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Theranostics for Cancer Imaging and Therapy

Disclosures

- I have no conflicts-of-interest to declare.

- I am collaborating with scientists at TRIUMF on development of novel theranostic agents for imaging and treatment of cancer, especially using novel Auger electron-emitting radionuclides.

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TRIUMF

Valerie Radchenko

Hua Yang

Caterina Ramogida

Cornelia Hoehr

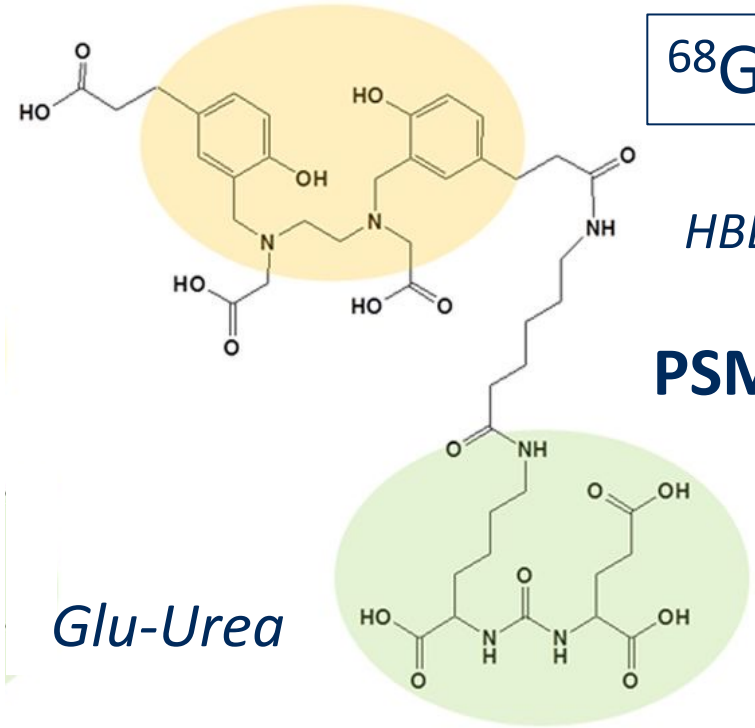
Theranostics Concept

- **Theranostics** (sometimes termed “theragnostics”) combine a **ther**apeutic agent with a diag**nostic** imaging agent for cancer.

- Radiopharmaceuticals offer the opportunity to construct a theranostic using the same molecule labeled with a radionuclide for treatment and another radionuclide for diagnostic imaging.

- In some cases, the same radionuclide may be used by administering a low dose for imaging and a high dose for treatment of cancer.

