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ORIGINAL RESEARCH ARTICLE

Lutetium-177 Labelled Anti-PSMA Monoclonal Antibody (Lu-TLX591) Therapy for Metastatic Prostate Cancer: Treatment Toxicity and Outcomes

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Abstract

Introduction Whilst prostate cancer is the fourth most common cancer globally, effective therapies for patients with advanced disease are lacking. In recent years, interest in using theranostic agents to treat castrate-resistant prostate cancer (CRPC) and metastatic prostate cancer has emerged. Lu-TLX591 monoclonal antibody is a potential agent of significance; however, to date, reports on its toxicity and efficacy have been limited to small clinical trials in heavily pretreated patients. This retrospective study describes the real-world toxicity and efficacy profile of Lu-TLX591.

Methods Eighteen patients received Lu-TLX591 at two private oncology centres in Australia. Patients were eligible if they had CRPC or metastatic prostate cancer and prostate-specific membrane antigen (PSMA)-avid disease confirmed by PSMA-positron emission tomography (PET). Patients received two cycles of Lu-TLX591 monoclonal antibody (177 Lu-DOTA-rosopatamab) each dosed from 1.01–2.85 GBq, 14 days apart. Patient side effects, blood test results and radiology reports were recorded on the patient's electronic medical record (eMR).

Results Prominent side effects included fatigue (55.6%), anorexia (16.7%), nausea (11.1%), and transfusion reactions (11.1%). All-grade haematological toxicities included lymphopenia (61.1%), anaemia (22.2%), leukopenia (27.8%), neutropenia (27.8%), and thrombocytopenia (27.8%). Grade 4 toxicity included lymphopenia (6.7%) and thrombocytopenia (6.7%). Patients' prostate-specific antigen (PSA) responses were as follows; ≥ 30% PSA decline (27.8%), ≥ 50% PSA decline (11.4%) and any PSA decline (38.9%). Follow-up radiology revealed 54.5% stable disease, 45.4% disease progression and 9.1% disease regression.

Conclusion Lu-TLX591 was safely administered at acceptable toxicity and its efficacy reflects previous clinical trials. Larger studies are required and are underway (NCT04786847; NCT05146973; NCT04876651) to determine Lu-TLX591 effectiveness amongst different prostate cancer populations and compare its efficacy against peptide-based radiopharmaceutical agents.

Key Points

Lu-TLX591 is a monoclonal antibody used in the treatment of castrate-resistant and metastatic prostate cancer.

Lu-TLX591 was administered safely with acceptable levels of toxicity and the efficacy is comparable with previous clinical trials.

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1 Introduction

Prostate cancer is the second most common cancer amongst men and the fourth most common cancer globally [1]. Whilst advanced-stage prostate cancer is less common compared with localised and regional prostate cancer (16% versus 84%), it carries a particularly poor prognosis with a 5-year overall survival rate of 31% [1, 2]. Notably, the incidence of advanced prostate cancer has increased over the past few decades, particularly amongst low human development index (HDI) countries owing to factors including lack of screening, low disease awareness, late presentation, low socioeconomic status and healthcare system limitations [2].

In localised prostate cancer, radical prostatectomy and radiation therapy are conventional definitive treatment options that are expected to lower prostate-specific antigen (PSA) levels to low or undetectable levels [3]. If PSA levels increase, androgen deprivation therapy (ADT) is often

indicated [3, 4]. Whilst patients often initially respond to ADT, tumour resistance will invariably develop against ADT owing to tumour-initiated androgen drivers, in which case the patient is then deemed to have castration-resistant prostate cancer (CRPC) [3, 4]. Subsequent treatments for CRPC and metastatic prostate cancer include novel anti-androgen (NAA) drugs that inhibit androgen biosynthesis (e.g. abiraterone) and block androgen receptors (e.g. enzalutamide, apalutamide, and darolutamide) as well as taxane-based chemotherapy (e.g. docetaxel and cabazitaxel) [5, 6]. Options following standard treatments are often limited in their effectiveness [3, 7]. As such, there is great interest in harnessing theranostics for CRPC and metastatic prostate cancer.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein found on prostate epithelial cells, salivary glands, proximal renal tubules, duodenal mucosa, spleen, liver, and colonic neuroendocrine cells [4, 8]. Its upregulation in prostate cancer cells makes it the molecular target of choice for prostate cancer theranostics [4]. Two agents that can be used to deliver radioisotopes to PSMA for prostate cancer diagnosis and therapy are antibodies and small-molecule ligands. [4].

