Imaging, targets and amplifying cell death in malignancy

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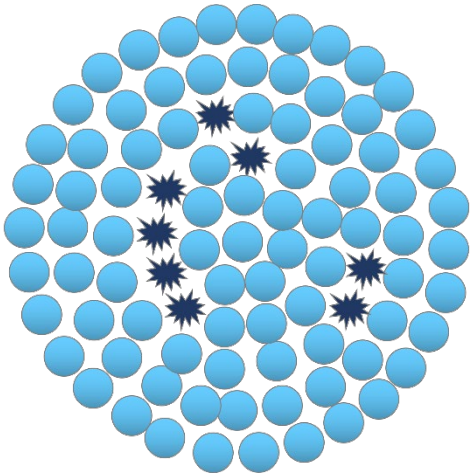
Centenary Institute life saving research
Cancer. Inflammation. Cardiovascular.

Constitutive cell death is a feature of tumours

Tumour



viable tumour cell

dying/dead tumour cell

Reason for formation

Some highly proliferative tumour cells don't receive enough of the blood's nutrients to survive

Reasons for slow clearance

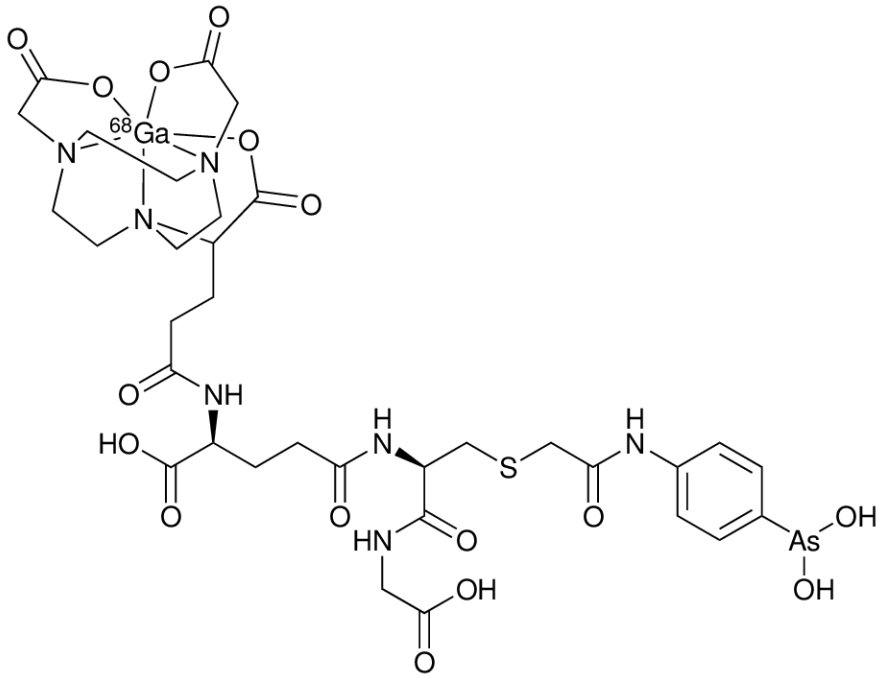
Not enough macrophages in tumours to clear the dying/dead cells

Dying/dead tumour cells express macrophage 'don't eat me' signals

High levels of constitutive tumour cell death correlates with poor outcomes in several cancers

Tumour type	Reference
Bladder carcinoma	Jalalinadoushan et al. *Urol J*, 2004
Breast carcinoma	Villar et al. *Tumour Biol*, 2001
Colorectal carcinoma	Bendardaf et al. *Oncology*, 2003
Glioblastoma	Sarkar et al. *J Neurooncol*, 2005
Malignant mesothelioma	Beer et al. *Ann Diagn Pathol*, 2000
Lymphoma	Leoncini et al. *Am J Path*, 1993
Non-small cell lung cancer	Tormanen et al. *Cancer Res*, 1995
Pancreatic duct carcinoma	Meggiato et al. *Pancreas*, 2000
Squamous carcinoma of the tongue	Naresh et al. *Cancer*, 2001

