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First-in-human clinical trial design of a first-in-class theranostic approach with a peptide-based radioligand targeting CAIX-expressing tumors

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KG and LT were employed at Debiopharm International SA at the time the study was designed

BACKGROUND

CAIX

- Expression of carbonic anhydrase IX (CAIX), a cell surface glycoprotein, can be induced by a state of hypoxia or by mutation of the Von Hippel-Lindau tumor suppressor gene[1]
- CAIX has been implicated throughout tumorigenesis, from early carcinogenesis to metastatic dissemination of tumor cells[1]
- Certain tumors have been found to express high levels of CAIX[2]
- CAIX expression is associated with progressive disease and overall poor outcomes in various solid tumors[3,4]
- High expression in hypoxic tumors and restricted expression in healthy tissues[5] make CAIX an attractive diagnostic and therapeutic target

Tissue	H-score	CRC	PDAC	ccRCC
Malignant	> 150	29% (25/85)	40% (26/65)	83% (25/30)
	> 100	41% (35/85)	51% (33/65)	83% (25/30)
	> 40	52% (44/85)	60% (39/65)	87% (26/30)
Healthy	> 150	0% (0/21)	0% (0/4)	0% (0/30)
	> 100	0% (0/21)	0% (0/4)	0% (0/30)
	> 40	0% (0/21)	0% (0/4)	0% (0/30)

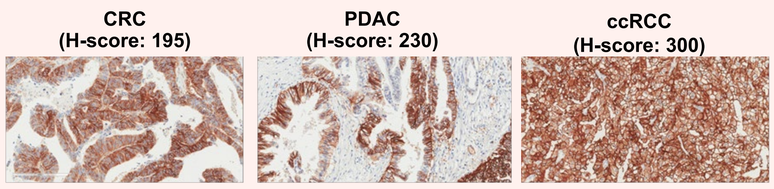


Figure 1. High expression of CAIX has been observed in various tumor types. An IHC score >40 can distinguish low from high CAIX expression.[6]

DPI-4452

- DPI-4452 is a first-in-class cyclic peptide that binds with high affinity to CAIX
- DPI-4452 can be radiolabeled with gallium-68 ([^{68}Ga]Ga-DPI-4452) or lutetium-177 ([^{177}Lu]Lu-DPI-4452) and may offer an innovative, theranostic approach for identification and treatment of patients with CAIX-expressing tumors (Figure 2)
- Pre-clinical studies have demonstrated that both [^{68}Ga]Ga-DPI-4452 and [^{177}Lu]Lu-DPI-4452 accumulate strongly in ccRCC and CRC xenograft tumors[2,7]
- It has also been shown that [^{177}Lu]Lu-DPI-4452 can induce dose-dependent tumor growth inhibition in xenograft mouse models[2,7]

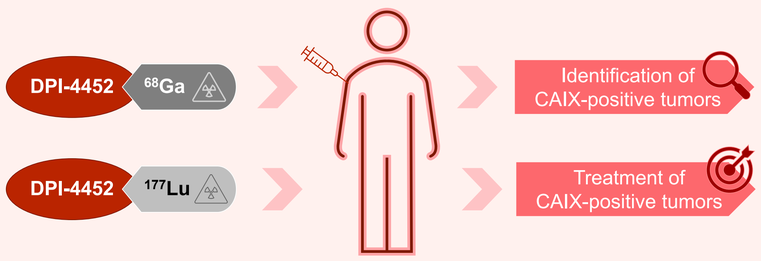
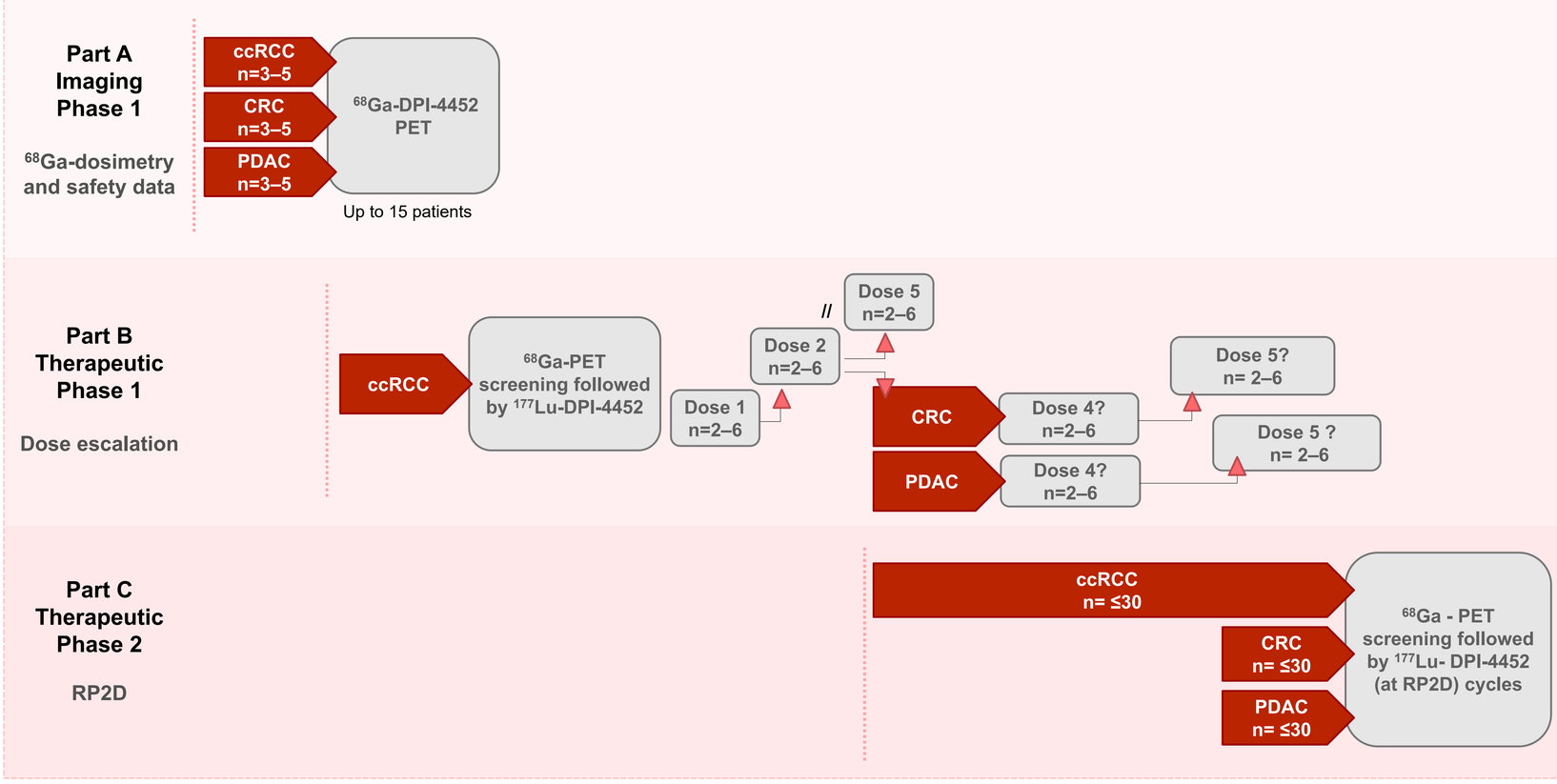