Diagnostically, small molecule ligand-bound gallium-68 (68Ga-PSMA-11) is the agent of choice for prostate PET imaging in Australia, North America and Europe [9]. However, due to its short half-life of 68 min, on-site production of 68-Ga-PSMA-11 is often required [10]. F-18 Pyl (Pylarify®) is a more recent agent of comparable efficacy with the additional advantage of a longer half-life of 110 min which may permit its off-site production [10, 11].

Therapeutically, research into the optimal theranostic agent for CRPC is still underway with a variety of antibodies (e.g. TLX951) and small molecule ligands (e.g. 617) available for radiolabelling with alpha (e.g. actinium 225) or beta (e.g. lutetium 177) particle emitting radioisotopes.

This retrospective study describes the medical experience of eighteen metastatic prostate cancer patients treated with lutetium-177 labelled anti-PSMA monoclonal antibody (Lu-TLX591) from January 2022 to September 2022 at two oncology institutions in Australia. The primary endpoint of this retrospective study is to determine the safety and toxicity profile of Lu-TLX591 on the basis of patient-reported symptoms and blood results. The secondary endpoint is the rate of disease progression based on follow-up PSA levels and PSMA-PET imaging.

2 Methods

2.1 Participants

A total of 18 patients received Lu-TLX591 from January 2022 to September 2022 at two private oncology centres located in Perth and Gold Coast Australia. Patients were eligible if they had CRPC or metastatic prostate cancer and PSMA-avid disease confirmed by PSMA-PET.

Patient medical history and baseline blood test results, including prostate-specific antigen (PSA), full blood count (FBC), urea-creatinine-electrolytes (UEC), liver function tests (LFT) and lactase dehydrogenase (LDH), were recorded onto their electronic medical records (eMR).

2.2 Protocol

Lu-TLX591 monoclonal antibody (177 Lu-DOTA-rosopatamab) was supplied on compassionate grounds by Telix Pharmaceuticals via the Therapeutic Goods Administration (TGA) Special Access Scheme (SAS). Lu-TLX591 was infused intravenously over 15 min for each treatment. Prescribed doses were guided by the clinical judgement and expertise of the treating medical specialist. For cycle 1, patients received 1.08–2.68 GBq of Lu-TLX591 based on their baseline blood results and clinical frailty. Depending on the patient's reported side effects and laboratory toxicity after the first cycle, they then received 1.01–2.85 GBq of Lu-TLX591 for their second cycle. Patients received treatment in the outpatient setting and were monitored for infusion-related adverse reactions for up to 4 h. In the absence of dose-limiting toxicity (DLT), a single repeat dose was administered after 14 days. DLT was defined as an anaphylactic reaction or therapy-associated adverse event necessitating hospital admission.

2.3 Follow-Up

Patient-reported side effects were recorded on the patient's eMR on the day of their treatment and at their follow-up appointments. Blood tests monitored monthly included FBC, LFT, LDH, UEC, eGFR and PSA. PSMA-PET was standardly scheduled at 3–6 months following treatment.

2.4 Statistical Design

The primary objective of this retrospective longitudinal cohort study was to document the toxicity profile of Lu-TLX591 on the basis of patient-reported symptoms and serial blood results. All toxicity data were applied to the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) V5 to determine occurrences of treatment toxicity and, in such instances, quantify the worse grade of each type of toxicity.

The secondary objective was to assess the effect of Lu-TLX591 on the rate of disease progression on the basis of serial PSA levels and follow-up PSMA-PET imaging. Rates of PSA decline, PSA progression and PSA stability within 8

weeks of treatment cessation were attained and the duration of such responses was monitored. PSA decline was taken at ≥ 30% and ≥ 50% PSA from baseline, PSA progression was defined as ≥ 25% PSA rise from baseline and PSA stability was defined as ≤ 30% PSA decline and ≤ 25% PSA rise from baseline. To assess disease evolution on imaging, patients' pre-treatment PSMA-PET scan was compared with their follow-up PSMA-PET scan. The radiologist's report was then used to categorise the patient's disease response into regression, stability, or progression.