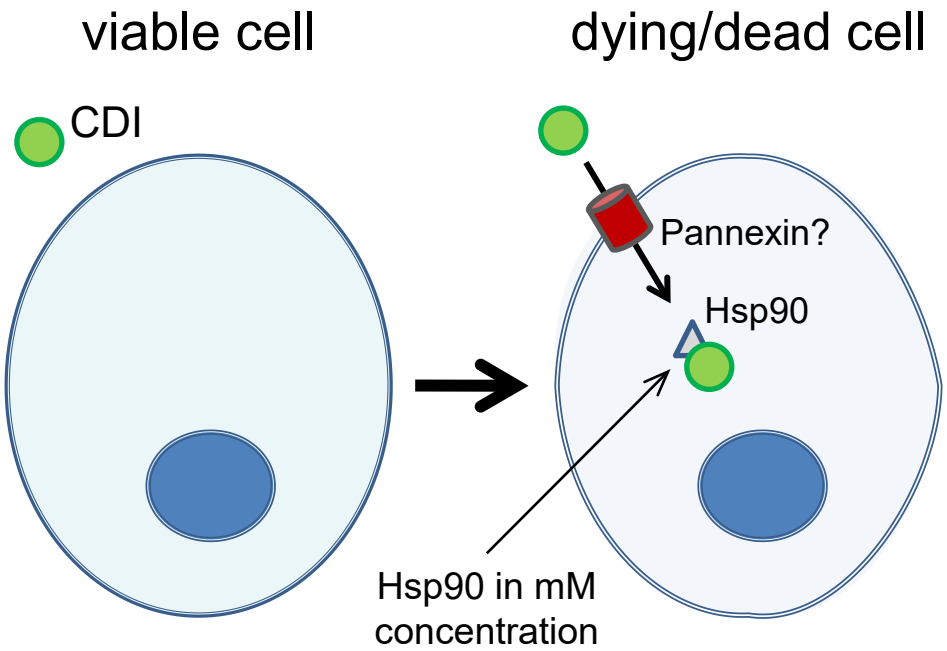
^{68}Ga-CDI (Cell Death Indicator) for PET imaging of tumour cell death

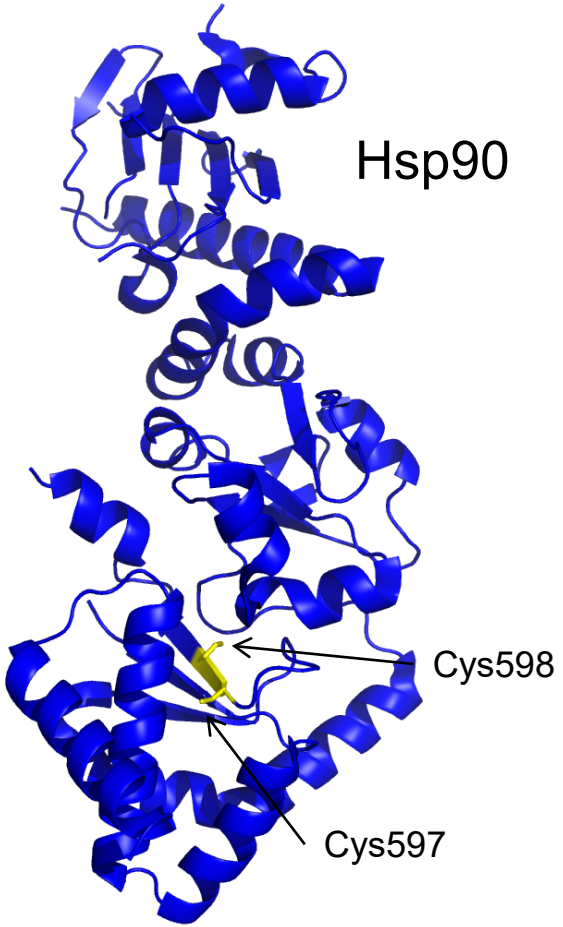


^{68}Ga-CDI

Ho Shon…Hogg, *Methods Mol Biol*, 2019
Ho Shon…Hogg, *EJNMMI*, 2020
Ho Shon…Hogg, *Curr Radiopharm*, 2021

CDI mechanism of action





Park…Hogg, *JACS*, 2011
Xie…Hogg, *Cell Death Dis*, 2013

Clinical development of CDI-PET

First-in-human trial

5 participants at Prince of Wales Hospital with at least one extracranial site of solid malignancy >2 cm and no active cancer treatment in the 8 weeks prior to the study were enrolled.

