrant Sugar or Peptide Core Protein in metastatic Ca Prostate



# RIT in brain tumours

- Pagenelli et al Milan leaders in this field
- Use antibodies directed against Tenascin, over expressed in gliomas
- Have used three step biotin-streptavidin approach
- On own and in combination with chemotherapy –Temozolomide
- 75% of patients treated showed stabilisation in rapidly growing tumours

# The three stage technique



# Conclusions

- New horizons depend on where you are looking from
- Advances unlikely to be cheap
- Best results will be based on molecular knowledge of disease
- Part of combination therapy likely to provide best answers to therapy of common tumours