All patient baseline data, treatment toxicity data and disease progression data were collated and tabulated into Microsoft Excel. The Jamovi statistic platform was then employed for descriptive statistics calculations [12].

3 Results

Eighteen patients received Lu-TLX591 treatment from January 2022 to September 2022. Patient baseline characteristics are presented in Table 1. The median time between the patient's original diagnosis and their first cycle of Lu-TLX591 was 93.5 months. All patients had developed metastatic prostate cancer and had received multiple primary and secondary oncological therapies prior to commencing Lu-TLX591.

Patient baseline blood test results are displayed in Table 2. No patients possessed baseline results that met toxicity criteria under the CTCAE V5 classification system. Baseline PSA was variable with a median value of 31 (range 0.011–625).

Table 3 details the dose and timing of Lu-TLX591 treatment cycles. The mean delivered dose was 1.92 GBq (range; 1.08–2.68 GBq) for cycle 1 and 2.12 GBq (range; 1.01-2.85 GBq) for cycle 2. In all instances where two cycles were administered, the time between cycle 1 and cycle 2 was 14 days as planned.

Adverse non-haematological treatment events are detailed in Table 4. All patient-reported side effects were grade 1–2. The most common side effect was fatigue, followed by a few patients with anorexia, nausea, and acute transfusion reactions. Xerostomia, diarrhoea, fever, urinary frequency and nail changes were only reported on a single occasion.

Adverse haematological toxicities are depicted in Fig. 1. Lymphocytopenia was experienced by most patients; as grade 1–2 or grade 3 toxicity, and rarely as grade 4 toxicity. Five patients had leukopenia, neutropenia and thrombocytopenia. Whilst all leukopenia and neutropenia cases received a toxicity grade of 1–3, one thrombocytopenia case received a toxicity grade of grade 4. Four patients had anaemia, two experienced grade 1–2 toxicity and two experienced grade 3 toxicity.

Table 1: Baseline patient characteristics

Patient baseline characteristics	
Age, years (n = 18)	
Median	72.0
Range	60–82
Country of residence (n = 18), (%)	
Australia	8 (44.4)
Japan	4 (22.2)
USA	4 (22.2)
Canada	1 (5.6)
Vietnam	1 (5.6)
ECOG performance status (n = 18)	
0	11 (61.1)
1	7 (38.9)
Time from original diagnosis (n = 18), months	
Median	93.5
Range	36–203
Gleason score (summed) (n = 17), (%)	
7	7 (41.2)
8	2 (11.8)
9	8 (47.1)
Tumour stage at diagnosis (n = 16), n (%)	
1	1 (6.3)
2	3 (18.8)
3	6 (37.5)
4	6 (37.5)
PSA at diagnoses (n = 15) (ng/mL)	
Median	43.0
Range	3.2–445
Previous primary therapy (n = 18), n (%)	
ADT	9 (50.0)
Prostatectomy	6 (33.3)
Novel ADT	5 (27.8)
Radiation therapy	3 (16.7)
Previous adjuvant therapy (n = 18), n (%)	
Radiation therapy	13 (72.2)
Novel ADT	13 (72.2)
Chemotherapy	11 (66.7)
Anti-resorptive	10 (55.6)
ADT	10 (55.6)
Lu-177 PSMA I&T	7 (38.9)
Radium-223	4 (22.2)
Immunotherapy	3 (16.7)
Ethinylestradiol	2 (11.1)
PARP inhibitor (Olaparib)	1 (5.6)
Actinium	1 (5.6)
Nanoknife irreversible electroporation	1 (5.6)
Metastatic burden pre- Lu-TLX591 (n = 18), n (%)	
Metastasis	18 (100.0)
Bone	14 (78.0)
Lymph node	13 (72.0)

Table 1: (continued)

Patient baseline characteristics	
Other	5 (28.0)

