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RESEARCH

The GLP-1 receptor is expressed *in vivo* by human metastatic prostate cancer

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Abstract

Objectives: The glucagon-like peptide-1 (GLP-1) receptor agonist, liraglutide, reduces human prostate cancer incidence, and similar GLP-1 receptor agonists reduce *in vitro* proliferation and *in vivo* growth of prostate cancer cell lines. Primary human prostate cancer expresses the GLP-1 receptor (GLP-1R) *in vitro*. Cancer evolves with stage, and whether advanced-stage human prostate cancer expresses GLP-1R is unknown. We hypothesised and aimed to prove that human metastatic castrate-resistant prostate cancer (mCRPC) expresses the GLP-1R *in vivo*. We hypothesised that mCRPC would thus be detectable by positron emission tomography/computed tomography (PET/CT) using a radiotracer bound to a GLP-1R ligand, as in exendin PET/CT.

Materials and methods: Men with mCRPC, with more than one prostate-specific membrane antigen (PSMA)-avid lesion on PET/CT scanning (pathognomic in that setting for prostate cancer lesions), were approached to undergo PET/CT with gallium^{68}-Dota-exendin-4. We documented PET/CT PSMA-avid lesions, which were also PET/CT exendin avid, as evidence of *in vivo* GLP-1R expression.

Results: Out of the 24 men referred, three did not meet the inclusion criteria. Seventeen declined, largely because the study offered them no therapeutic benefit. Among the four men imaged, three had no exendin-avid lesions, while one had six osseous PSMA-avid lesions, three of which were also exendin avid.

Conclusions: We demonstrated *in vivo* GLP-1R expression by human mCPRC, detecting PET/CT lesions avid for both PSMA and exendin, in one of four participants. GLP-1R expression may thus occur even in advanced-stage prostate cancer. Our data contribute to growing evidence supporting the testing of GLP-1 receptor agonists for therapeutic benefit in prostate cancer.

Keywords: glucagon-like peptide 1 (GLP-1); exenatide; prostate cancer; PET scan

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Introduction

Endocrine treatment of prostate cancer has focused on androgen receptor pathways. Recent evidence raises the possibility that a different endocrine pathway could also offer therapeutic benefit. This involves the activation of the glucagon-like peptide-1 receptor (GLP-1R) by GLP-1R agonists.

GLP-1 is an endogenous peptide that induces insulin secretion after binding GLP-1R on pancreatic beta cells (Drucker *et al.* 2017). Synthetic GLP-1 analogues are used to treat diabetes. Liraglutide is one such analogue and was found, in a large randomised placebo-controlled trial for type-2 diabetes, to halve prostate cancer incidence, with a hazard ratio of 0.54 (95% confidence limits, 0.38–0.88) (Marso *et al.* 2016, Nauck *et al.* 2018). This was consistent with laboratory data reporting *in vitro* expression of GLP-1R by both primary human prostate cancer and human prostate cancer cell lines (Nomiyama *et al.* 2014) and reduced *in vitro* proliferation and *in vivo* growth of prostate cancer cell lines after treatment with GLP-1R agonist (Nomiyama *et al.* 2014, Tsutsumi *et al.* 2015).

These data provide a rationale for testing GLP-1R agonists for therapeutic benefit in prostate cancer. However, the rationale for such testing would be strengthened by evidence of *in vivo* expression of GLP-1R by human prostate cancer. Additionally, whilst primary human prostate cancer expresses the GLP-1R *in vitro*, cancer evolves as it advances, and it remains unknown whether late stages of human prostate cancer express the GLP1-R.

We hypothesised that human metastatic castrate-resistant prostate cancer (mCRPC), a very late stage of prostate cancer, expresses the GLP-1R *in vivo* and that mCRPC would thus be detectable by positron emission tomography/computed tomography (PET/CT) if the radiotracer used was bound to a GLP-1R ligand.