Prostate-Specific Membrane Antigen (PSMA) Theranostics

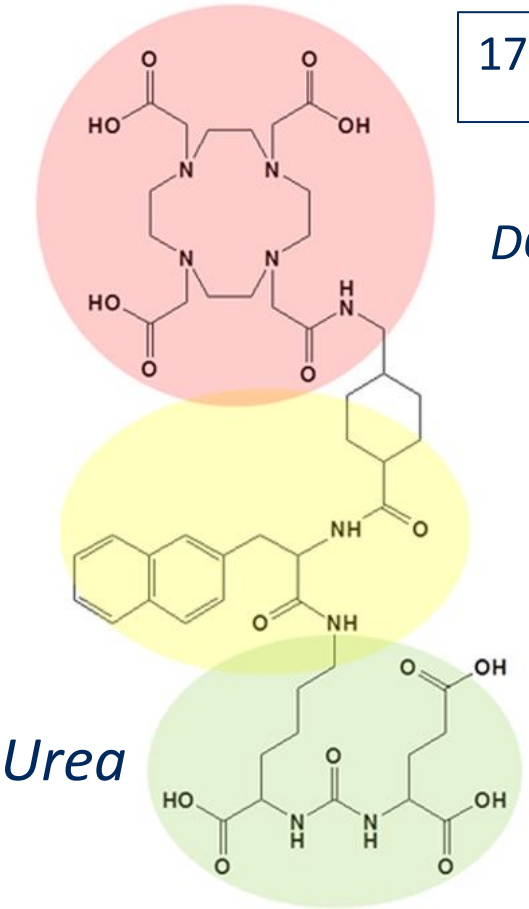


^{68}Ga

HBED-CC

PSMA-11

Glu-Urea

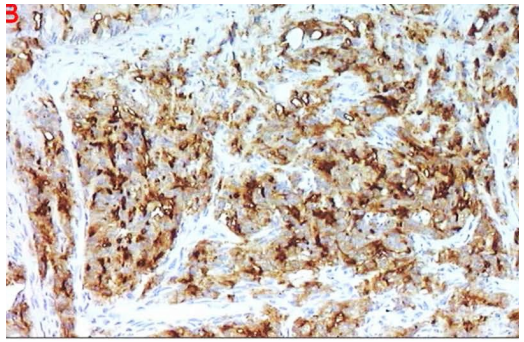


^{177}Lu ^{225}Ac

DOTA

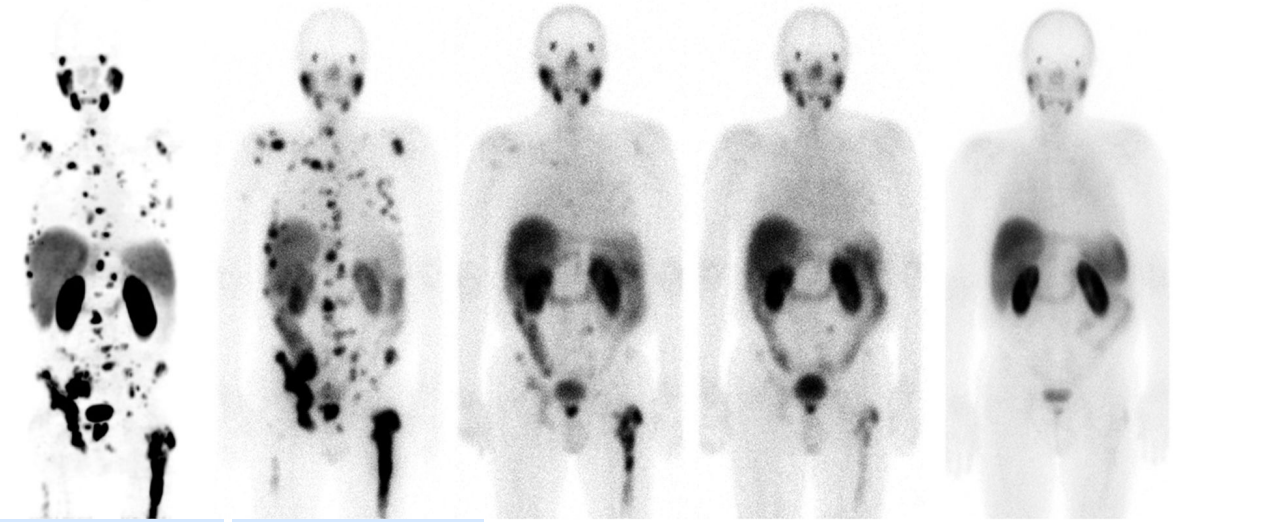
Glu-Urea

PSMA-617



PSMA Expression

Imaging and Treatment of Prostate Cancer

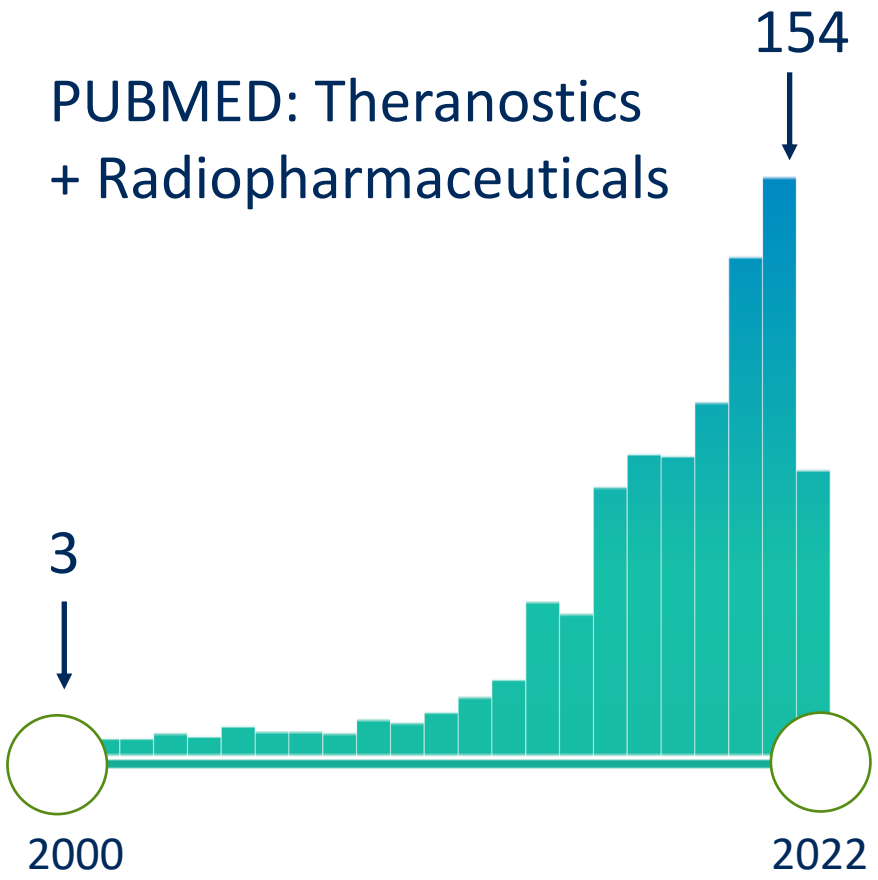


- Imaging of metastases and evaluation of treatment response by PET using ^{68}Ga-PSMA-11
- Treatment of metastatic prostate cancer with ^{177}Lu-PSMA-617 (6,000 MBq/dose)

Very successful theranostic example!

Kratochwil C. et al. J Nucl Med 2016; 57: 1170-1176

Growth in Interest in Theranostics



Novartis Pluvicto™ approved by FDA as first targeted radioligand therapy for treatment of progressive, PSMA positive metastatic castration-resistant prostate cancer

Mar 23, 2022

NOVARTIS

Global radiopharmaceutical market is expected to grow to **>$11 billion** from 2019-2023. High fraction of this market is for cancer imaging and treatment.

CANADIAN NUCLEAR ISOTOPE COUNCIL

Two Theranostic Examples from My Team's Research

Anthony Ku

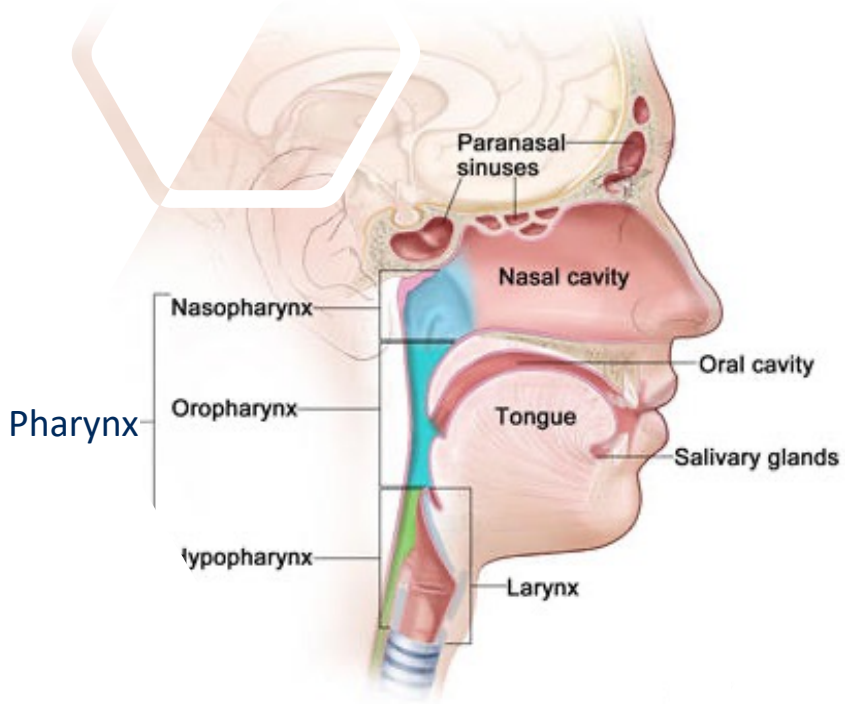
Imaging and radioimmunotherapy (RIT) of head and neck cancer (HNSCC)

Valerie Facca

Imaging and RIT of triple-negative breast cancer (TNBC)

Head and Neck Cancer (HNSCC)

