[^{89}Zr]Zr-girentuximab for PET–CT imaging of clear-cell renal cell carcinoma: a prospective, open-label, multicentre, phase 3 trial

Brian Shuch, Allan J Pantuck, Jean-Christophe Bernhard, Michael A Morris, Viraj Master, Andrew M Scott, Charles van Praet, Clement Bailly, Bülent Önal, Tamer Aksoy, Robin Merkx, David M Schuster, Sze Ting Lee, Neeta Pandit-Taskar, Alice C Fan, Phillip Allman, Karl Schmidt, Libuse Tauchmanova, Michael Wheatcroft, Christian Behrenbruch, Colin R W Hayward, Peter Mulders

Summary

Background With limitations of conventional imaging and biopsy, accurate, non-invasive techniques to detect clear-cell renal cell carcinoma in patients with renal masses remain an unmet need. ^{89}Zr-labelled monoclonal antibody ([^{89}Zr]Zr-girentuximab) has high affinity for carbonic anhydrase 9, a tumour antigen highly expressed in clear-cell renal cell carcinoma. We aimed to evaluate [^{89}Zr]Zr-girentuximab PET–CT imaging for detection and characterisation of clear-cell renal cell carcinoma.

Methods ZIRCON was a prospective, open-label, multicentre, phase 3 trial conducted at 36 research hospitals and practices across nine countries (the USA, Australia, Canada, the UK, Türkiye, Belgium, the Netherlands, Spain, and France). Patients aged 18 years or older with an indeterminate renal mass 7 cm or smaller (cT1) suspicious for clear-cell renal cell carcinoma and scheduled for nephrectomy received a single dose of [^{89}Zr]Zr-girentuximab (37 MBq ±10%; 10 mg girentuximab) intravenously followed by abdominal PET–CT imaging 5 days (±2 days) later. Surgery was performed no later than 90 days after administration of [^{89}Zr]Zr-girentuximab. Blinded central review, conducted by three independent readers, determined the histology from surgical samples. The coprimary endpoints, determined for each individual reader, were the sensitivity and specificity of [^{89}Zr]Zr-girentuximab PET–CT imaging to detect clear-cell renal cell carcinoma, with histopathological confirmation as standard of truth. Analyses were on the full analysis set of patients, defined as patients who had evaluable PET–CT imaging and a confirmed histopathological diagnosis. The trial is registered with ClinicalTrials.gov, NCT03849118, and EUDRA Clinical Trials Register, 2018-002773-21, and is closed to enrolment.

Findings Between Aug 14, 2019, and July 8, 2022, 371 patients were screened for eligibility, 332 of whom were enrolled. 300 patients received [^{89}Zr]Zr-girentuximab (214 [71%] male and 86 [29%] female). 284 (95%) evaluable patients were included in the primary analysis. The mean sensitivity was 85·5% (95% CI 81·5–89·6) and mean specificity was 87·0% (81·0–93·1). No safety signals were observed. Most adverse events were not or were unlikely to be related to [^{89}Zr]Zr-girentuximab, with most (193 [74%] of 261 events) occurring during or after surgery. The most common grade 3 or worse adverse events were post-procedural haemorrhage (in six [2%] of 261 patients), urinary retention (three [1%]), and hypertension (three [1%]). In 25 (8%) of 300 patients, 52 serious adverse events were reported, of which 51 (98%) occurred after surgery. There were no treatment-related deaths.

Interpretation Our results suggest that [^{89}Zr]Zr-girentuximab PET–CT has a favourable safety profile and is a highly accurate, non-invasive imaging modality for the detection and characterisation of clear-cell renal cell carcinoma, which has the potential to be practice changing.

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Introduction

Renal cell carcinomas make up 90% of solid renal masses. Although there are more than 12 subtypes, 75% of renal cell carcinomas are clear-cell renal cell carcinomas, which account for 90% of patient deaths.[1–5] Small renal masses, up to 4 cm in diameter, are often identified incidentally in patients due to increasing frequency of abdominal imaging, and the incidence of small renal masses is increasing with the ageing population and obesity epidemic.[6–8] In an era with gross overtreatment, identification of clear-cell renal cell carcinoma, the most aggressive and common form of kidney cancer, can help optimise patient stratification for appropriate treatment.