Exendin-4 is a reptilian salivary peptide that also binds to the mammalian GLP-1R (Eng *et al.* 1992, Raufman *et al.* 1992, Drucker *et al.* 2017), and synthetic exendin-4, called exenatide, has been used as a radionuclide carrier in PET/CT imaging. Exendin PET/CT imaging is used to visualise insulinoma owing to GLP-1R expression by pancreatic beta cells (Pattison & Hicks 2017, Kalff *et al.* 2021).

Our aim was to use exendin PET/CT imaging to prove *in vivo* expression of GLP-1R by human mCRPC to strengthen the rationale for testing GLP-1R agonists for therapeutic benefit in prostate cancer.

Materials and methods

We conducted an open-label pilot trial of exendin PET/CT imaging in men with mCRPC recruited between May 2019 and December 2021. The trial was approved by the Human Research Ethics Committee (HREC) of Melbourne Health, Parkville, Australia. Written informed consent was obtained from all participants. The trial was prospectively registered with Australian New Zealand Clinical Trials Registry (www.anzctr.org.au) registration number: ACTRN12619000791134.

Participants

Inclusion criteria were as follows: (a) mCRPC; (b) a history of radical prostatectomy to provide histology for the recruitment strategy below and (c) more than one lesion on a prostate-specific membrane antigen (PSMA) PET/CT scan. PSMA is highly expressed on the cell surface by prostate cancer. Hence, PSMA-positive imaging lesions in men with mCRPC are considered pathognomonic for prostate cancer lesions.

Exclusion criteria were as follows: (a) history of allergy or adverse reaction to exenatide or meta-cresol; (b) creatinine clearance less than 30 mL/min and/or dialysis-dependent renal failure; (c) type-1 diabetes; (d) severe gastrointestinal disease including gastroparesis and dumping syndrome (as exenatide may worsen nausea or vomiting); (e) use of warfarin (as exenatide may increase the INR); (f) past pancreatitis because of the rare (<0.1%) risk of pancreatitis when exenatide is used as a treatment for diabetes; (g) history of adverse reaction or allergy to other GLP-1 agonists; (h) New York Heart Association Class-IV dyspnoea (because of limited data with GLP-1 agonists in that setting); (i) intercurrent severe depression, as GLP-1 receptor agonist may increase depressive symptoms; (j) factors that make it impractical to have radioactive urine, including intercurrent urinary incontinence, history of ongoing symptoms from past radiation cystitis and history of cystectomy; (k) cognitive impairment, psychiatric disorder or other variables that, in the opinion of an investigator, preclude informed consent and/or adherence to the study protocol; (l) inability to understand English because of lack of trial funding for interpreters and (m) most recent PSMA PET/CT scan conducted more than 2 weeks ago.

We aimed to recruit ten men, a pragmatic sample size given the nature of the pilot study, designed to provide initial data regarding the detection of metastatic CRPC with exendin (GLP-1 agonist) PET/CT scanning. Men were to be recruited to fulfil three conditions. First, five would have type-2 diabetes because the effect of liraglutide on prostate cancer incidence was demonstrated in men with type-2 diabetes (Marso *et al.* 2016). Hence, initial trials of liraglutide for prostate cancer may consider type-2 diabetes an inclusion criterion.

Secondly, two men with type-2 diabetes and two without diabetes would have surgical histopathological evidence of the intraductal histological type of prostate

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cancer), as the genetic bases and response to therapy of the mCRPC could differ between these groups.

Thirdly, at least two men with type 2 diabetes and two without diabetes would have intraosseous lesions on PSMA PET/CT scans. This may be relevant for future treatment trials with GLP-1R agonists for those at risk of marrow toxicity from other therapies.

In July 2020, we amended the inclusion criteria, as it became apparent that only about 1 in 12 participants who had PSMA scans at the PeterMacCallum Cancer Centre was eligible. This was common because they had not undergone prostatectomy, being diagnosed with prostate cancer at the metastatic stage. By then, we had also identified data (from one of the participants in our study reported in the 'Results' section below) consistent with *in vivo* GLP-1R expression by mCRPC. Accordingly, with approval from the HREC, we simplified the inclusion criteria to (a) mCRPC and (b) more than one lesion on a PSMA PET/CT scan.