^{68}Ga-CDI is safe, has low radiation dosimetry and excellent biodistribution and imaging characteristics. It images constitutive tumour cell death and correlates with tumour cell death on histology.

Ho Shon…Hogg, *EJNMMI*, 2022

Diagnostic proof-of-concept trial

36 participants at 5 sites (POWH, SGH, SVH, Concord, Westmead) with oesophageal/gastro-oesophageal junction carcinoma or rectal cancer, breast cancer, diffuse large B cell lymphoma or grade III follicular lymphoma.

13 enrolled (5 GI, 4 lymphoma, 4 BC)

Pre-treatment CDI-PET scan within 14 days prior to cancer treatment. Post-treatment CDI-PET scan between 3-8 days or 15-20 day following commencement of treatment.

Pancreatic cancer trial

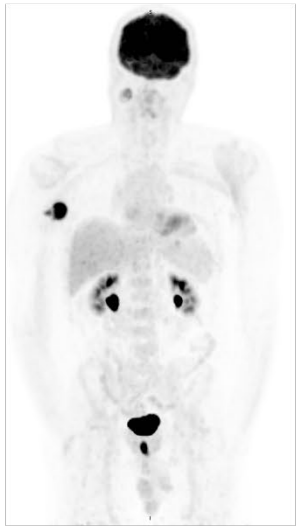
96 participants at up to 10 sites with borderline resectable, locally advanced and metastatic pancreatic ductal adenocarcinoma (PDAC).

First patient December 2024

Pre-treatment CDI-PET scan within 14 days prior to cancer treatment. Phase 1 is post-treatment CDI-PET scan between 3-7 days and 17-21 days following commencement of treatment. Phase 2 will utilise one of those time points.

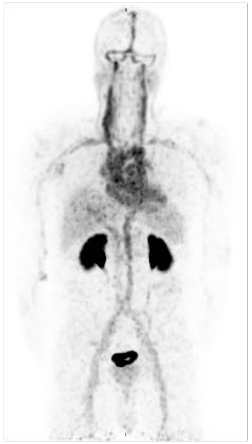
Primary end points 4 months after Tx initiation. Long term follow-up 12 or 24 months after Tx initiation.

Metastatic squamous cell carcinoma (from 2 primaries)

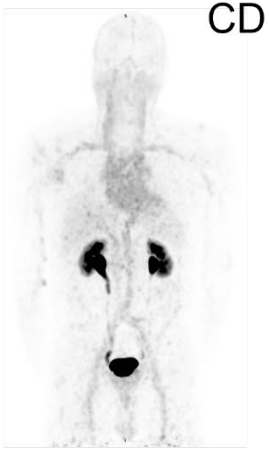


FDG-PET CT
60 min

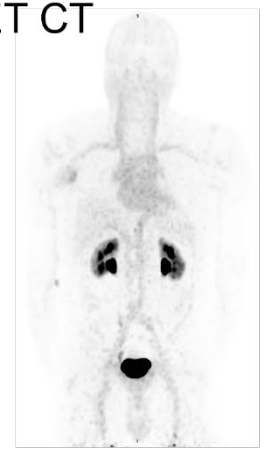
CDI-PET CT



0 min



7 min



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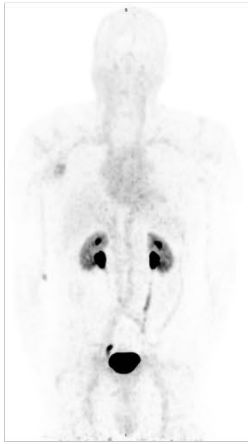
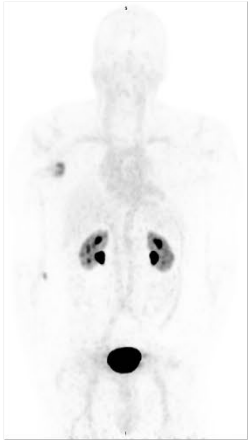