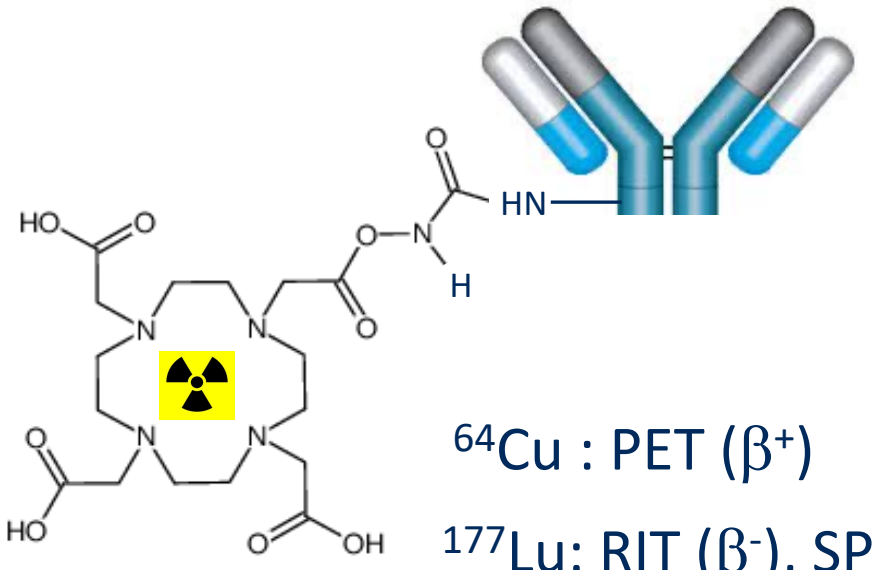
- 7,500 cases and 2,100 deaths per year in Canada. Long-term outcome is variable.
- EGFR overexpression is present on 38-47% of tumours and is targeted by cetuximab therapy but is a poor prognostic marker
- Recurrence and metastatic progression are major challenges after treatment by surgery, radiation, anti-EGFR cetuximab and chemotherapy.



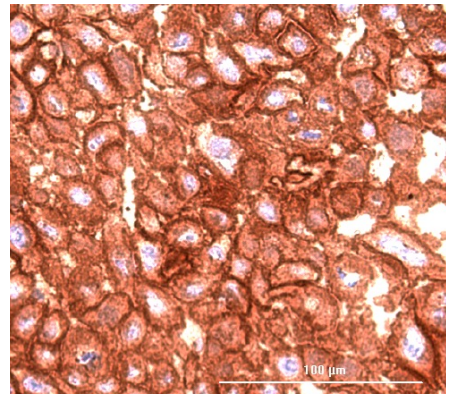
Hypotheses

- HNSCC tumours in mice could be imaged by PET/CT using ^{64}Cu-labeled anti-EGFR panitumumab F(ab')$_2$ fragments
- PET could be extended to radioimmunotherapy (RIT) in a theranostic approach using ^{177}Lu-panitumumab F(ab')$_2$
- PET with ^{64}Cu-panitumumab F(ab')$_2$ would predict the radiation absorbed doses to the tumour and normal organs from RIT with ^{177}Lu-panitumumab F(ab')$_2$

$^{64}Cu/^{177}Lu$-DOTA-Panitumumab F(ab')$_2$



DOTA



EGFR Positive HNSCC

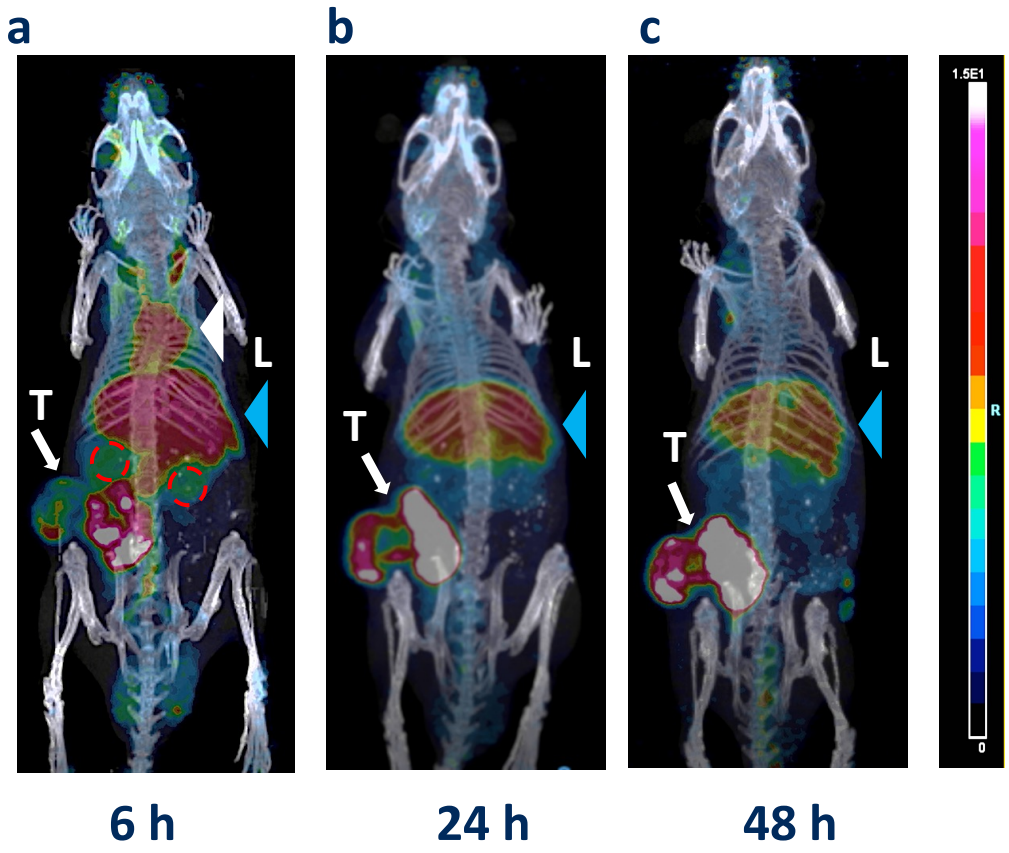
^{64}Cu : PET (β^+)

^{177}Lu: RIT (β^-), SPECT (γ)

$K_d = 2.9 \pm 0.7 \times 10^{-9}$ M

F(ab)$_2$ fragments were used to achieve high tumour uptake and rapid elimination from the blood for PET with ^{64}Cu ($t_{1/2}$ = 12.7 h)

