Preclinical evaluation of ^{68}Ga/^{177}Lu-KK02, a theranostic targeting PARP for PARP-expressing cancers

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Background:
Radioligand therapy (RLT) represents a promising approach in cancer treatment, leveraging radiopharmaceuticals to deliver highly localised radiation directly to tumour cells. A notable target in this approach is poly(adenosine diphosphate-ribose)-polymerase (PARP), a key enzyme involved in DNA damage repair enzyme. PARP-targeting compounds, when radiolabelled with an appropriate therapeutic radionuclide, can selectively bind to damaged DNA within tumour tissue, where the emission of high-energy ionising radiation induces complex DNA damage ultimately leading to cancer cell death. Coupled with the elevated expression of PARP in many aggressive cancer cells relative to normal tissues (1), enables for more precise delivery of radiopharmaceuticals, hence enhancing the therapeutic index and minimising damage to surrounding tissues. Here, we report the development of KK02, a novel PARP-targeting compound designed for chelation with various radiometals, including ^{68}Ga and ^{177}Lu, for use in PET imaging and RLT applications.

Methods:
Radiolabelling efficiency, purity and stability of the matched-pair radiopharmaceuticals, [^{68}Ga]Ga-KK02 and [^{177}Lu]Lu-KK02, were assessed using radio-TLC and HPLC. *In vitro* uptake and specificity of [^{68}Ga]Ga/[^{177}Lu]Lu-KK02 were determined in human triple-negative breast cancer (TNBC) and prostate cancer (PCa) cells. Therapeutic efficacy of [^{177}Lu]Lu-KK02 were evaluated in TNBC and PCa cells. *In vivo* imaging, biodistribution studies and autoradiography were conducted using naïve and TNBC-bearing mouse models. Preliminary assessment of efficacy and safety for [^{177}Lu]Lu-KK02 was performed in a murine PCa models.

Results:
[^{68}Ga]Ga-KK02 and [^{177}Lu]Lu-KK02 were obtained in good yields and remained stable in serum. *In vitro* studies showed selective uptake of [^{68}Ga]Ga/[^{177}Lu]Lu-KK02 across all models, and was dependent on cellular PARP-1 expression levels. A significant reduction in clonogenicity was observed after treatment with 100 Bq and 1000 Bq [^{177}Lu]Lu-KK02 in TNBC cells and PCa cells, respectively. *In vivo* studies demonstrated that both [^{68}Ga]Ga-KK02 and [^{177}Lu]Lu-KK02 exhibited similar hepatobiliary and renal clearance profiles and showed bioequivalence. For [^{177}Lu]Lu-KK02, rapid blood clearance was observed at 1 h (0.14±0.05 %ID/g), with little kidney retention seen at 24 h (0.28±0.05 %ID/g) post-injection. A single, high-dose administration of [^{177}Lu]Lu-KK02 (60 MBq) resulted in a significant delay in MyC-CaP tumour growth compared to the vehicle control, without causing body weight loss and hematopoietic toxicity.

Conclusion:
Our study demonstrates the strong potential for KK02 as a theranostic tool for the diagnosis and treatment of PARP-expressing cancers, with improved radiotoxicity profiles. Ongoing investigations

are exploring the therapeutic effects of alternative radiometals and the impact of multiple-dose administration.

1. CY Chan, KV Tan, B Cornelissen; Clinical Cancer Research 27 (6), 1585-1594.

Conflict of interest statement

CYC and KVT hold patents on technology relating to the compound in this manuscript (International application no. PCT/GB2024/052297). KVT is full-time employees of Perceptive Inc. No other potential conflicts of interest relevant to this article exist.