24 min



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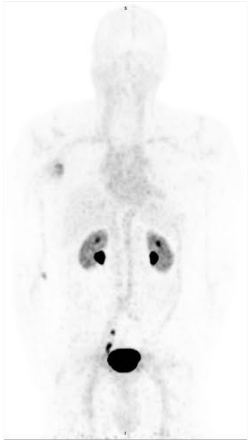
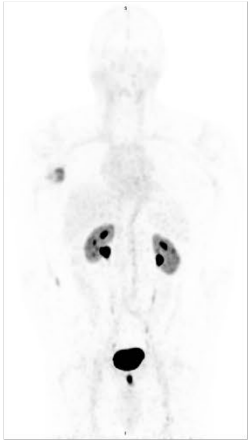
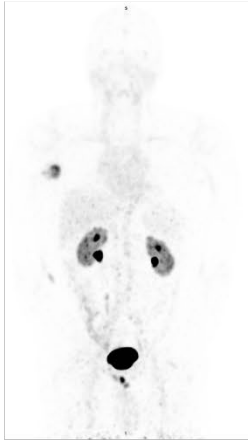


60 min

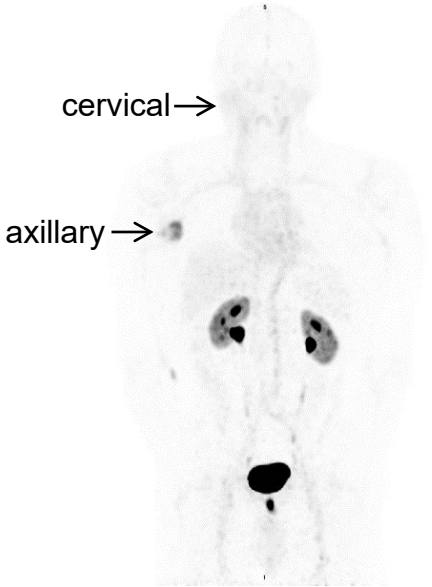


120 min

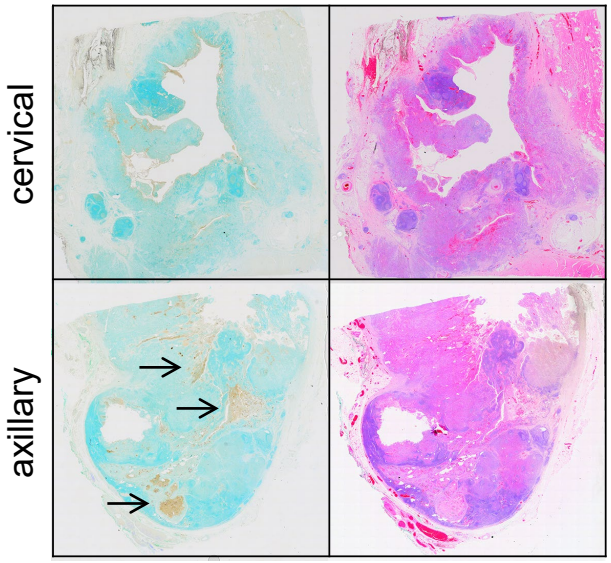


185 min

CDI-PET intensity correlates with extent of dead cells in human tumours

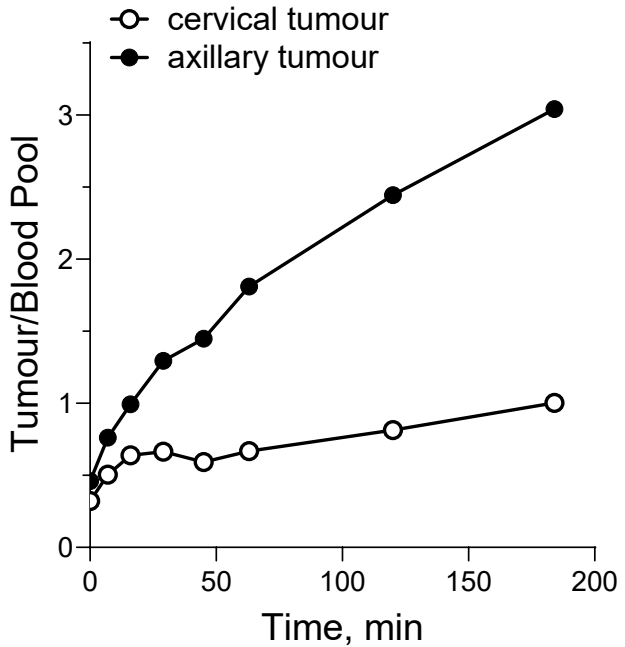


CDI-PET



TUNEL H&E

CDI continues to accumulate in dead and dying tumour cells



CDI-PET imaging of lymphoma

Intensely metabolically active disease centred on the right palatine tonsil and right level IIA lymph nodes.

