Gothenburg: Intraperitoneal ^{211}At-mAb treatment

The vector

- **Murine MX-35** (Sloan-Kettering Institute)
- Recognize, membrane sodium transporter (NaPi2b)
- $F(ab')_2$ fragments in Phase I study
- >90% of human epithelial ovarian cancers

A phase-I biodistribution and pharmacokinetic study

INCLUSION CRITERIA

- Histological confirmed ovarian adenocarcinoma
- Intra peritoneal recurrency following platinum/taxane based chemotherapy
- Treated by secondline to complete or good partial remission
- Normal baseline ***blood, liver, kidney, thyroid*** laboratory results
- Perfomance status of 2 or better
- Written informed consent prior to trial procedures.

EXCLUSION CRITERIA

- Active parenchymal disease, (i.e. FIGO IV)
- Prescence of symptomatic extra abdominal met
- Significant heart disease /arrythmias
- Concomittant serious illnesses, infection, bleeding
- Chronic inflammatory disease
- Treated with chemo or immunotherapy within 4w
- Previously recieved a murine antibody

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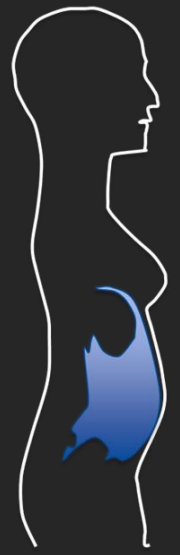


Clinical phase I trial

- J Nucl Med. 2019; 60:1073-1079
- J Nucl Med 2009; 50:1153-60

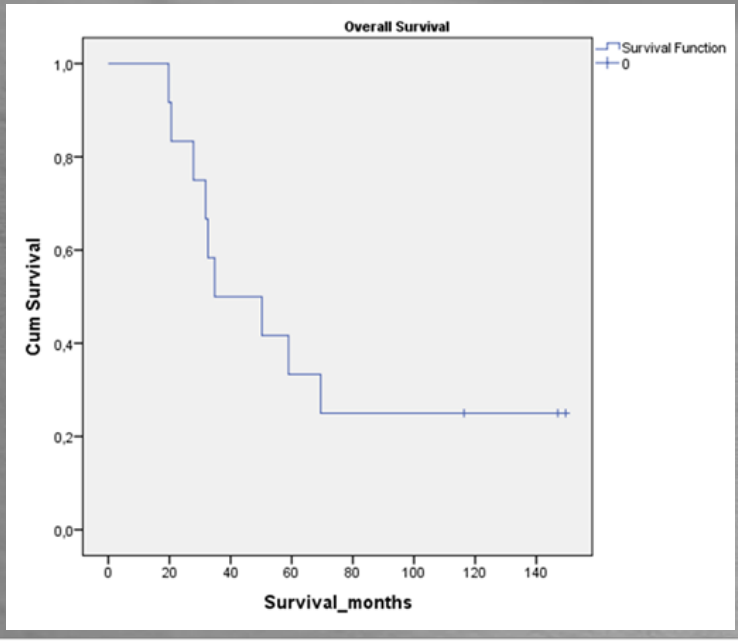
Modelling and dosimetry

- J Nucl Med. 2018; 59:646-651
- J Nucl Med, 2016; 57:594-600
- Int J Radiation Oncol Biol Phys, 2015; 93:569-576