Table 2: Baseline blood parameters

Baseline blood parameters ($n = 18$)	Median	Range
PSA (ug/L)	31.0	0.01–625
Haemoglobin (g/L)	121.7	90–159
WBC ($\times 10^9$/L)	4.5	2.5–10.8
Neutrophil ($\times 10^9$/L)	3.7	1.8–7.6
Platelet count ($\times 10^9$/L)	223.5	117–499
Lymphocytes ($\times 10^9$/L)	0.9	0.3–1.7
LDH (U/L)	192.0	121–396
Na (mmol/L)	139.0	138–145
K (mmol/L)	4.3	3.7–5.5
ALT (U/L)	21.5	7–39
AST (U/L)	22.0	10–39
Albumin (g/L)	37.5	29–47
Total bilirubin (µmol/L)	6.5	3–21
Creatinine (µmol/L)	91.0	57–168
eGFR (mL/min/1.73 m^2)	75.5	46–106

Table 3: Lu-TLX591 treatment details

Lu-TLX591 treatment details	
Cycle 1 ($n = 18$) administered activity (GBq)	
Mean	1.92
Range	1.08–2.68
Cycle 2 ($n = 16$) administered activity (GBq)	
Mean	2.12
Range	1.01–2.85
Time between cycle 1 and 2 ($n = 16$) (days)	
Mean	14

Data on treatment outcomes measured within 8 weeks of treatment are displayed in Table 5. Most patients had either a stable or declining PSA; amongst this cohort, the mean time to subsequent PSA progression was 41 weeks. Notably, the actual time to PSA progression will exceed current reported values as four patients still had not experienced PSA progression at the time of writing.

Follow-up radiology demonstrated that half of patients ($n = 6$) had stable disease and around two-fifths ($n = 5$) had disease progression. Notably, one patient experienced disease regression.

Table 6 displays each patient's Lu-TLX591 dose per cycle, their highest grade of haematological toxicity and their disease outcome.

4 Discussion

Theranostics has garnered much momentum and interest for patients with CRPC and metastatic prostate cancer. One agent of potential significance in this landscape is the Lu-TLX591 monoclonal antibody (previously known as Lu-J591). The primary objective of this retrospective longitudinal cohort study was to document the toxicity profile of Lu-TLX591. The secondary objective was to assess the effect of Lu-TLX591 on the rate of prostate cancer disease progression. To address the above objectives, 18 patients who received Lu-TLX591 on compassionate grounds at two cancer institutions in Australia were analysed using descriptive statistics.

In this study, the most common patient-reported side effect, affecting over half of patients, was fatigue. Fatigue was also the most common side effect in early clinical trials, reported to affect a third to half of patients [13–15]. Notable rates of anorexia, nausea and transfusion reactions in this study were likewise in keeping with past studies as were less-reported side effects of xerostomia, diarrhoea, fever, urinary frequency, and nail changes [13–15]. Evidently, the single case of xerostomia in this cohort highlights the salivary gland-sparing benefit of monoclonal antibodies, such as Lu-TLX591, compared with small molecule ligands where salivary gland toxicity is a common dose-limiting factor [16, 17]. Side effects affecting over 10% of trial participants in past studies that were not reported amongst this cohort included weight loss, dyspnoea, limb oedema, constipation, insomnia, cough, and joint pain [13–15].

Haematological toxicity rates were considerably lower in this study compared with the reported literature. Anaemia affected just over one-fifth of patients in this cohort versus over half of patients in clinical trials [13–15]. Moreover, less than one-third of patients in this study experienced leukopenia, neutropenia and thrombocytopenia compared with over two-thirds of patients in past studies [13–15]. Of the five patients with thrombocytopenia, two died with thrombocytopenia whilst three recovered after a mean time of 63 days. Concerning the degree of toxicity, only a single case of grade 4 thrombocytopenia was observed, which is five times lower than the reported literature [14, 15]. Moreover, whilst over one-fifth and around one-tenth of patients experienced grade 4 neutropenia and grade 4 leukopenia, respectively, in past clinical trials, neither were observed in this study [14, 15]. Unlike previous clinical trials, this study also specifically quantified rates of lymphocytopenia and found that it was the most common haematological toxicity. Other laboratory parameters provide reassurance that Lu-TLX591 does not cause hepatic or renal toxicity. The latter holds true even amongst patients with stage 2 (eGFR 60-89) and stage G3a (eGFR 45-59) chronic kidney disease. Lastly, of the 18

Table 4: Non-haematological adverse events, worse grade as defined by the CTCAE V5