Figure 2. Radiolabeled DPI-4452 represents an innovative theranostic approach for CAIX-positive tumors.

STUDY DESIGN

- We present the design of a Phase I/II, interventional, non-randomized, open-label, study of [^{68}Ga]Ga-DPI-4452 and [^{177}Lu]Lu-DPI-4452 in patients with unresectable, locally advanced or metastatic cancers, namely ccRCC, CRC or PDAC
- This three-part study, initiated in March 2023, is registered as NCT05706129 and has an estimated primary completion date of January 2026
- **Part A** consists of a 1-week evaluation of the safety, tolerability and tracer uptake of a single IV dose of [^{68}Ga]Ga-DPI-4452
  - Up to 15 patients with ccRCC, CRC or PDAC will be enrolled
  - Imaging using PET/CT at 4 timepoints on Day 1 will allow evaluation of standard uptake value characteristics and dosimetry in tumor lesions and organs
  - Safety will be evaluated over a 7-day period
- **Part B**, enrolling approximately 42 patients, involves dose-escalation, aiming to estimate the MTD of [^{177}Lu]Lu-DPI-4452 and determine the RP2D
  - A Bayesian model-based decision procedures using the form of a two-parameters logistic regression modelling the relationship between the dose and the probability of observing a DLT is implemented
  - MTD is defined as the [^{177}Lu]Lu-DPI-4452 dose that maximizes the posterior probability of DLT rate being in the 20%–35% interval, while controlling the risk of overdose (DLT) at the level of 25%
  - Patients will receive escalating doses of [^{177}Lu]Lu-DPI-4452 for 28-day cycles, up to 8 cycles
  - DLTs during the first cycle will be considered for dose escalation rules
  - A safety monitoring committee will review data after each cohort
  - Cumulative safety, dosimetry and PK will also be considered for the determination of the RP2D
  - The dose escalation will initially be conducted in the group of ccRCC patients; dose escalation in the CRC and PDAC groups will start after the RP2D is established for ccRCC
- **Part C** consists of a three single arms that will assess the preliminary anti-tumor efficacy of [^{177}Lu]Lu-DPI-4452 at the RP2D in ccRCC, CRC and PDAC
  - The primary endpoint is ORR, defined as the percentage of patients who achieve a partial response or complete response as measured by RECIST v1.1
  - Enrolling ~30 patients per tumor type, and assuming an ORR response of 10% with SOC, Part C will have ~90% power to detect an improvement of 30%

Figure 3. Study design schematic. NCT05706129



ELIGIBILITY

KEY INCLUSION CRITERIA

Parts A, B and C

- Aged ≥18 years old
- Provision of written informed consent, dated and signed by the patient prior to any study-specific procedure
- Histologically confirmed, unresectable locally advanced or metastatic ccRCC, PDAC or CRC
- Participants with CRC or PDAC: availability of fresh biopsy or archival biopsy/surgical tumor specimens (preferably, taken after last prior line of therapy)
- Presence of ≥1 non-irradiated tumor lesion detected at conventional imaging (CT/MRI) documented within 4 weeks prior to [^{68}Ga]Ga-DPI-4452 administration
- Measurable disease as per RECIST v1.1