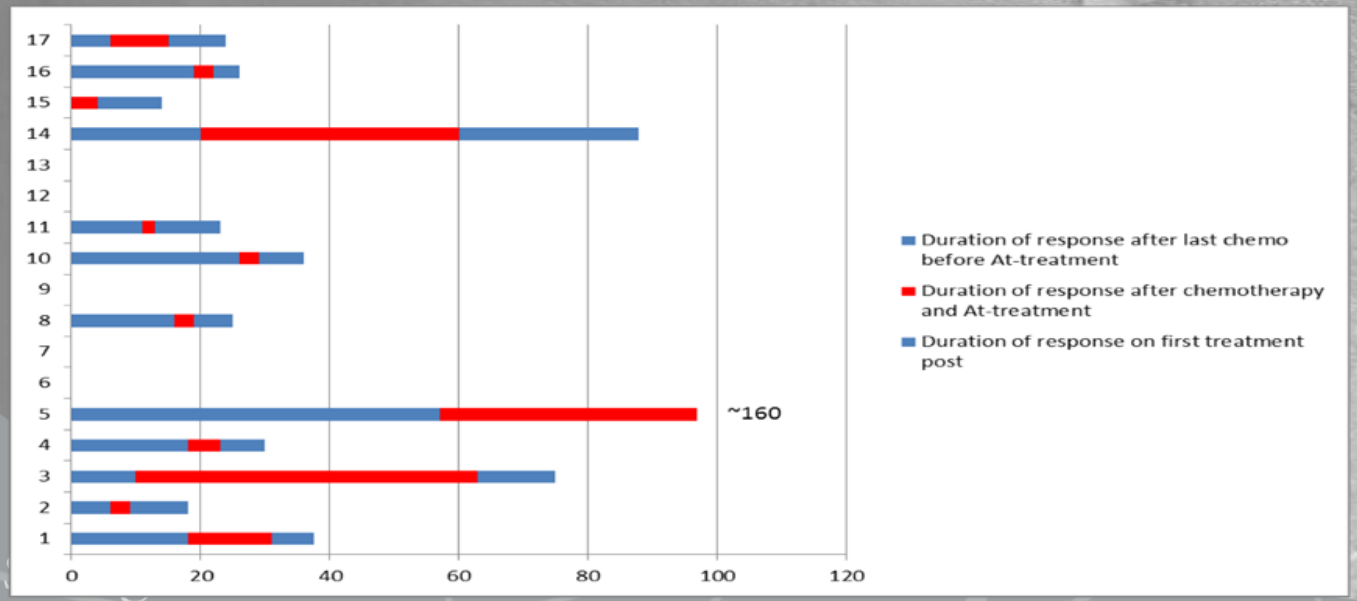
Patient-specific dosimetry

Patient No.	Conc. of IP infusion [MBq L^{-1}]	Administered activity [MBq]	Absorbed dose [mGy]			
			Red bone marrow	Thyroid	Peritoneum	Urinary bladder epithelium
P10	180	295	17	490	2300	80
P11	203	334	29	91	2800	300
P12	215	355	44	1200	2500	480

Clinical outcomes



Time to progression post-^{211}At (months)	Survival (years)	Time on chemo post-^{211}At (months)	Nb of lines§ post-^{211}At	Admin. total activity (MBq)	Activity concentration MBq/L	Approx. Specific Activity (nb ^{211}At/mAb)	Effective dose (Sv)
14.1	1.7	6.5	2	34	22	1/2400	0.3
4.0*	4.1	43	6	48	24	1/1400	0.3
54†	12.3‡	28	6	40	20	1/1800	0.3
5.1	5.7	46	10	42	21	1/700	0.3
N.A†	12.1‡			92	46	1/2100	0.6
3.3*	2.6	22	4	103	47	1/1800	0.6
4.0	2.3	26	6	119	101	1/1500	1.3
3.0	2.7	21	5	83	73	1/2300	0.9
41.3†	9.6‡	22	5	65	53	1/2900	0.7
5.0*	2.9	14	2	297	180	1/500	2.3
3.7*	1.6	14	3	333	203	1/200	2.6
9.6†	4.8	36	6	355	215	1/200	2.8



Single cell dose (Gy)	200µm sphere 10Gy isodepth(µm)	200µm sphere Vol(%) >10Gy	300µm sphere 10Gy isodepth(µm)	300µm sphere Vol(%) >10Gy
4.5	88	99.8	72	86
7.0	88	99.8	73	86
5.5	85	99.7	72	86
9.9	82	99.4	72	86
6.0	100	100.0	85	92
6.9	100	100.0	85	92
9.2	100	100.0	98	96
6.0	100	100.0	95	95
4.7	100	100.0	88	93
24.6	100	100.0	101	97
45.1	100	100.0	97	96
52.2	100	100.0	97	96