CTCAE V5 toxicity (worse grade)	Grade 1-2	Grade 3	Grade 4	Total
Patient-reported toxicity, *n* (%)				
Fatigue	10 (55.6)			10 (55.6)
Anorexia	3 (16.7)			3 (16.7)
Nausea	2 (11.1)			2 (11.1)
Hypersensitivity (infusion reaction)	2 (11.1)			2 (11.1)
Xerostomia	1 (5.6)			1 (5.6)
Diarrhoea	1 (5.6)			1 (5.6)
Fever	1 (5.6)			1 (5.6)
Urinary frequency	1 (5.6)			1 (5.6)
Nail changes	1 (5.6)			1 (5.6)
Bloods: non-haematologic toxicity, *n* (%)				
Increased LDH	4 (22.2)			4 (22.2)
Hyponatremia				
Hyperkalaemia				
Hypokalaemia				
Increased ALT				
Increased AST				
Increased bilirubin				
Hypoalbuminemia	4 (22.2)			4 (22.2)
Increased Cr				

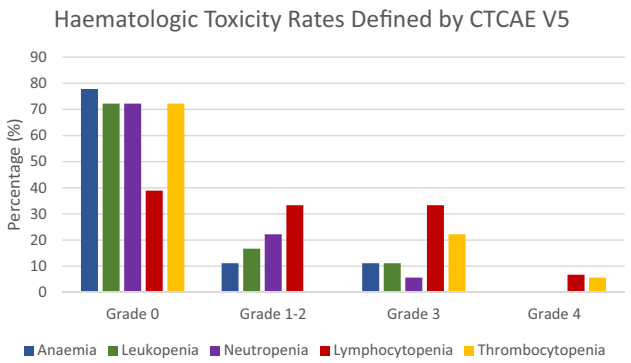

Figure 1: Rates of Grade 0–4 haematologic toxicity as defined by the CTCAE V5

Table 5 Patient PSA and imaging outcomes

Treatment outcomes	
PSA (*n* = 18), *n* (%)	
Any PSA decline	7 (38.9)
≥ 50% PSA decline	2 (11.1)
≥ 30% PSA decline	5 (27.8)
Stable PSA (< 30% decline, < 25% rise)	6 (33.3)
≥ 25% PSA rise	7 (38.9)
Imaging (*n* = 12), *n* (%)	
Stable	6 (50.0)
Progression	5 (41.2)
Regression	1 (8.3)

patients in this study, four required packed red blood cell transfusions and three required platelet transfusions.

Lymphopenia was the most common haematological toxicity in this study. Indeed, lymphocytes are the most radiosensitive cells amongst erythroid, myeloid and lymphoid lineages and are commonly depleted following both external beam and radionuclide therapies [18, 19]. Despite this, opportunistic infections are rare. Terrones and colleagues investigated the rates of hospitalised infections in radiotherapy patients with and without radiotherapy-induced thrombocytopenia and found no difference between the two cohorts 1 month after treatment [20]. Amongst patients with persistent lymphopenia, rates of hospitalised infections were only marginally higher after 6 months [20]. Furthermore, the study by Muacevic and Adler on patients with prostate cancer reported that rates of opportunistic infections were consistently low regardless of whether patients underwent no therapies, surgery, or radiotherapy [21]. Whilst the above studies are not specific to Lu-TLX591, they provide reassurance that complications owing to radiation-induced lymphopenia are relatively low. Lastly, whilst research specifically on the immunomodulatory effects of theranostics is warranted, it is known that radiation can also have immunostimulatory effects on the cancer microenvironment, such as promoting the release of tumour-associated antigens (TAA), expression of heat shock proteins (HSP) and induction of the abscopal effect [18, 22, 23].

Table 6: Lu-TLX591 dose versus haematological toxicity (highest grade) versus disease outcome

Patient	Lu-TLX591 dose (GBq) Cycle 1	Lu-TLX591 dose (GBq) Cycle 2	Haematological toxicity (highest grade)	Outcome
1	2.53	2.85	G3	Progression
2	2.68	2.55	G3	Progression
3	1.48	1.50	G3	Stable
4	1.081	1.01	G1–2	Stable
5	1.49	1.52	G0	Progression
6	2.08	2.80	G0	–
7	2.20	–	G0	Stable
8	2.59	2.80	G0	Stable
9	1.50	2.05	G3	Progression
10	1.49	1.53	G4	Progression
11	2.02	2.06	G0	–
12	2.07	2.55	G0	Stable
13	2.03	2.07	G3	–
14	1.58	–	G3	–
15	1.58	1.51	G3	Regression
16	1.90	2.55	G1–2	Stable
17	2.13	2.02	G1–2	–
18	2.04	2.54	G1–2	–

