It has also been shown that [177Lu]Lu-DPI-4452 can induce dose-dependent tumor growth inhibition in xenograft mouse models. It has also been shown that [177Lu]Lu-DPI-4452 can induce dose-dependent tumor growth inhibition in xenograft mouse models.

Figure 1. High expression of CAIX has been observed in various tumor types. An IHC score > 100 can distinguish low from high CAIX expression.6

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

**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.
- CAIX has been implicated throughout tumorigenesis, from early carcinogenesis to metastatic dissemination of tumor cells.
- Certain tumors have been found to express high levels of CAIX.
- CAIX expression is associated with progressive disease and overall poor outcomes in various solid tumors.
- High expression in hypoxic tumors and restricted expression in healthy tissues make CAIX an attractive diagnostic and therapeutic target.

**STUDY DESIGN**

- We present the design of a Phase III, interventional, non-randomized, open-label, study of [68Ga]Ga-DPI-4452 in patients with unselectively 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 2028.
- Part A consists of a 1-week evaluation of the safety, tolerability and tracer uptake of a single IV dose of [68Ga]Ga-DPI-4452.
- Up to 15 patients with cCRCC, CRC or PDAC will be enrolled.
- Imaging using PETCT 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 [177Lu]Lu-DPI-4452 and determine the RP2D.
  - A Bayesian model-based decision procedures using the form of a two-parameters logistic regression modeling the relationship between the dose and the probability of observing a DLT is implemented.
  - MTD is defined as the [177Lu]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 [177Lu]Lu-DPI-4452 for 28 days, 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 single arm that will assess the preliminary anti-tumor efficacy of [177Lu]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 rate of 10% with 80% power to detect a worsening of 30% compared to baseline.

**REFERENCES**


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