Preceding PSMA PET/CT scans

PSMA PET/CT scans were acquired after a 60-min uptake period. Patients were asked to empty their bladder prior to the scan. Scans were acquired from the base of brain to mid-thigh with arms up. The bed-step acquisition time frame was adjusted according to the administered radioactivity and patient weight, with a minimum bed-step time of 2 min (as seen in Table S3 of Hofman *et al.* 2020).

Exendin PET/CT scans

Each participant underwent exendin PET/CT scanning as follows: gallium-68 was eluted from an onsite germanium-68/gallium-68 generator (ITM, Munich, Germany) using 0.05 M hydrochloric acid (4 mL). Ga-68 eluate was added to a mixture of Nle14–Lys40(Ahx-DOTA)-exendin-4 (60 µg; piChem, Raaba-Grambach, Austria) in 1 M HEPES buffer (1.2 mL) containing 0.05 M 2,5-dihydroxybenzoic acid (200 µL), 0.05 M sodium L-ascorbate (200 µL), 10 mg/mL L-methionine (100 µL) and ethanol (200 µL). After labelling, [68Ga]Ga-DOTA-exendin-4 was diluted with water (5 mL) and trapped on a Strata-X SPE cartridge. The trapped product was rinsed with water (5 mL), eluted with ethanol (~0.5 mL) and diluted with saline (9 mL). It was delivered into a sterile vial through a 0.22 ìm Cathivex-GV 25 mm PVDF sterile filter. This labelling process was automated on an iPHASE MultiSyn radiochemistry module, and the product was thoroughly tested to meet all pre-release criteria. High-performance liquid chromatography (HPLC) and thin-layer chromatography (TLC) confirmed radiochemical purity to be >92% and >99%, respectively.

Bilateral upper limb intravenous cannulation was performed. Gallium-68-DOTA-exendin-4 (2.6 MBq/kg, maximum peptide administered 20 µg/participant) was injected into the first cannula over a period of 30 s to 5 min. After 1 h of rest (bed or chair), each participant emptied his bladder and was positioned on a PET/CT scanner.

Scanning was carried out for approximately 20 min, covering from the vertex to upper thighs on a PET/CT scanner (GE Discovery 690 or 710-1, General Electric Company, Boston, MA, USA) equipped with time of flight. A simultaneous low-dose non-contrast multislice CT scan was performed for anatomic correlation and attenuation correction. The effective radiation dose was approximately 10 milliSieverts (mSv).

Capillary blood glucose levels were measured prior to tracer injection and every 15 min thereafter until 30 min after scanning or stable normal blood glucose, whichever was later. The second cannula was for the administration of intravenous dextrose if needed to treat hypoglycaemia.

The scans were reported, unblinded and compared with the respective preceding PSMA PET/CT images.

Primary outcomes

For each participant, (i) the number of PET/CT PSMA-avid lesions that are also PET/CT exendin avid, defined by any uptake with intensity greater than adjacent background tissue and (ii) the proportion of PSMA-avid lesions that are Exendin avid.

Secondary outcomes

For each participant: (A) the primary outcomes were stratified based on lesions that are: (i) visceral, (ii) nodal and (iii) osseous. (B) Total lesion uptake as a proportion of administered imaging radiation dose compared between PSMA and Exendin PET scanning for each participant. (C) Lesion uptake as a proportion of administered imaging radiation dose compared between PSMA and exendin PET scanning, stratified based on lesions that are (i) visceral, (ii) nodal and (iii) osseous.

Results

Early termination of the trial

The trial ended in December 2021 prior to the recruitment of ten participants due to several reasons: (1) data consistent with *in vivo* expression of GLP-1R by mCRPC had been obtained (reported in the 'Results' below), (2) recruitment was slow owing to the combination of lack of therapeutic benefit for participants, many of whom preferred to reserve their research participation for therapeutic trials and (3) interference by coronavirus infection waves and public health lockdown orders in Melbourne.