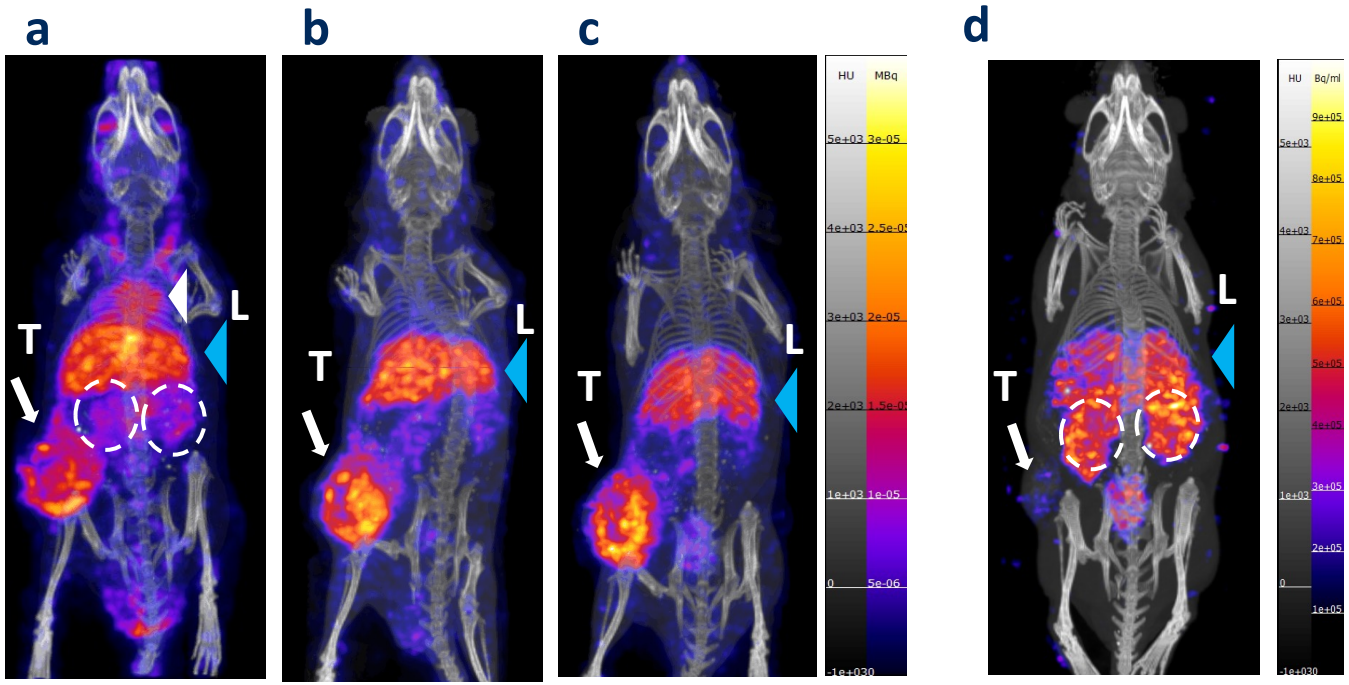
PET/CT Imaging with ^{64}Cu-DOTA-Panitumumab F(ab')$_2$



NRG mice with s.c. patient-derived HNSCC xenografts imaged at selected times post-i.v. injection of ^{64}Cu-panitumumab F(ab')$_2$ fragments. Normal liver uptake.

Ku, A et al. EJNMMI Radiopharmacy and Chemistry 2021 Aug 12;6(1):25.

SPECT/CT Imaging with ^{177}Lu-DOTA-Panitumumab F(ab')$_2$



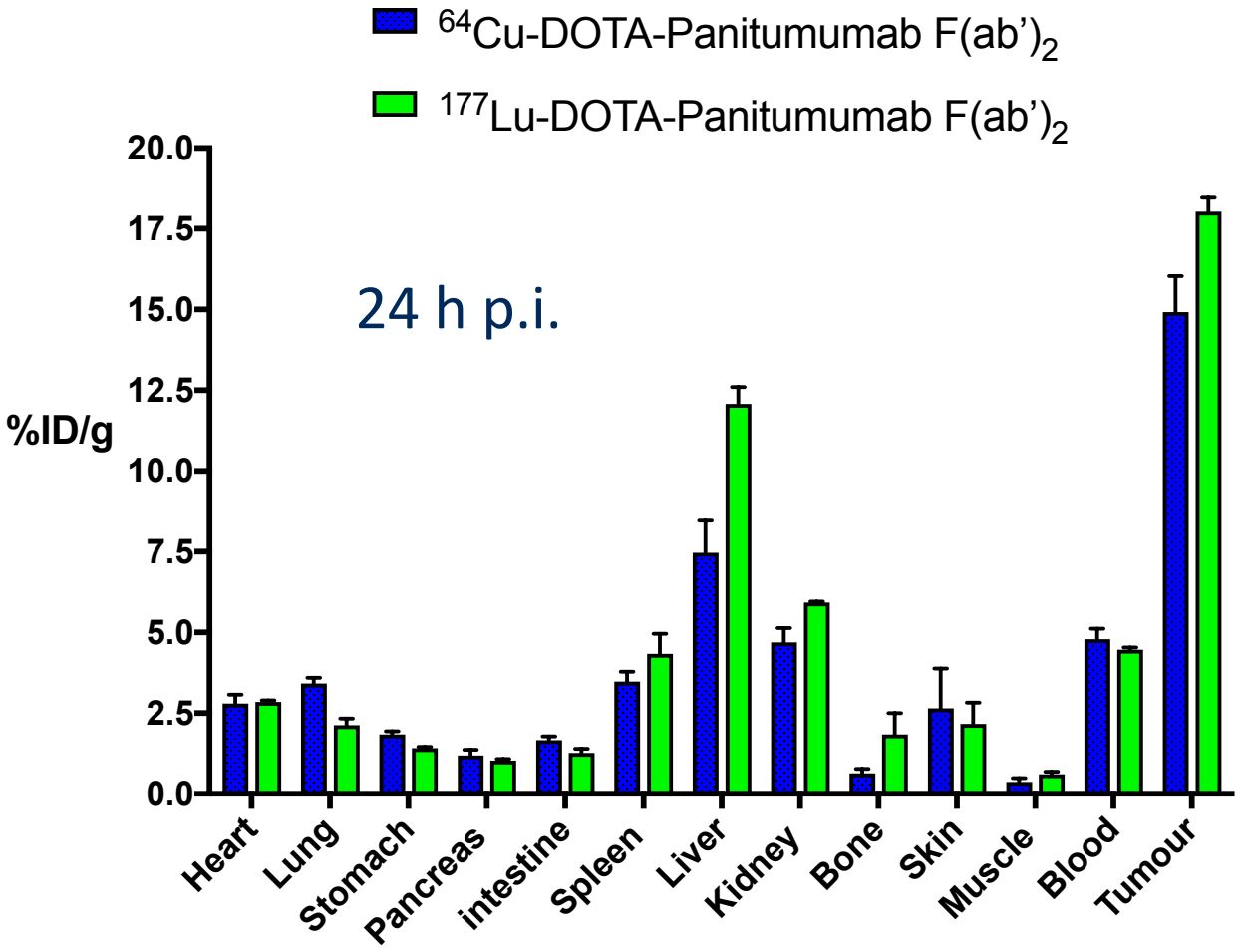
NRG mice with s.c. patient-derived HNSCC xenografts imaged at selected times post-i.v. injection of ^{177}Lu-panitumumab F(ab')$_2$ fragments.