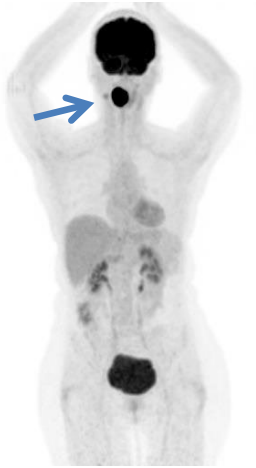
Low levels of cell death.

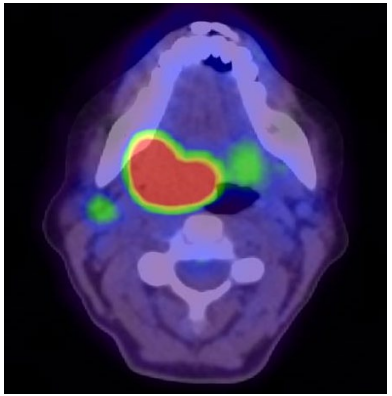
Stable disease for at least 6 weeks and responded well to treatment.

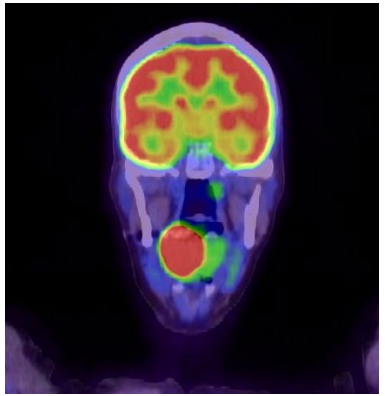
transaxial

coronal

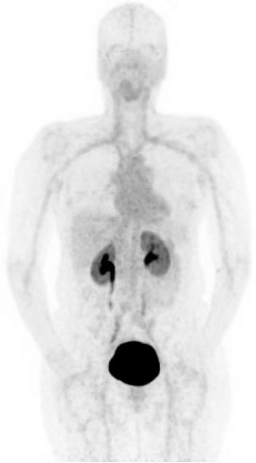
FDG-PET

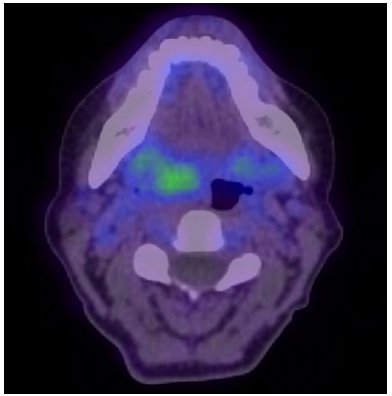


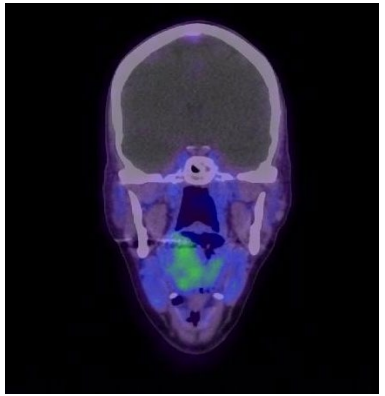




CDI-PET







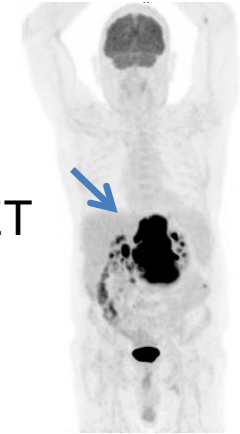
CDI-PET imaging of lymphoma

Intensely metabolically active disease in the abdomen centred on the stomach and involving multiple mesenteric and retroperitoneal lymph nodes.