Participants

Twenty-four men were deemed potential participants and were contacted by an investigator. Three did not meet inclusion criteria as follows: two did not have prior prostatectomy and one had prostate cancer

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that had not progressed to a castrate-resistant stage. Seventeen did not wish to participate, mainly because they did not foresee any potential therapeutic benefit from this trial. Ultimately, four consented to participate and successfully completed the study procedures.

Participants were aged 56, 75, 77 and 78 years, with respective weights and body mass indices, weight (kg)/(height (m))^2, of 71, 99, 82.5 and 73 kg and 27.5, 31, 27 and 24.5 kg/m^2, respectively. The first three participants did not have diabetes, while the fourth had type-2 diabetes treated with a combination of sitagliptin 50 mg/metformin 1 g tablet twice daily. All had mCRPC with past grade, respectively: Gleason 8, Gleason unknown to investigators, Gleason 9 and grade group 4 (Gleason 4+4).

Past treatments for prostate cancer included (number who had treatment): prostatectomy (2), androgen deprivation therapy (4), radiation therapy (3), docetaxel (3), enzalutamide (2), abiraterone (2), carbazetaxel (1) and talazoparib (1).

Primary outcomes

One participant had six PSMA-avid lesions, three of which were also Exendin avid. This participant did not have diabetes. The remaining three participants did not demonstrate exendin-avid lesions (Table 1 and Fig. 1).

Secondary outcomes

The location of the exendin-avid lesions in the participant with exendin-avid lesions was osseous. Given the limited number of exendin-avid lesions, the proportion of total administered dose expressed by these avid lesions was not calculated. However, the SUV_{max} of these lesions was 4.3 (left proximal humerus), 1.5 (left posterior 8th rib) and 3.2 (right ilium). This compares with his SUV_{max} of 14 for diffuse pancreatic uptake (Fig. 1).

Table 1 Exendin and preceding PSMA PET/CT scan results.

Lesion location	PSMA-avid lesions (*n*)	Exendin-avid lesions also avid on PSMA (*n*)	Exendin-avid lesions not avid on PSMA (*n*)
Participant 1			
Visceral	>10	0	0
Osseous	>100	0	0
Lymphatic	8	0	0
Participant 2			
Visceral	0	0	0
Osseous	6	3	0
Lymphatic	0	0	0
Participant 3			
Visceral	0	0	0
Osseous	1	0	0
Lymphatic	>10	0	0
Participant 4			
Visceral	3	0	0
Osseous	0	0	0
Lymphatic	0	0	0

Adverse events

Two participants reported no adverse events. One (initial capillary glucose 8.7 mM) felt hot and nauseated after injection of the tracer. His capillary glucose levels dropped to 4.8 mM at the time of symptoms, with a nadir of 3.8 mM. The capillary glucose level stabilised at 5 mM after receiving 10 mL and then 15 mL of 50% dextrose intravenously, oral feeding and two separate doses of 2 mg dexamethasone intravenously. Another participant (initial capillary glucose 6.8 mM) developed hypoglycaemia (nadir glucose 2.7 mM), which responded to oral simple carbohydrate (jellybeans) and 50 mL of 50% dextrose intravenously. When hypoglycaemia recurred (capillary glucose 3.4 mM), a dextrose 10% infusion at 500 mL/h was initiated, and the participant was monitored for an additional approximately 2.5 h.

Discussion

Endocrine treatment for prostate cancer has focused on androgen receptor pathways. We sought data to support testing a new endocrine pathway, through the GLP-1R, for therapeutic benefit in prostate cancer. In exendin PET/CT scanning, the injected radiotracer has a radionuclide bound to exenatide, a synthetic GLP-1R agonist. As this radiopharmaceutical binds the GLP-1R, exendin PET/CT thus identifies tissue expressing the GLP-1R. We used this technology to seek evidence of *in vivo* GLP-1R expression by mCRPC, an advanced stage of prostate cancer.

