Theranostic targeting of CAIX in patients with clear cell renal cell carcinoma: first-in-human safety, imaging and dosimetry findings with [^{68}Ga]Ga-DPI-4452

Paper #14

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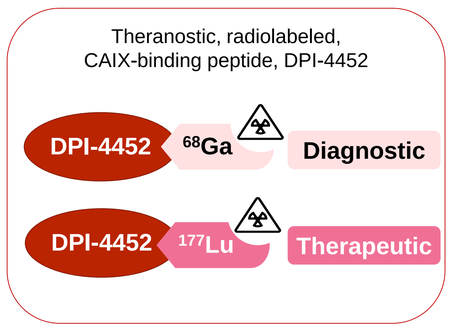
BACKGROUND

Carbonic anhydrase IX (CAIX) and cancer

- The cell surface glycoprotein CAIX is overexpressed in ~97% of clear cell renal cell carcinoma (ccRCC) cases,[1] often due to mutations in the Von Hippel-Lindau tumour suppressor gene[2]
- High levels of CAIX are linked to aggressive tumour behavior, including, treatment resistance and poor outcomes[2–6]
- High tumoural expression of CAIX but limited expression in healthy tissues[3,7] make CAIX an attractive diagnostic and therapeutic target
- Antibody-based tumour imaging for CAIX expression using zirconium-89-labeled girentuximab (an anti-CAIX antibody) allows tumour visualisation in 3–7 days post-administration[8,9]

DPI-4452

- DPI-4452 is a first-in-class, DOTA cage-containing, cyclic peptide with high-affinity binding to CAIX[3]
- Radiolabeling DPI-4452 with gallium-68 ([^{68}Ga]Ga-DPI-4452) or lutetium-177 ([^{177}Lu]Lu-DPI-4452) is an innovative and theranostic approach for identifying and treating patients with CAIX-expressing tumours[3]
- Radiolabeled DPI-4452 may confer better characteristics for both imaging and therapy compared with existing antibody approaches[10]



STUDY DESIGN AND METHODS

- NCT05706129 is a first-in-human, Phase 1/2, interventional, non-randomised, open-label, study of [^{68}Ga]Ga-DPI-4452 and [177Lu]Lu-DPI-4452 in patients with unresectable metastatic ccRCC, colorectal cancer or pancreatic ductal carcinoma
- Here we report findings from the completed Phase 1, Part A, ccRCC imaging cohort, which consisted of a 1-week evaluation of the safety, tolerability and tracer uptake of a single intravenous (IV) dose of [^{68}Ga]Ga-DPI-4452
- Standard uptake value characteristics and dosimetry in tumours and organs were evaluated via serial positron-emission tomography (PET)/computed tomography (CT) imaging, plus urine and blood sampling
- Safety, assessed by treatment-emergent adverse events (TEAEs), was evaluated over the 7-days post-injection

Part A primary objective	Evaluate the safety and tolerability of a single IV administration of [^{68}Ga]Ga-DPI-4452			
Part A secondary objectives	Assess pharmacokinetics, biodistribution, and dosimetry of [^{68}Ga]Ga-DPI-4452	Establish optimal procedures for determining location and burden of lesions on [^{68}Ga]Ga-DPI-4452 imaging	Assess concordance between [^{68}Ga]Ga-DPI-4452 PET vs. conventional imaging	

RESULTS

Patient demographics and [^{68}Ga]Ga-DPI-4452 administration

- Three patients with metastatic ccRCC, all male, were enrolled in the Part A imaging cohort of the study
- The mean administered [^{68}Ga]Ga-DPI-4452 activity across the 3 patients was 189.9 ± 13.74 MBq

Patient	Age	Sex	Cancer type	ECOG score	Prior systemic anti-cancer therapy lines, n*
1	54	Male	Metastatic ccRCC	1	2
2	51	Male	Metastatic ccRCC	0	2
3	48	Male	Metastatic ccRCC	0	2

*All patients received/were on 2nd-line treatment at study entry; 2nd-line therapy was stopped for 10 days in two patients during the study.