^{177}Lu-DOTA-panitumumab F(ab')$_2$ ^{177}Lu-DOTA-trastuzumab F(ab')$_2$

Anti-HER2

Comparison of Biodistribution

- No significant differences at 24 h post-injection but small differences were found at 6 or 48 h in intestine, liver, blood, muscle, but not in the tumour



PET with ^{64}Cu Predicts the Dosimetry of ^{177}Lu

MIRD Equation:

$$D = \tilde{A}_s \times S \times W_R$$

^{64}Cu ^{177}Lu

Surrogate for ^{177}Lu

Organ	Radiation Equivalent Dose (Gy/MBq)	
	Predicted Based on ^{64}Cu	Estimated Based on ^{177}Lu
Heart	0.35 ± 0.06	0.32 + 0.13
Lungs	0.51 ± 0.05	0.38 ± 0.04
Liver	1.22 ± 0.13	1.82 ± 0.14
Spleen	0.71 ± 0.20	0.66 ± 0.18
Pancreas	0.26 ± 0.08	0.16 ± 0.04
Stomach	0.33 ± 0.03	0.27 ± 0.04
Intestines	0.31 ± 0.05	0.21 ± 0.05
Kidneys	0.63 ± 0.09	0.75 ± 0.08
Tumour	2.00 ± 0.60	2.50 ± 0.80
Whole Body	0.26 ± 0.02	0.34 ± 0.02

No significant differences

Toxicity of ^{177}Lu-DOTA-Panitumumab F(ab')$_2$

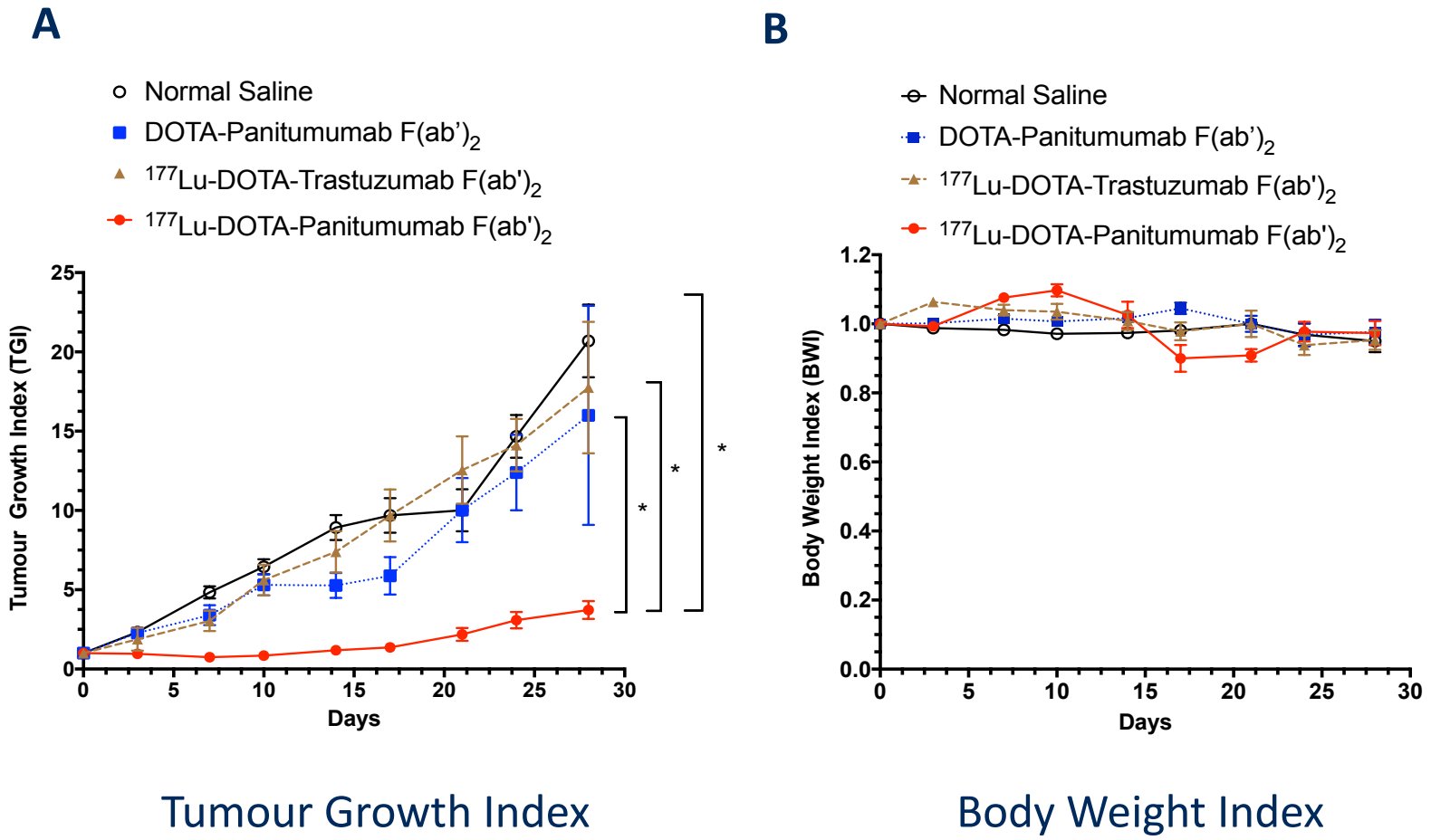
Injected dose = 6 MBq (50 μg)