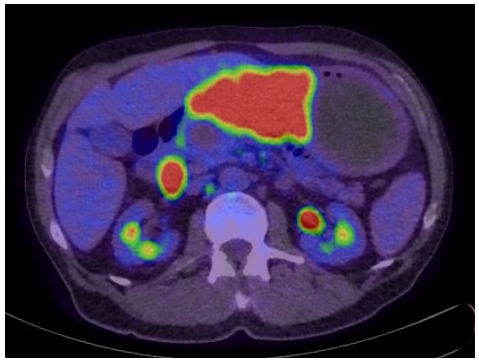
Substantial heterogeneous cell death.

Condition rapidly deteriorated and was moved to palliative care.

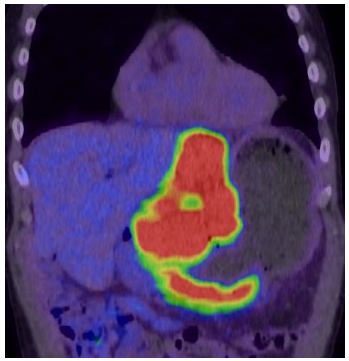
FDG-PET



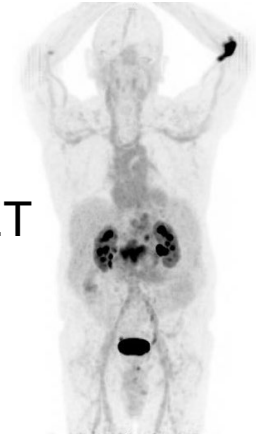
transaxial

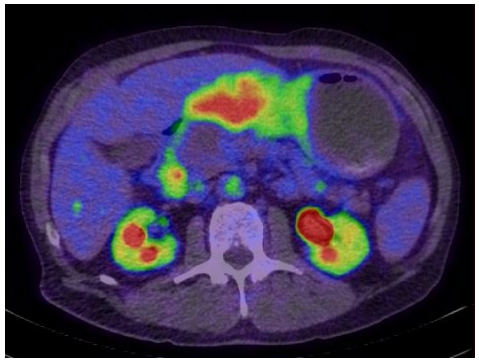


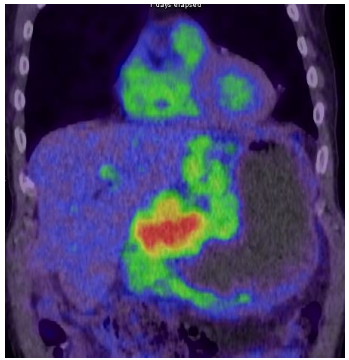
coronal



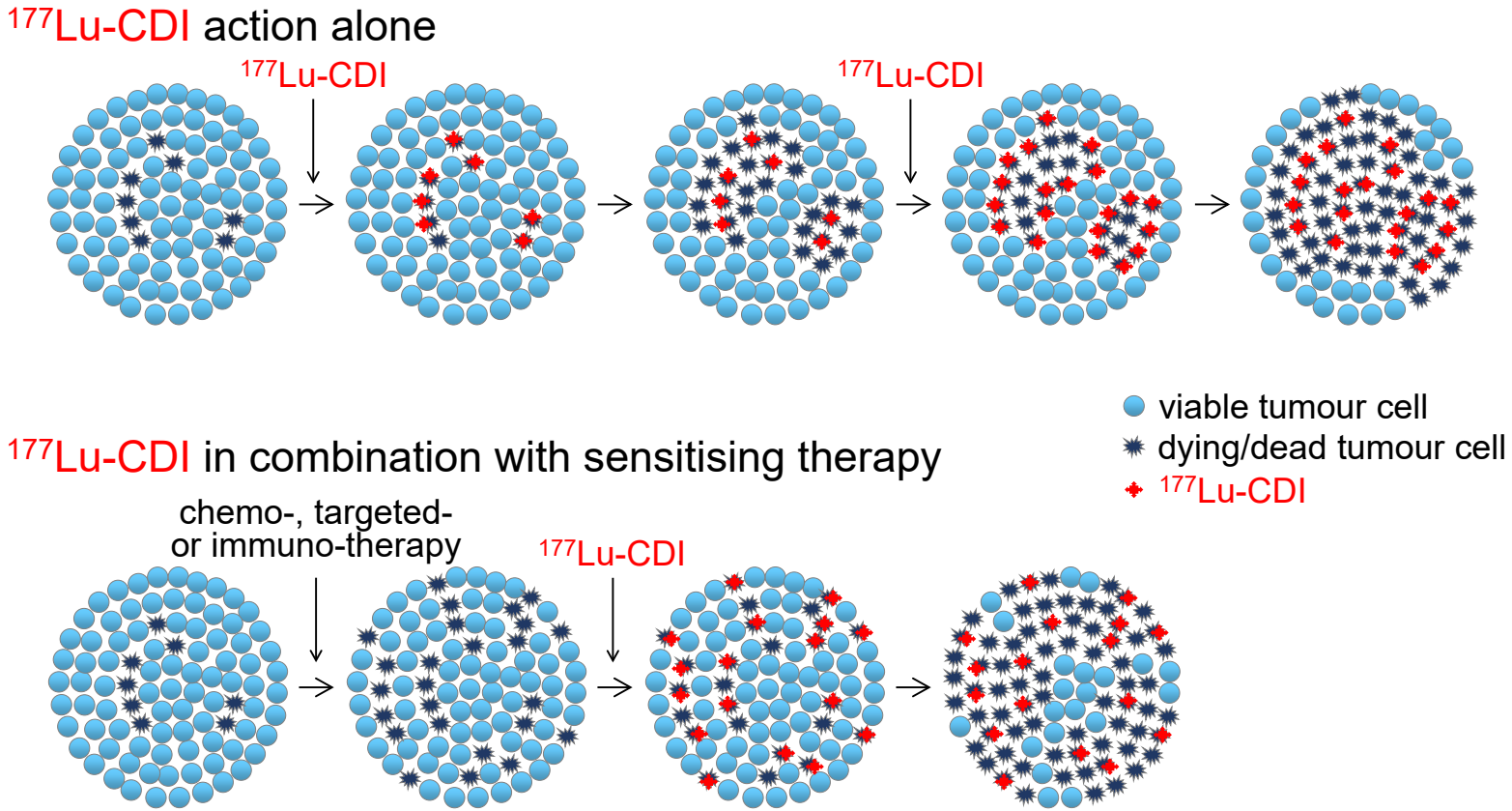
CDI-PET







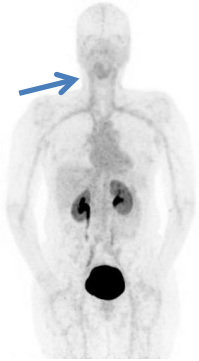