Pharmacokinetics and dosimetry

- Over 80% of total administered radioactivity cleared from the bloodstream within 1 hour
- Between early and late intervals, the average % injected dose in urine declined from 13.3 (SD, 4.5) to 6.1 (3.6)

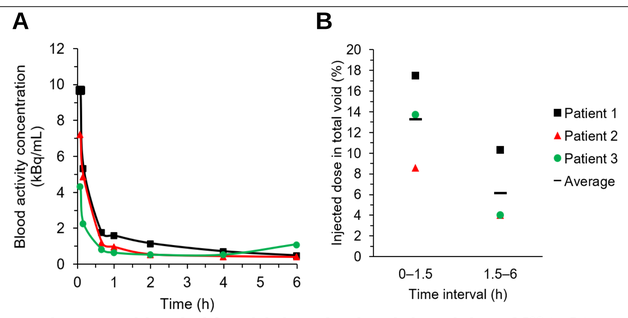


Figure 1. Pharmacokinetic blood (A) and urine (B) activity of [^{68}Ga]Ga-DPI-4452.

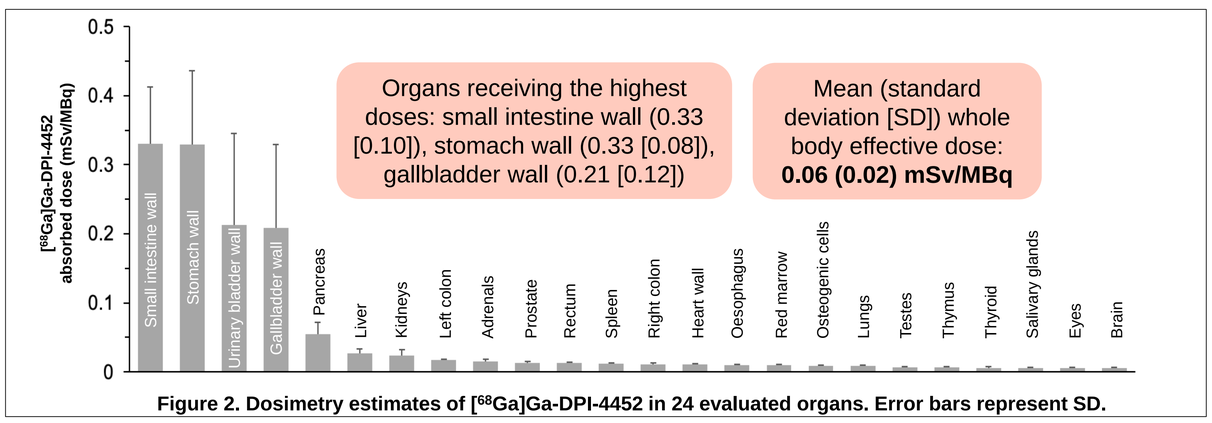


Figure 2. Dosimetry estimates of [^{68}Ga]Ga-DPI-4452 in 24 evaluated organs. Error bars represent SD.

Safety

- Two grade 1 TEAEs were reported in two patients (increased blood creatine phosphokinase and headache); neither were causally related to [^{68}Ga]Ga-DPI-4452 administration

[^{68}Ga]Ga-DPI-4452 uptake

- The optimal tumour visualisation timepoint (based on central reader visual assessment of image quality, visualisation of all lesions, and tumour uptake heterogeneity) was 1-hour post-[^{68}Ga]Ga-DPI-4452 administration