Deliver a tumour absorbed dose of 12-15 Gy based on 2.0-2.5 Gy/MBq

Parameter	Normal Saline	^{177}Lu-DOTA-Panitumumab F(ab')$_2$
WBC (x 10^9/L)	1.4 ± 0.4	1.0 ± 0.3
RBC (x 10^{12}/L)	9.0 ± 0.2	8.7 ± 0.2
PLT (x 10^9/L)	527.3 ± 66.9	413.0 ± 15.3
Hb (g/L)	14.5 ± 0.6	13.4 ± 0.3
Hct (%)	39.9 ± 0.8	39.4 ± 0.7
ALT (U/L)	41.0 ± 13.1	31.5 ± 9.3
Cr (μmole/L)	18.0 ± 0.0	21.0 ± 2.1

No significant differences

RIT of HNSCC Tumours with ^{177}Lu-DOTA-Panitumumab F(ab')$_2$



Tumour Growth Index

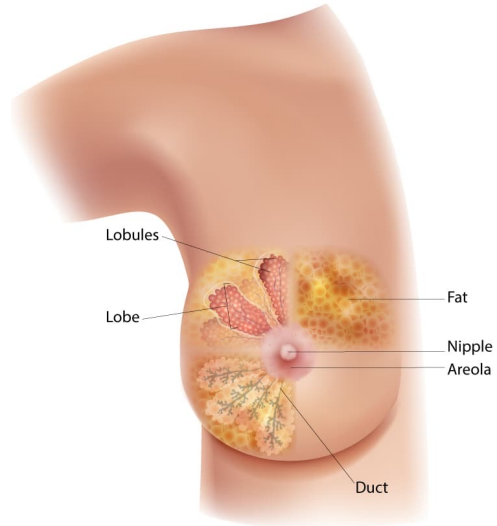
Body Weight Index

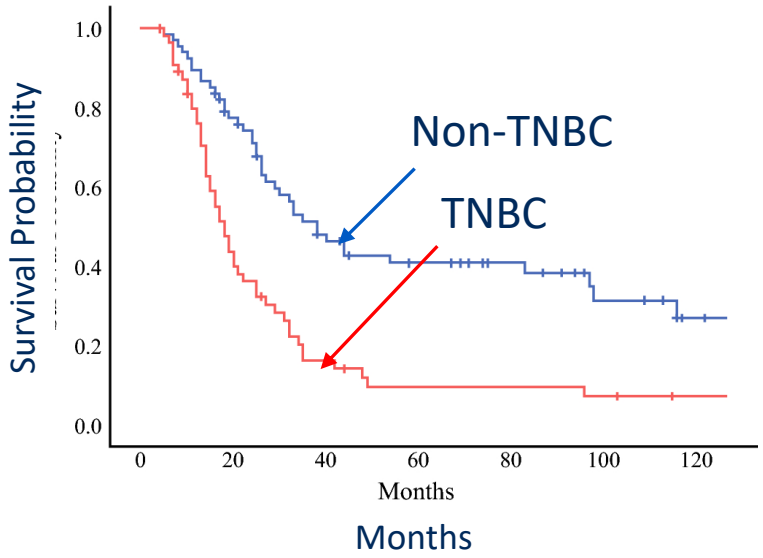
Conclusions and Implications

- HNSCC was imaged by PET with ^{64}Cu-DOTA-Panitumumab F(ab')$_2$. PET predicted the radiation absorbed doses from RIT with ^{177}Lu-panitumumab F(ab')$_2$
- ^{177}Lu-DOTA-panitumumab F(ab')$_2$ was safe and effective for RIT of HNSCC tumours in NRG mice.
- A theranostic approach combining ^{64}Cu- and ^{177}Lu-DOTA-panitumumab F(ab')$_2$ is promising for imaging and treatment of HNSCC

Triple-Negative Breast Cancer (TNBC)

- 28,900 cases and 5,500 deaths from breast cancer each year in Canada. TNBC accounts for 10-15% of cases but has a higher risk for progression and poor outcome.
- TNBC is defined as breast cancer that does not express estrogen or progesterone receptors or HER2.
- EGFR overexpression is present on 50-90% of tumours and is a poor prognostic marker but a good target.



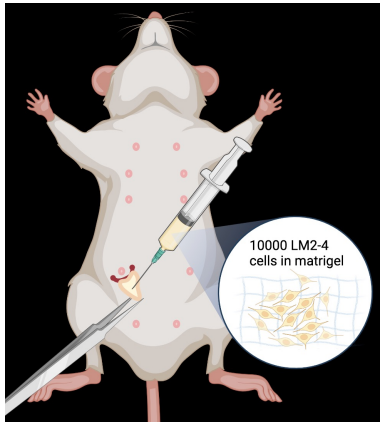


Hamy A-S, et al. (2020) PLoS ONE 15(6): e0234191.

Hypotheses

- TNBC tumours in NRG mice could be imaged by SPECT/CT using ^{111}In-panitumumab intact IgG.
- SPECT/CT could be extended to RIT in a theranostic approach by exploiting the Auger electron (AE) emissions of ^{111}In.
- RIT with ^{111}In-panitumumab IgG would be safe and effective for treatment of primary and metastatic TNBC tumours in NRG mice.