Lower rates of haematological toxicity in this study may be attributed to two factors. First, prescribed doses were guided by the clinical judgement and expertise of the treating medical specialist and based on the patient's clinical frailty, blood results and previous cycle side effects, if relevant. The correlation between dose and toxicity has been described in previous studies. Bander's 2005 study concluded that whilst significant haematological toxicity was seen in patients who received more than one Lu-TLX591 dose of ≥ 45 mCi/m^2, multiple doses of 30 mCi/m^2 were well tolerated. In Tagawa's 2013 study, patients who received a single fraction of 70 mCi/m^2 were more likely to experience grade 4 thrombocytopenia (27% versus 56.3%) and neutropenia (0% versus 37.5%) than those who received 65 mCi/m^2 of Lu-TLX591; however, the former patients also experienced higher rates of ≥ 30% PSA declines (46.9% versus 13.3%) and overall survival (21.8 versus 11.9 months) [14]. Lastly, patients in Tagawa's study in 2019 received 20–45 mCi/m^2 of Lu-J591 2 weeks apart. In the study, the low-dose cohort (20–35 mCi/m^2) again experienced lower rates of grade 4 thrombocytopenia (12.5% versus 36.4%) and neutropenia (0% versus 33.3%) compared with the higher-dose cohort (40–45 mCi/m^2) at the expense of lower ≥ 30% PSA decline (12.5% versus 42.4%) and median survival (14.6 versus 27.8 months). Such findings highlight the fine balance between dose toxicity and achieving disease remission with Lu-TLX591 and that fractionation can help mitigate toxicity. Secondly, whilst the median age of patients in this study mirrored past clinical trials, their Eastern Cooperative Oncology Group (ECOG) status was notably lower; grade 0 (61.1% versus 14.3–27.7%), grade 1 (38.9% versus 72.3–72.6%) and grade 2 (0% versus 0–8.2%). Thus, patients with a more favourable premorbid state may experience lower associated rates of haematological toxicity.

Two patients in this study did not receive their second dose of Lu-TLX591. The first case was due to administrative reasons whilst the second case was due to treatment toxicity. After their first cycle, the latter patient experienced an acute transfusion reaction (grade 1) followed by subsequent fatigue (grade 1), anaemia (grade 3) and thrombocytopenia (grade 3). As the patient required one pack of red cell and platelet transfusion after only one cycle of 1.58 GBq Lu-TLX591 and had diffuse disease in their marrow as demonstrated on PSMA-PET, treatment was discontinued at the discretion of the treating medical specialist. All remaining patients received two cycles of Lu-TLX591 with a 14-day interval as planned, which demonstrates that early treatment toxicity was rarely a limiting factor for further Lu-TLX591 treatment amongst this cohort.

Therapeutically, this study closely matched overall treatment outcomes reported by Bander and colleagues in both its rate of ≥ 50% PSA decline and disease progression [13]. Moreover, rates of ≥ 30% PSA decline, ≥ 50% PSA decline and any PSA decline in this study were only slightly higher and slightly lower than patients who had received 65 mCi/m^2 and 70 mCi/m^2 of Lu-TLX591 respectively in Tagawa's 2013 unfractionated study [14, 15]. Similarly, PSA outcomes in this study were only marginally higher and marginally

lower than those patients who received 20–35 mCi/m^2 versus 40–45 mCi/m^2, respectively, in Tagawa's 2019 fractionated trial. Thus, data from this study largely aligns with those in past clinical trials and demonstrates the notable effect of Lu-TLX591 on patient PSA levels even when prescribed at fractionated and tolerable doses.

Amongst patients who underwent follow-up imaging after 3–6 months, half had stable disease, around four-fifths had disease progression and a small percentage had disease regression. It should be noted that, owing to the sample size of this study, statistical correlations were not drawn between patient doses and their disease outcomes. However, Table 6 reveals that patients who received higher therapeutic doses did not necessarily achieve better outcomes than patients who received lower therapeutic doses. Future research on the factors that influence disease outcomes in patients receiving TLX951 therapy would be valuable.