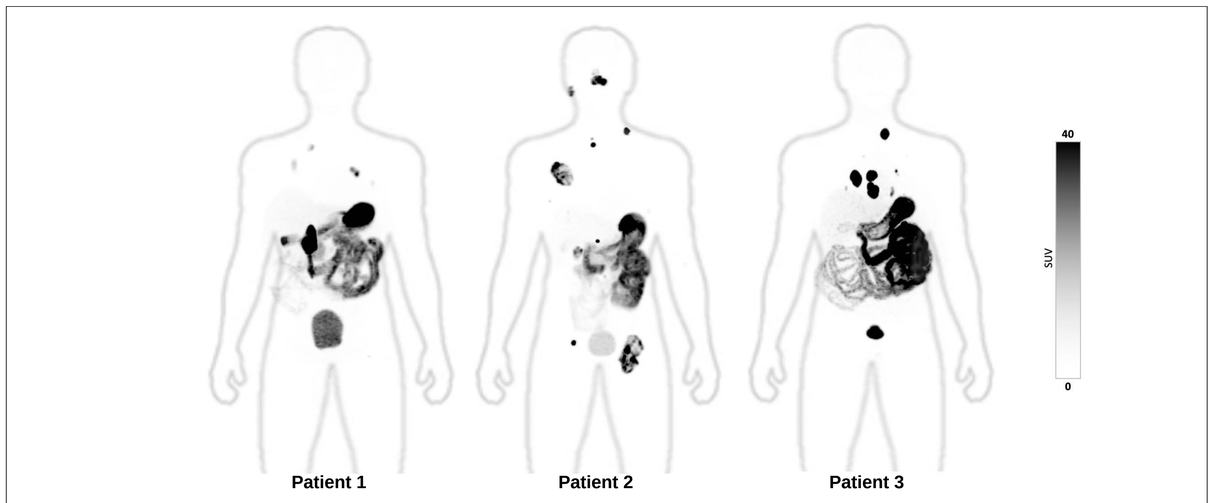


Figure 3. Whole-body maximum intensity projections 1-hour post [^{68}Ga]Ga-DPI-4452 administration.

- At 1-hour post-[^{68}Ga]Ga-DPI-4452 administration, the maximum tumour standardised uptake value (SUV_{max}) across 36 lesions ranged from 6.8 to 211.6, with a mean of 64.7 (SD, 54.8)
- Use of [^{68}Ga]Ga-DPI-4452 enabled identification of 17 lesions (in the lymph nodes, lung, pancreas, parotid gland and other sites) that were not detectable with prior conventional imaging approaches (CT)

	Patient 1	Patient 2	Patient 3
Lesions detected by CT and PET	5	6	8
Discordant lesions (not detected by PET)	1	0	0
Lesions found by PET only	0	8	9
Lesion SUV_{max} range	9–109	7–106	9–212

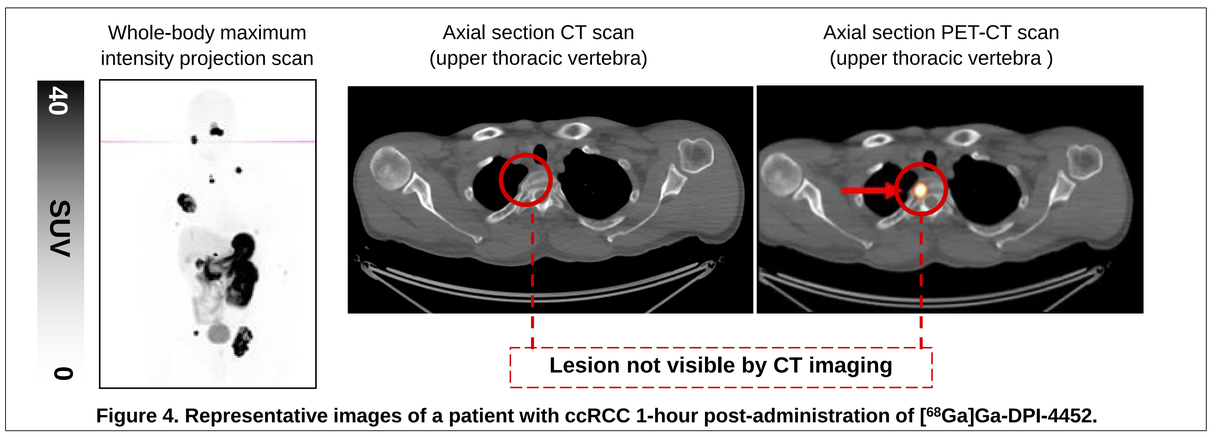


Figure 4. Representative images of a patient with ccRCC 1-hour post-administration of [^{68}Ga]Ga-DPI-4452.

CONCLUSIONS and FUTURE STUDIES

- DPI-4452 radiolabeled with gallium-68 provides exceptional tumour images in patients with ccRCC without clinically significant toxicities
- Imaging with [^{68}Ga]Ga-DPI-4452 offers tumour visualisation within minutes of administration; this is considerably faster than current approaches using zirconium-89-labeled girentuximab
- Very high SUV values and tumour-to-background ratios with [^{68}Ga]Ga-DPI-4452 suggest the potential for use in both diagnostics, as well as patient selection for therapy; assessment of the theranostic pair [^{68}Ga]Ga-DPI-4452/ [^{177}Lu]Lu-DPI-4452 is ongoing
- A multicentre investigator-initiated study to evaluate the management impact and accuracy of [^{68}Ga]Ga-DPI-4452 in the Australia-New Zealand region is planned

ABBREVIATIONS

CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; [^{68}Ga]Ga, gallium-68; [^{177}Lu]Lu, lutetium-177; PET, positron emission tomography; SD, standard deviation; SUV_{max}, maximum standardized uptake value; TEAE, treatment-emergent adverse event.

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