Delivering a therapeutic isotope to tumours: ^{177}Lu-CDI

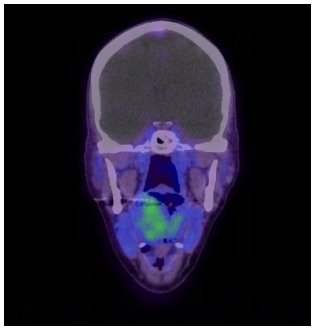


CDI-PET guides patient selection for ^{177}Lu-CDI treatment

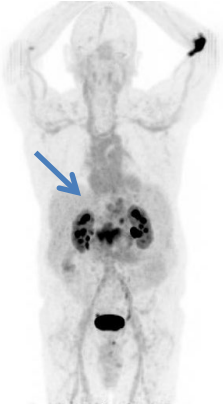
CDI-PET

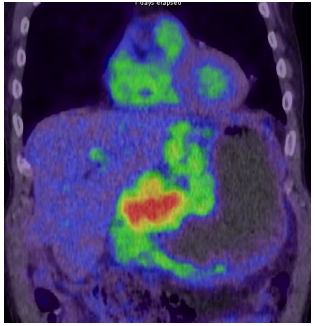
Patient 1





Patient 2





Questions

What are the best indications?

What combination therapy?

Timing of repeat dosing to maximise the self-amplifying therapeutic effect?