TNBC Tumour Xenograft Models

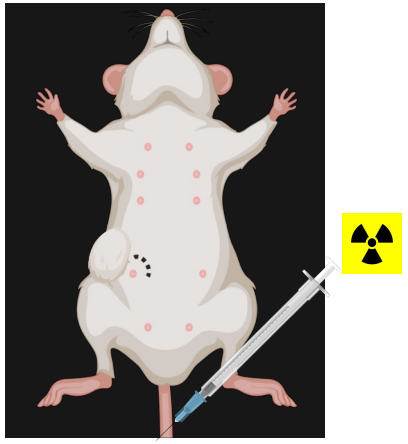


21 days

Inoculate LM2-4/Luc Cells into the MFP of NRG mice

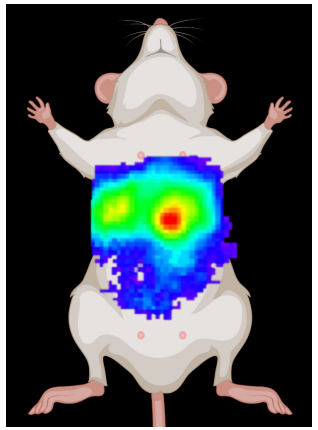
Surgical Excision

Local XRT



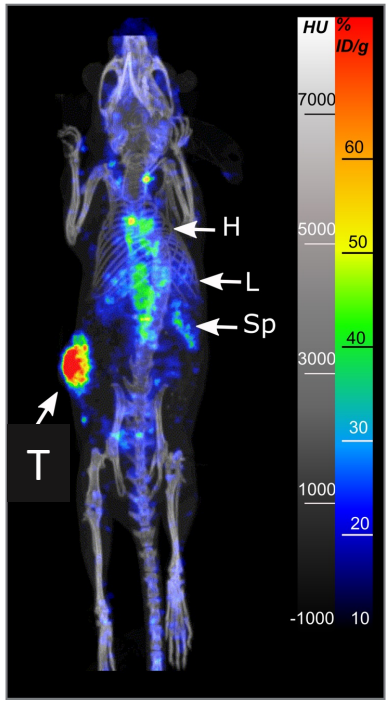
RIT

1-2 weeks



BLI

SPECT/CT Imaging with ^{111}In-DOTA-Panitumumab IgG (48 h post-injection)

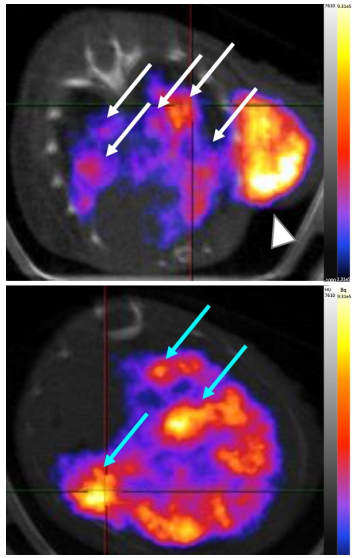


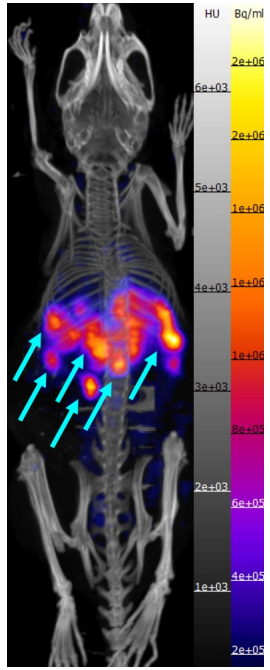
Primary Tumour

Transaxial

Lungs

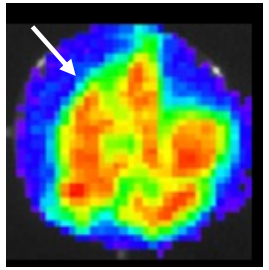
Liver

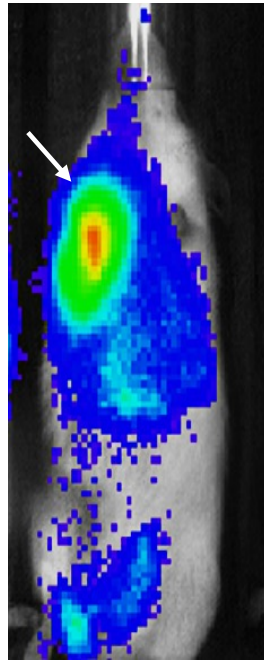




Metastases

Transaxial





BLI

Toxicity of ^{111}In-DOTA-Panitumumab IgG

Injected dose = 24 MBq (15 μg)

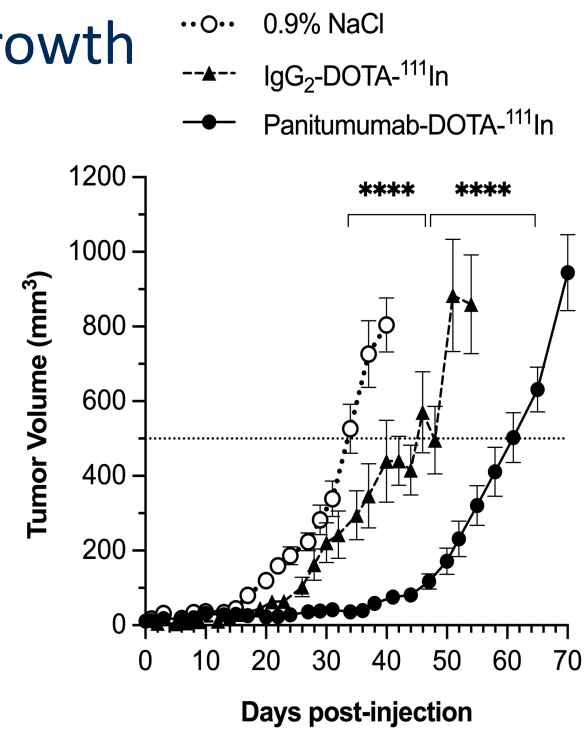
Selected in a dose-escalation study.

Parameter	Normal Saline	^{111}In-DOTA-Panitumumab IgG
WBC (x 10^9/L)	0.9 ± 0.2	0.5 ± 0.1
RBC (x 10^{12}/L)	9.4 ± 0.2	8.5 ± 0.2
PLT (x 10^9/L)	497.5 ± 46.2	254.0 ± 62.6 *
Hb (g/L)	14.2 ± 0.3	13.0 ± 0.3
Hct (%)	41.2 ± 0.9	38.3 ± 1.1
ALT (U/L)	40.9 ± 7.6	47.3 ± 11.8
BUN (μmole/L)	7.9± 0.4	8.5 ± 0.4

