FIRST-IN-HUMAN SAFETY, IMAGING AND DOSIMETRY OF [^{68}GA]GA-DPI-4452, A NOVEL CA IX-TARGETING PEPTIDE, IN PATIENTS WITH CLEAR CELL RENAL CELL CARCINOMA

ABSTRACT #373

Michael S. Hofman,[1] Ben Tran,[1] Darren R. Feldman,[2] Anna Pokorska-Bocci,[3] Solen Pichereau,[3] Jonathan Wessen,[3] Mohammad B. Haskali,[1] Richard Sparks,[4] Olena Vlasyuk,[3] Ivana Galetic[3]

[1]Peter MacCallum Cancer Center, 305 Grattan Street. Melbourne, Victoria 3000, Australia; [2]Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY, USA; Department of Medicine, Weill Cornell Medical College, New York, NY, USA; [3]Debiopharm International SA, Lausanne, Switzerland; [4]CDE Dosimetry Services, Inc., Knoxville, TN USA

BACKGROUND

Carbonic anhydrase IX (CA IX) and cancer

- In tumors, hypoxic conditions or mutation of the Von Hippel-Lindau tumor suppressor gene can induce the expression of the cell surface glycoprotein, CA IX[1]
- CA IX expression has been linked to tumorigenesis from early carcinogenesis through to metastasis[1]
- Various tumors, including clear cell renal cell carcinoma (ccRCC), colorectal cancer (CRC) and pancreatic ductal adenocarcinoma (PDAC), have been shown to express high CA IX levels; this expression is linked to aggressive tumor behavior, treatment resistance and poor outcomes[2–4]
- The high expression of CA IX in hypoxic tumors and limited expression in healthy tissues[5] make CA IX an attractive diagnostic and therapeutic target

DPI-4452

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

STUDY DESIGN AND METHODS

- NCT05706129 is a first-in-human, Phase 1/2, interventional, non-randomized, open-label, study of [^{68}Ga]Ga-DPI-4452 and [177Lu]Lu-DPI-4452 in patients with unresectable metastatic ccRCC, CRC or PDAC
- 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 tumors and organs were evaluated via serial positron-emission tomography (PET)/computed tomography (CT) imaging, plus urine and blood sampling
- Safety, assessed by incidence of treatment-emergent adverse events (TEAEs), was evaluated over a 7-day period 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

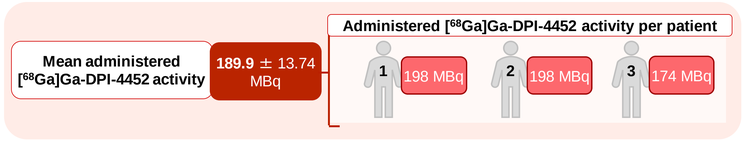
RESULTS

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

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.



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

- The optimal tumor visualization timepoint, based on central reader visual assessment of image quality, visualization of all lesions, and heterogeneity in tumor uptake, was established as 1 hour post-administration of [^{68}Ga]Ga-DPI-4452

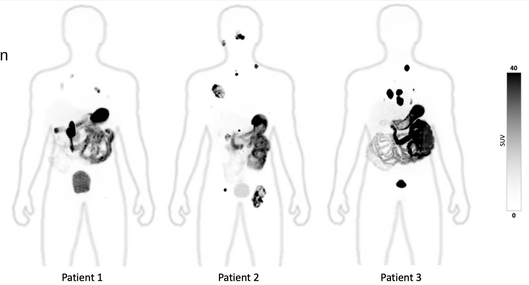


Figure 1. Whole-body maximum intensity projections 1-hour post-[^{68}Ga]Ga-DPI-4452 administration.

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

- At 1-hour post-[^{68}Ga]Ga-DPI-4452 administration, the maximum tumor standardized 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

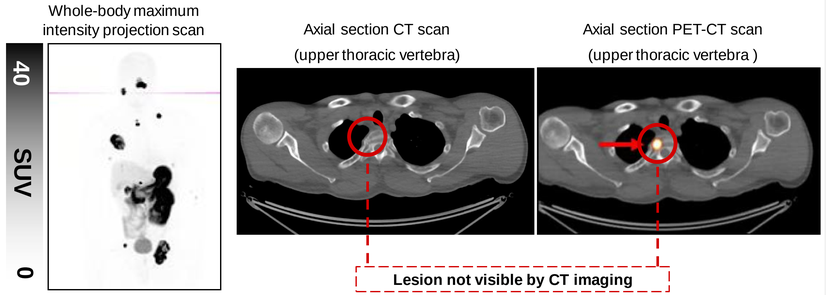


Figure 2. Representative images of a patient with ccRCC 1-hour post-administration of [^{68}Ga]Ga-DPI-4452.

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

Pharmacokinetics and dosimetry

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

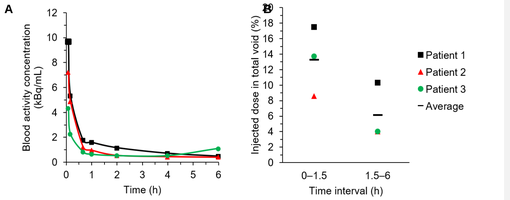


Figure 3. Pharmacokinetic blood (A) and urine (B) activity of [^{68}Ga]Ga-DPI-4452.

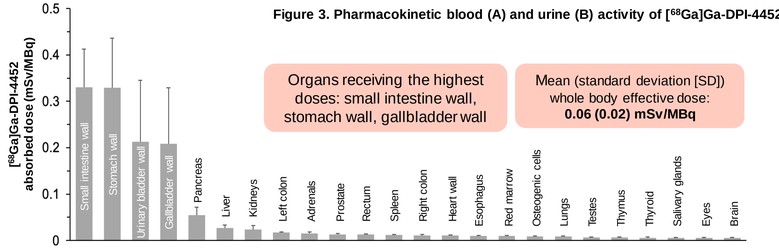


Figure 4. Dosimetry estimates of [^{68}Ga]Ga-DPI-4452 in 24 evaluated organs. Error bars represent SD.

CONCLUSIONS

- DPI-4452 radiolabeled with gallium-68 provides exceptional tumor images in patients with ccRCC without clinically significant toxicities
- Very high SUV values and tumor-to-background ratios with [^{68}Ga]Ga-DPI-4452 suggest potential for use in both diagnostics and patient selection for therapy
- Imaging with [^{68}Ga]Ga-DPI-4452 offers tumor visualization within minutes; this is considerably faster than current approaches using girentuximab (a zirconium-89-labeled anti-CAIX antibody) which allows tumor visualization around 3–7 days post-administration
- These first-in-human findings with radiolabeled DPI-4452 are encouraging for the subsequent evaluation of treatment with [^{177}Lu]Lu-DPI-4452

ABBREVIATIONS

CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; CRC, colorectal cancer; ECOG, Eastern Cooperative Oncology Group; CT, computed tomography; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; SD, standard deviation; SUV_{max}, maximum standardized uptake value; TEAE, treatment-emergent adverse event.

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STUDY CONTACT

michael.hofman@petermac.org
olena.vlasyuk@debiopharm.com