The optimal theranostic agent for CRPC is still underway with a variety of antibodies (e.g. TLX951) and small molecule ligands (e.g. 617) available for radiolabelling with alpha (e.g. actinium 225) or beta (e.g. lutetium 177) particle emitting radioisotopes. The interest in antibodies lies in their larger size. Monoclonal antibodies cannot penetrate and cause significant renal, intestinal, or salivary gland toxicity and are also more slowly cleared from the body, enabling them to be coupled with lower and therefore less expensive, radioisotope activity [24, 25]. Further benefits associated with monoclonal antibody retention rates may include their delivery of higher therapeutic doses over time versus rapidly cleared peptides and small molecules [26]. Small molecule ligands, however, have the theoretical advantage of achieving better tumour penetration [27, 28]. Their faster biodistribution and clearance rate may also result in lower bone marrow doses and enhanced tumour visualisation on diagnostic PET scans [28].

Whilst no head-to-head studies have been conducted on Lu-TLX591 monoclonal antibodies versus small molecule ligands for advanced prostate cancer, the latter has gained much independent interest in recent years. The landmark phase 3 VISION trial evaluating Lu-177-PSMA-617 in patients with metastatic castration-resistant prostate cancer reported improved radiological progression-free survival (8.7 months versus 3.4 months), ≥ 50% PSA decline (46% versus 7.1%) and overall survival (15.3 months versus 11.3 months) amongst patients who underwent Lu-PSMA-617 and conventional therapy versus conventional therapy alone [29]. Whilst higher rates of grade 3–4 toxicity were experienced in the Lu-PSMA-617 cohort, rates of all-grade haematological toxicity were clinically acceptable and lower than in this current study [29]. In future, studies comparing the effectiveness, toxicity and feasibility of prescribing monoclonal antibodies and small-molecule ligands in the real world would be valuable alongside explorations of potential synergy between monoclonal antibodies, small-molecule ligands and other oncological therapies for advanced prostate cancer.

The retrospective nature of this study carries inherent limitations. Notably, approximately half of the patients were international patients travelling to Australia for treatment, which posed logistical challenges concerning follow-up imaging data and blood results. As such, in certain cases, it was difficult for disease progression data to be obtained. Moreover, owing to the recency of the data set, the relatively small data set and the loss of several subjects to follow up, patient overall survival and disease progression-free survival could not be definitively calculated at the time of writing. Lastly, owing to the small nature of our cohort, statistical relationships between patients' administered dose, haematological toxicity and disease outcomes were not made.

5 Conclusion

In summary, Lu-TLX591 monoclonal antibody was safely administered with acceptable toxicity to a small cohort of metastatic prostate cancer patients. The lower rates of haematological toxicity recorded in this study versus previous clinical trials likely reflect the study's fractionated and personalised approach to dose administration and better premorbid patient profiles. In keeping with previous trial data, PSA monitoring and radiology reveal that half had stable disease, around four-fifths had disease progression and a small percentage had disease regression. Going forward, larger studies on Lu-TLX591 are underway (NCT04786847; NCT05146973; NCT04876651) to determine its effectiveness amongst different prostate cancer populations and to compare its efficacy with the recently approved peptide-based radiopharmaceutical agents.

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Declarations

Conflict of interest NL is a scientific advisor to Telix Pharmaceuticals and a principal investigator on the ProstACT trials using Lu-TLX591. No other authors (KH, JC, SS and HN) have relevant financial or non-financial interests to declare.

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Ethics approval Low or negligible risk research approval by St Vincent's Hospital Human Research Ethics Committee (HREC), ETH00247 in accordance with the National Statement on Ethical Conduct in Human Research, 2007 (NHMRC). Cross-institutional approval reviewed by the University of Notre Dame HREC, 2023-052F in accordance with the National Statement on Ethical Conduct in Human Research.

Consent to participate Not applicable

Consent for publication Not applicable

Data availability The datasets generated during and/or analysed during the current study are available from the corresponding author upon reasonable request.

Author contribution All authors contributed to the study's conception and design. Material preparation, data collection and analysis were performed by NL, KH, JC, SS, and HN. The first draft of the manuscript was written by HN and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Code availability Not applicable

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