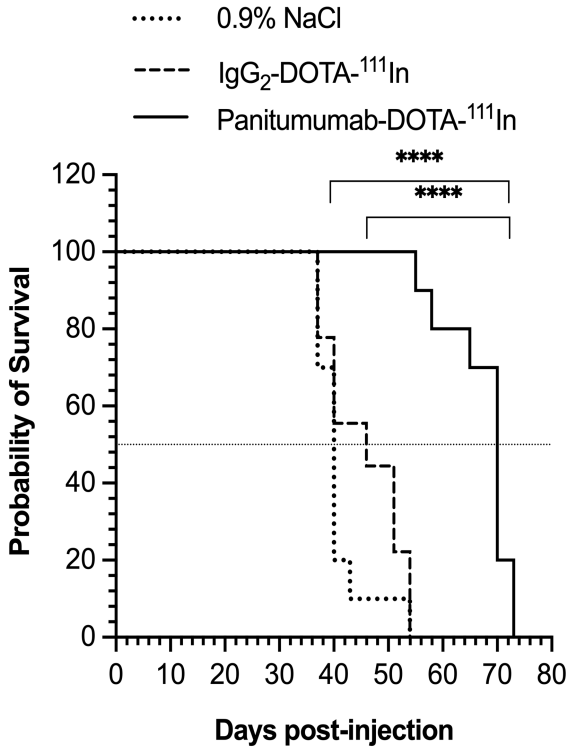
* Significant difference

RIT of Primary TNBC Tumours in the MFP with ^{111}In-DOTA-Panitumumab IgG

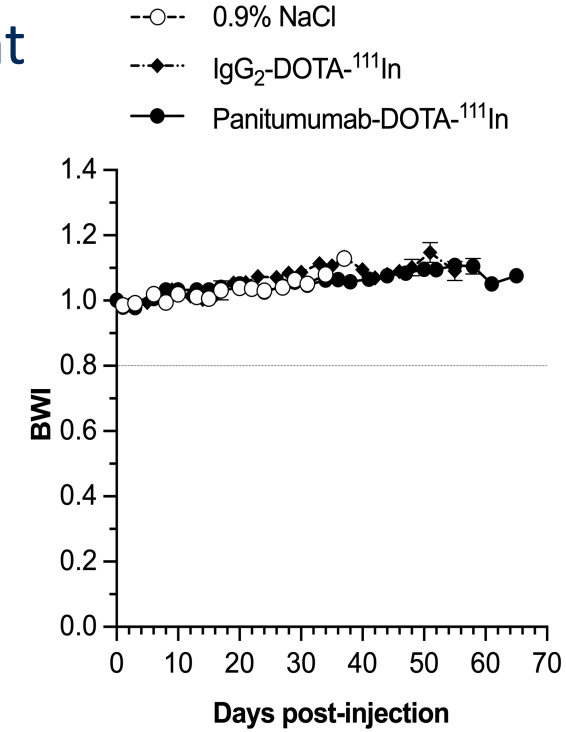
Tumour Growth



Survival

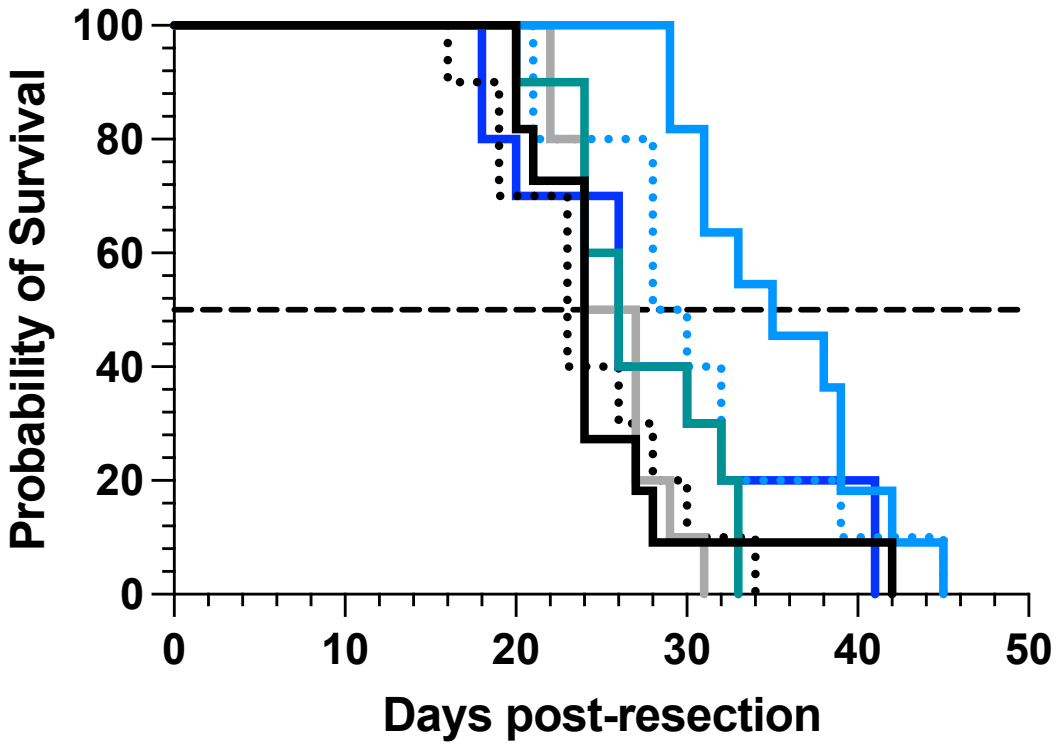


Body Weight



Facca, V et al. Mol. Pharm. 2022 (in revision).

RIT of Metastatic TNBC Tumours with ^{111}In-DOTA-Panitumumab IgG



- Saline
- 24 MBq Panitumumab-DOTA-^{111}In
- XRT + Saline
- XRT + 24 MBq PmAb-DOTA-^{111}In
- XRT + 2x10 MBq PmAb-DOTA-^{111}In
- XRT + PmAb-DOTA
- XRT + 24 MBq IgG_2-DOTA-^{111}In

RIT improves survival in mice with metastatic TNBC, when combined with other treatments including surgery and local radiation of the primary tumour

Conclusions and Implications

- EGFR-positive primary and metastatic TNBC tumours in NRG mice were imaged with ^{111}In-DOTA-Panitumumab IgG
- RIT with ^{111}In-DOTA-Panitumumab exploiting the AE emissions delayed tumour growth and improved survival of mice with primary or metastatic TNBC tumours
- A theranostic approach with ^{111}In-DOTA-Panitumumab IgG is promising for imaging and RIT of TNBC and may improve patient outcomes

Alternative Auger Electron-Emitters

Radionuclide	T1/2 (days)	AEs/decay	Total Energy (keV)	Other Emissions/AEs	Production
^{197}Hg	2.7	~30	13.4	10:1	^{197}Au(p,n)^{197}Hg
^{119}Sb	1.6	24	26.0	0.9:1	^{119}Sn(p,n)^{119}Sb
^{111}In	2.8	14.5	7.0	62:1	^{111}Cd(p,n)^{111}In

Novel chelators are needed to complex ^{197}Hg to panitumumab
(collaboration with Dr. Caterina Ramogida, SFU)

TRIUMF

Thank you for the invitation to speak at the TRIUMF Science Week!

Acknowledgments

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Canadian Cancer Society

NSERC CRSNG