In one of four participants, we identified three osseous lesions that expressed the GLP-1R. These lesions were also PSMA avid on preceding PSMA PET/CT. As PSMA is expressed by prostate cancer, this is interpreted as evidence that these imaged lesions were metastatic prostate cancer. We have thus developed data consistent with *in vivo* GLP-1R expression by human mCRPC.

However, only a small minority of the mCRPC lesions detected by PSMA imaging were exendin imaging positive. Hence, only a small minority of the mCRPC lesions demonstrated *in vivo* expression of GLP-1R with the technique we employed.

We do not know whether this is because most of the PSMA lesions do not express the GLP-1R or whether they do express GLP-1R but at concentrations below the sensitivity of our exendin PET/CT scanning. Similarly, we do not know whether, in the participants we studied, the very small proportion of the PSMA-avid

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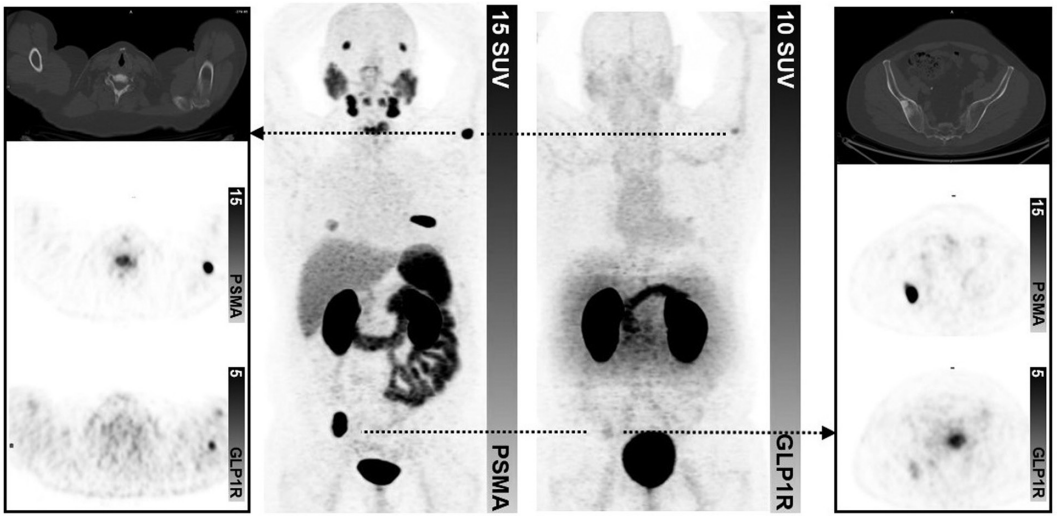

Figure 1

PSMA and GLP-1R PET/CT images from the participant demonstrating exendin-avid lesions. The central two panels are PSMA (left) and GLP-1R (right) PET scans. The outer two panels provide axial imaging of osseous lesions which were both PSMA and GLP-1R positive from the left proximal humerus (left outer panel) and right ilium (right outer panel). In each outer panel, the respective osseous lesion is presented as imaged (top of panel to bottom of panel), respectively, by CT, PSMA PET and GLP-1R PET scanning. Broken lines in the central two panels identify the corresponding left proximal humeral and right ilial osseous lesions on the total body PSMA and GLP-1R PET scan views.

mCRPC lesions demonstrating exendin avidity reflects a loss of or downregulation of GLP-1R expression either in response to past cancer therapies or secondary to molecular mutations during cancer clonal evolution. At least three of our four imaged participants had high-grade prostate cancer. Since this trial began, it has been reported that *in vitro* GLP-1R expression by human prostate cancer is lower in high-grade (Gleason 8–10 grade) surgical and biopsy specimens compared with lower-grade prostate cancer specimens (Shigeoka *et al.* 2020). One of the participants who received a negative Exendin PET/CT scan had been taking sitagliptin. This may have reduced the scan sensitivity to detect GLP-1R expression, because it may have increased endogenous GLP-1 levels, which could have interfered with radiotracer binding. As the pharmacological dose of the injected radiotracer used in our study is comparably high and GLP-1R expression in tissues is comparably low, it may be that lower pharmacological doses are required for GLP-1R imaging in mCRPC to avoid reduced binding through ligand binding competition at the receptor. Kondo *et al.* (2021), using a different radionuclide bound to exendin than that used in our study, reported that *in vivo* tracer uptake was lower in mice in prostate cancer cell lines xenografts compared with insulinoma cell line xenografts. They considered this to be due to lower GLP-1R density in the prostate cancer xenografts. When they examined *in vitro* binding by their radiolabelled exendin to prostate cancer cell lines, they did not find an effect from excess non-radiolabelled exendin.