The relevance of calculating long term risk

- An adjuvant treatment to a curative treatment
- Enables an informed risk-benefit analysis
- Risk of adjuvant TAT vs risk of not giving adjuvant treatment

Estimating risk

- Effective dose (Sv) with W_r=20 for α-particles
- Correlating excess induced cancers with dose (Gy) from α-emitters

Absorbed dose and Effective dose estimate

Tissues	Abs. dose from α-particles [mGy]		Abs. dose from photons [mGy]			Tissue weighting factor w_T	Contribution to effective dose [mSv]
	Clinical data	Extrapolation of preclinical data	*Source:* IP fluid	*Source:* Circulation	Sum		
Breasts	20		0.10	0.06	0.15	0.12	48
Colon		33	1.31	0.10	1.41	0.12	79
Lungs	130	(150)	0.34	0.09	0.44	0.12	312
RBM	30		0.54	0.07	0.61	0.12	72
Stomach		192	1.39	0.10	1.49	0.12	461
Liver	50	(31)	1.25	0.09	1.34	0.04	40
Oesophagus	*55*				*0.08*	0.04	*44*
Thyroid	595	(977)	0.01	0.07	0.08	0.04	476
Urine Bladder	276		0.91	0.10	1.01	0.04	221
Bone surfaces	*55**		0.70	0.22	0.92	0.01	*11*
Brain	*55**		<0.01	0.08	0.08	0.01	*11*
Salivary glands		180			*0.08*	0.01	*36*
Skin	*55**		0.08	0.04	0.12	0.01	*11*
Adrenals			1.95	0.10	2.05	0.12	132
Gall bladder§				0.10			
Heart§	70	(60)	0.87	0.10	0.97		
Kidneys§	84	(97)	1.42	0.09	1.51		
Pancreas§			5.64	0.11	5.74		
Muscle§		18	0.49	0.07	0.57		
Small intestine§		45	2.33	0.10	2.43		
Spleen§		58	0.72	0.09	0.82		
Thymus§			0.12	0.09	0.21		

Methods – Inclusion criteria for studies

- Long time data for exposure to α-emitters
- Must include on an organ basis:

  - a measure of risk i.e. Standardized Incidence Ratio, Standardized Mortality Ratio or a control group.

  - dose (Gy) or activity that can be used to calculate the dose.

- 7 Thorotrast[1] (^{232}Th) studies and 3 ^{224}Ra[2] studies were suitable

1. Becker 2008, Travis 2003 (incidence + mortality), Dos Santos Silva 2003, Mori 1999 (mortality + autopsy), Kido 1999
2. Nekolla 2010, Wick 1999, Wick 2009