KEY EXCLUSION CRITERIA

Parts A, B and C

- Known hypersensitivity to the active substance, to any of the excipients of DPI-4452, or to radiographic contrast agents
- Any major surgery within 12 weeks before enrollment
- Lack of resolution of clinically significant toxic effects of prior systemic cancer therapy, surgery, or radiotherapy to Grade ≤1 (except for certain laboratory parameters, Grade 2 alopecia, and/or stable Grade 2 sensory neuropathy, according to NCI-CTCAE)
- Bladder outflow obstruction or unmanageable urinary incontinence
- Inability to stay in the scanner bed with the arms resting out of the thoracic and abdominal fields for the duration of the scan
- Prior EBRT to >25% of the bone marrow, as judged by the investigator

Part A only

- Administration of a radiopharmaceutical within a period corresponding to 10 half-lives of the radionuclide used prior to injection of [^{68}Ga]Ga-DPI-4452
- Previous CAIX-targeting treatment

Parts B and C only

- Administration of a radiopharmaceutical with therapeutic intent within a period of 6 months prior to injection of [^{68}Ga]Ga-DPI-4452
- Any previous CAIX-targeting treatment for more than 1 cycle or 1 month
- Receipt of any systemic antineoplastic therapy for the underlying disease and/or other investigational agents within ≤5 half-lives or ≤4 weeks (whichever is shorter)

KEY OBJECTIVES

PART	OBJECTIVE
	PRIMARY
A	To evaluate safety and tolerability of a single IV administration of [^{68}Ga]Ga-DPI-4452 for each tumor type
B	To determine the RP2D (MTD or lower dose) of [^{177}Lu]Lu-DPI-4452 for each tumor type
C	To evaluate the preliminary antitumor activity of [^{177}Lu]Lu DPI-4452 as monotherapy
	SECONDARY
A	To assess PK, biodistribution, and dosimetry of [^{68}Ga]Ga DPI 4452 for each tumor type
A	To establish the optimal imaging procedure (timing) for determining location and burden of positive lesions on [^{68}Ga]Ga-DPI-4452 imaging, by tumor type
A	To assess concordance between [^{68}Ga]Ga-DPI-4452 PET imaging of tumor lesions versus conventional imaging (CT/MRI) on a per patient basis and by tumor type
B	Safety and tolerability of [^{68}Ga]Ga-DPI-4452 and [^{177}Lu]Lu-DPI-4452
B	PK, biodistribution, and dosimetry of [^{177}Lu]Lu-DPI-4452
C	Preliminary activity of [^{177}Lu]Lu-DPI-4452 (PFS rate at 6 months)
C	PFS of [^{177}Lu]Lu-DPI-4452 in each tumor type
C	OS of [^{177}Lu]Lu-DPI-4452 in each tumor type
C	DoR of [^{177}Lu]Lu-DPI-4452 in each tumor type
C	DCR of [^{177}Lu]Lu-DPI-4452 in each tumor type
C	PK, biodistribution, and dosimetry of [^{177}Lu]Lu-DPI-4452

SUMMARY

- The glycoprotein CAIX is overexpressed in certain tumors and may have multifaceted roles in tumorigenesis, thus is an attractive therapeutic target
- DPI-4452 is a first-in-class, cyclic peptide that binds with high affinity to CAIX, and can be radiolabelled for theranostic use
- Following pre-clinical data demonstrating that [^{177}Lu]Lu-DPI-4452 can induce dose-dependent tumor growth inhibition, this Phase I/II study will evaluate the theranostic use of [^{68}Ga]Ga-DPI-4452 and [^{177}Lu]Lu-DPI-4452 in patients with ccRCC, CRC or PDAC
- The study is divided into 3 parts which will evaluate the safety and tolerability of imaging with [^{68}Ga]Ga-DPI-4452, determine the RP2D of [^{177}Lu]Lu-DPI-4452 and assess the safety and preliminary efficacy of [^{177}Lu]Lu-DPI-4452 monotherapy
- As of April 2023, the study is recruiting patients at 2 centres in Australia

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ABBREVIATIONS

CAIX, carbonic anhydrase; ccRCC, clear cell renal cell cancer; CRC, colorectal cancer; CT, computed tomography; DCR, disease control rate; DLT, dose-limiting toxicity; DoR, duration of response; EBRT, external beam radiation therapy; IHC, immunohistochemistry; IV, intravenous; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; NCI-CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; ORR, overall response rate; OS, overall survival; PDAC, pancreatic ductal adenocarcinoma; PET, positron emission tomography; PFS, progression-free survival; PK, pharmacokinetics; RECIST, Response Evaluation Criteria In Solid Tumors; RP2D, recommended Phase 2 dose; SAE, serious adverse event; SOC, standard of care; TEAE, treatment-emergent adverse event.

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