We have demonstrated *in vivo* GLP-1R expression in a single case of mCRPC. We are unaware of radiolabelled exenatide successfully imaging, *in vivo* in humans, cancers other than insulinoma. Our three other participants with mCRPC did not demonstrate such expression. This small number of participants is a significant limitation of our study and does not enable us to determine the prevalence of such expression, as detected by exendin PET/CT, at this very late stage of prostate cancer. In a small sample size study, finding an outcome in a single participant may raise concerns that the outcome could relate to artefact in that participant. However, we consider the *in vivo* co-expression of PSMA and GLP-1R in one of our participants with mCRPC to be entirely consistent with past demonstrations of *in vitro* expression of GLP-1R in human primary prostate cancer and human prostate cancer cell lines (Nomiyama *et al.* 2014).

As primary human prostate cancer specimens demonstrate *in vitro* expression of GLP-1R (Nomiyama *et al.* 2014), a cell line derived from human prostate cancer, which was metastatic to the lymph node, demonstrates *in vitro* expression of GLP-1R (Nomiyama *et al.* 2014) and we have demonstrated *in vivo* GLP-1R expression in osseous lesions from a single case of mCRPC; there are now data consistent with GLP-1R expression across the continuum of human prostate cancer stages from primary to metastatic castrate-resistant states.

PSMA PET/CT demonstrates very high tumour-to-background contrast and has become a new standard-of-care for imaging patients with prostate cancer (Hofman *et al.* 2020, Jadvar *et al.* 2022). Whilst this study demonstrates *in vivo* GLP-1R expression by mCRPC, the intensity of exendin uptake was very low

compared with the intensity of PSMA uptake on the preceding PSMA PET/CT scans. Although caution is required when comparing the intensity of exendin-4 vs PSMA PET/CT scans because different targets are bound, our findings suggest that GLP-1R density is much lower than PSMA density in mCRPC and that exendin-4 will not be a useful diagnostic imaging tool in patients with mCRPC. Low GLP-1R expression does not discount a potential therapeutic benefit from GLP-1R agonists in prostate cancer. The epidemiology associating GLP-1R agonist use with lower incident prostate cancer (Lu *et al.* 2022, Wang & Kim 2022, Skriver *et al.* 2023) and the randomised control trial treatment arms difference in prostate cancer incidence reported by Marso *et al.* (2016) are all in keeping with a potential therapeutic benefit from GLP-1R agonists despite low GLP-1R expression.

In this study, hypoglycaemia occurred in two of four participants. Hypoglycaemia is unusual with subcutaneous GLP-1 agonist administration for diabetes. Hypoglycaemia in this study may relate to the dose of GLP-1 agonist given, together with the administration being intravenous. We injected radiolabelled exendin-4 at a maximum dose of 20 µg per participant intravenously over 30 s to 5 min. A slower injection may have reduced the occurrence of hypoglycaemia. Our dose contrasts with the injection of 0.2 µg exenatide administered intravenously within the first 5 min in cardiac surgery patients already on intensive insulin therapy in whom there was no increase in hypoglycaemic events, although that study defines hypoglycaemia as less than 3.3 mM (Lipš *et al.* 2017). Similarly, no episode of hypoglycaemia was reported when 0.6 µg exenatide was injected intravenously in the first 5 min in 85 cardiac patients in the setting of myocardial infarction, although the sensitivity of that study to detect hypoglycaemia may be reduced by an apparent frequency of blood glucose measurement of only every 4 h (Lønborg *et al.* 2012). We also do not know whether hypoglycaemia in this study after intravenous exendin relates to the frail physical state of the participants, their past treatments for mCRPC, or mCRPC itself.