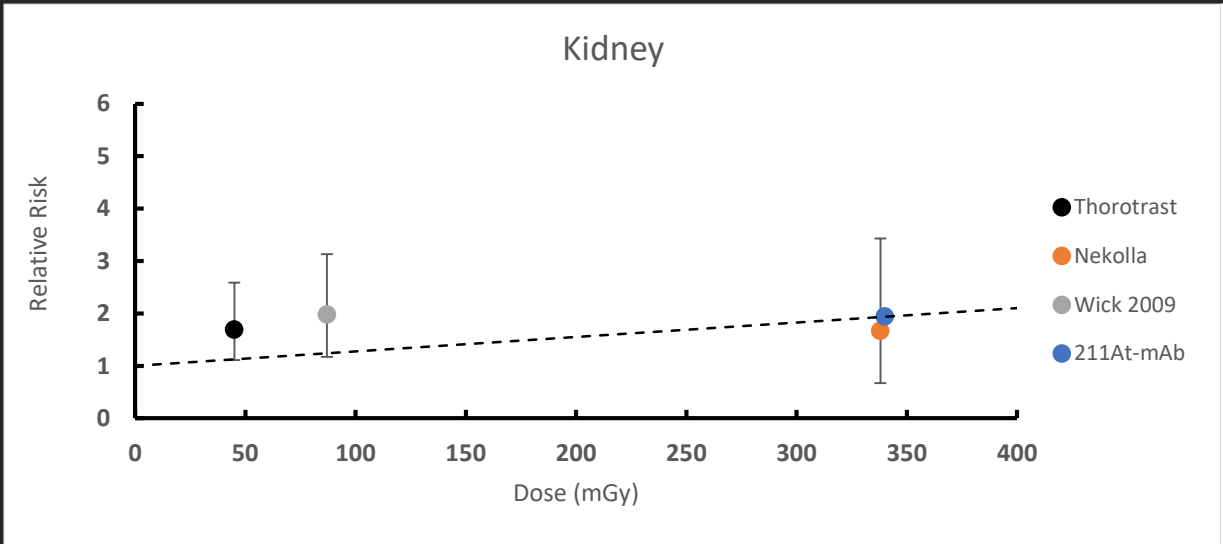
Methods

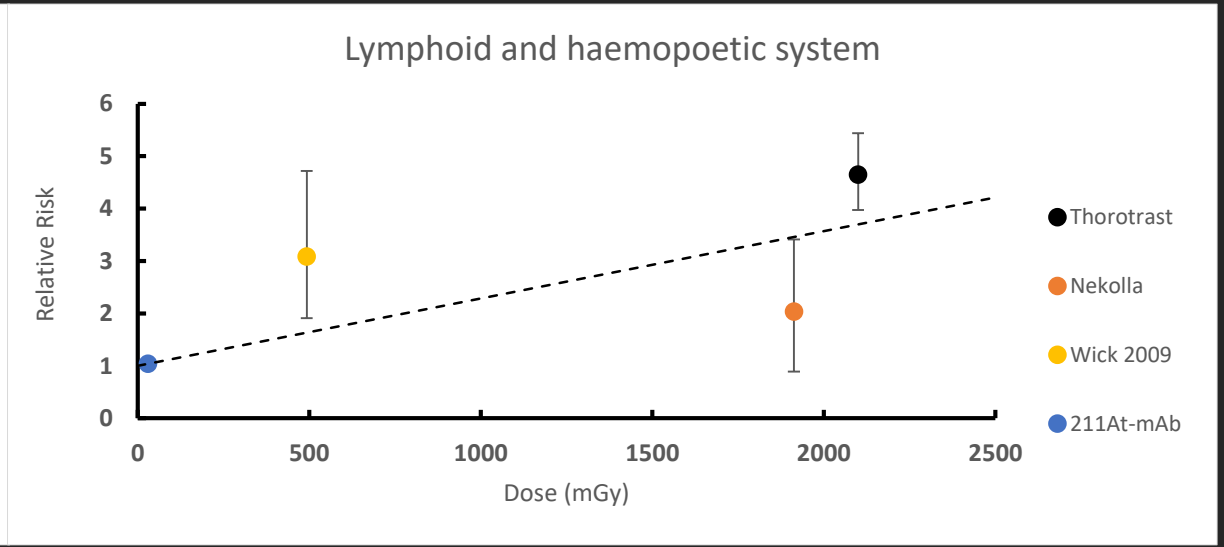
- Pooling data to reduce statistical uncertainty
- Calculating dose[3] for studies where only activity is given
- Plotting Risk vs Dose using least squares method
- Using cancer mortality data[4] for a typical patient to estimate excess risk

3. Radiat Environ Biophys (2002)41:173–178, Radiat Res (1993)135:244-248, Health Phys (1978)35:113-121

4. Global cancer observatory, Estimated number of new cases in 2018 worldwide, 2016 Nordic countries

Results





- Error bars represent a statistical confidence interval of 95%
- Dose[5] for ^{211}At-mAb treatment plotted for comparison

5. Int J Radiat Oncol Biol Phys (2015)93:569-76

Conclusions

- Large uncertainties in both dosimetry and risk ratios
- It’s the best available estimate of long term risk
- Necessary for Risk-Benefit analysis for therapies with curative intent

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ESTIMATION OF LONG-TERM RISKS FOR CANCER INDUCTION FOLLOWING ADJUVANT TARGETED ALPHA THERAPY WITH CURATIVE INTENT

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