This trial included men with visceral, lymphatic and osseous PSMA-avid mCRPC lesions, but a limitation of our trial was the small number of participants. This prevents a determination of the true incidence of Exendin-avid lesions in mCRPC. Further, Exendin PET/CT trials may consider men at an earlier disease phase of prostate cancer. They may be healthier and more prepared to participate in trials that offer them no therapeutic benefit. Such trials may answer whether the extent of *in vivo* GLP-1R expression falls with the advancing stage of prostate cancer.

Since the initiation of our study, three studies have reported reduced incident prostate cancer in the presence of diabetes in association with the use of GLP-1R agonists. They compared GLP-1R agonist use versus sulphonylurea (Lu *et al.* 2022 and see Wang & Kim 2022 who compared GLP-1R agonist users (52% of whom used sulphonylurea at baseline) vs users of sulphonylurea who were not taking GLP-1R at baseline), GLP-1R agonist users (85% of whom were also using metformin at baseline) vs users of metformin who were not taking GLP-1R agonists at baseline (Wang & Kim 2022) and GLP-1R agonists vs basal insulin (Skriver *et al.* 2023), although caution may be required in interpreting some of the sulphonylurea and insulin comparisons (Windeler & Lange 1995). *In vitro* and *in vivo* animal studies are consistent with a potential therapeutic benefit from GLP1-R agonists on prostate cancer in the absence of intercurrent diabetes (Nomiyama *et al.* 2014, Tsutsumi *et al.* 2015, Shigeoka *et al.* 2020), but we are unaware of human incidence data in the absence of intercurrent diabetes.

The GLP-1R agonist liraglutide reduces prostate cancer incidence (Marso *et al.* 2016, Nauck *et al.* 2018). Primary human prostate cancer and prostate cancer cell lines express GLP-1R *in vitro* (Nomiyama *et al.* 2014, Shigeoka *et al.* 2020). Furthermore, GLP-1R agonists reduce the *in vitro* proliferation and *in vivo* tumour growth of prostate cancer cell lines (Nomiyama *et al.* 2014, Tsutsumi *et al.* 2015, Shigeoka *et al.* 2020). Whilst early-stage prostate cancer expresses the GLP-1R *in vitro*, cancer evolves as it advances, and whether late stages of prostate cancer express the GLP1-R was unknown. We demonstrate that, *in vivo*, the most advanced stage of human prostate cancer may express the GLP-1R; however, this was only detected in the minority of mCRPC lesions.

This study, when juxtaposed with the above *in vitro* studies, supports the hypothesis that the GLP-1R may be expressed across all stages of prostate cancer. It thus provides additional data in support of testing a new endocrine pathway, that of GLP-1R agonists acting through the GLP-1R, for therapeutic benefit in prostate cancer. As only a minority of mCRPC lesions demonstrated *in vivo* GLP-1R expression, initial trials of a therapeutic benefit from GLP-1R agonists in prostate cancer may be considered in earlier stages of disease, such as after attempted curative radical prostatectomy and/or in biochemical relapse thereafter.

Conclusion

We demonstrated *in vivo* GLP-1R expression by human mCRPC, detecting PET/CT lesions avid for both PSMA and exendin, in one of four participants. As primary human prostate cancer expresses the GLP-1R *in vitro*, a cell line derived from a human prostate cancer metastasis to a lymph node expresses the GLP-1R *in vitro,* and we have demonstrated GLP-1R *in vivo* expression in osseous lesions from a single case of mCRPC, GLP-1R expression has now been found in examples from all stages of human prostate

cancer. Our data contribute to growing evidence supporting the testing of GLP-1 receptor agonists for therapeutic benefit in prostate cancer.

Declaration of interest
The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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Data availability statement
Data sharing is not applicable to this article as no large datasets were generated or analysed and key data are included in this published article.

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