Delayed diagnosis of renal cell carcinoma might result in substantially decreased 5-year relative survival rates, which can be as low as 12% in patients with metastatic disease. However, if detected and treated early, patients

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Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, CA, USA (B Shuch MD, A J Pantuck MD); **Department of Urology, Centre Hospitalier Universitaire de Bordeaux—Groupe Hospitalier Pellegrin, Bordeaux, France** (J-C Bernhard MD); **United Theranostics, Glen Burnie, Baltimore, MD, USA** (M A Morris MD); **Department of Urology, Emory University School of Medicine, Atlanta, GA, USA** (V Master MD); **Department of Molecular Imaging and Therapy, Austin Health, Melbourne, VIC, Australia** (A M Scott MD, S T Lee MD); **Department of Medicine, The University of Melbourne, Melbourne, VIC, Australia** (A M Scott, S T Lee); **Olivia Newton-John Cancer Research Institute, Melbourne, VIC, Australia** (A M Scott, S T Lee); **School of Cancer Medicine, La Trobe University, Melbourne, VIC, Australia** (A M Scott, S T Lee); **Department of Urology, Ghent University Hospital, Ghent, Belgium** (C van Praet MD); **Department of Nuclear Medicine, Nantes University Hospital, Nantes, France** (C Bailly MD); **Department of Urology, Istanbul University-Cerrahpasa, Istanbul, Turkey** (B Önal MD); **Department of Nuclear Medicine, Istanbul Training and Research Hospital, Istanbul, Turkey** (T Aksoy MD); **Department of Medical Imaging, Nuclear Medicine, Radboud University Medical Center, Nijmegen, Netherlands** (R Merkx MD); **Department of Radiology and Imaging Sciences, Emory University,**

Atlanta, GA, USA (D M Schuster MD); **Memorial Sloan Kettering Cancer Center, New York, NY, USA** (N Pandit-Taskar MD); **Weill Cornell Medical College, New York, NY, USA** (N Pandit-Taskar); **Department of Medicine, Division of Oncology, Stanford University School of Medicine, Stanford, CA, USA** (A C Fan MD); **Premier Research, Morrisville, NC, USA** (P Allman PhD); **ABX-CRO Advanced Pharmaceutical Services Forschungsgesellschaft, Dresden, Germany** (K Schmidt); **Telix Pharmaceuticals, Melbourne, VIC, Australia** (L Tauchmanova MD, M Wheatcroft PhD, C Behrenbruch DPhil, C R W Hayward MBBS); **Department of Urology, Radboud University Medical Center, Nijmegen, Netherlands** (P Mulders MD)

Correspondence to: Brian Shuch, Institute of Urologic Oncology, University of California Los Angeles, Los Angeles, CA 90095, USA
bshuch@mednet.ucla.edu

Research in context

Evidence before this study

We searched PubMed on Oct 16, 2018, for the terms "indeterminate renal mass", "renal cell carcinoma histology", and "renal cell carcinoma imaging" with no language or time restrictions. Articles were screened by title and abstract for relevance, and those that explored renal cell carcinoma diagnosis and characterisation, patient management, and consensus guidelines were considered for full-text review. Evidence supports the unmet need for an accurate, non-invasive imaging modality for the detection and characterisation of clear-cell renal cell carcinoma from other renal and extrarenal lesions. The incidence of small renal masses is increasing. Diagnosis and treatment are limited by current imaging techniques, and renal mass biopsy is invasive, often incurs complications such as clinically significant renal haematoma and tumour seeding, and can underestimate tumour grade. Many patients undergo unnecessary surgery to remove masses that are later determined to be benign, and partial nephrectomies can have complications. In a phase 1 trial, [^{89}Zr]Zr-girentuximab PET accurately confirmed the presence or absence of metastatic clear-cell renal cell carcinoma and differentiated non-clear-cell renal cell cancers, which favourably impacted decisions for surgery. In line with previous research, this trial also confirmed a favourable safety profile of radiolabelled girentuximab.

Added value of this study

To our knowledge, ZIRCON is the first prospective, open-label, large, multinational, phase 3 trial to assess the diagnostic performance of [^{89}Zr]Zr-girentuximab PET–CT to non-invasively detect, differentiate, and characterise clear-cell renal cell carcinoma and other lesions in patients with indeterminate renal masses. Results support the high diagnostic performance and favourable safety profile of [^{89}Zr]Zr-girentuximab PET–CT.

Implications of all the available evidence

Delays in the diagnosis of renal cell carcinoma might result in substantially decreased 5-year relative survival rates. Therefore, a high unmet need exists for diagnostic tools that can more accurately classify tumour subtypes, support staging, and help risk stratify patients earlier. [^{89}Zr]Zr-girentuximab PET–CT imaging accurately identified clear-cell renal cell carcinoma in patients with a cT1 indeterminate renal mass (≤7 cm), with a favourable safety profile. Given its high diagnostic performance, including for very small lesions, [^{89}Zr]Zr-girentuximab PET–CT imaging could support early and accurate diagnosis, inform patient risk stratification and clinical decision making, and reduce overtreatment and undertreatment, thereby leading to improved patient outcomes. Our data support the value of [^{89}Zr]Zr-girentuximab PET–CT imaging as a new standard, non-invasive tool for the diagnosis and detection of clear-cell renal cell carcinoma from other renal and extrarenal lesions in clinical practice, minimising the risk of unnecessary invasive interventions. Imaging using [^{89}Zr]Zr-girentuximab has the potential to change clinical practice in renal cancer, including staging and monitoring patients at high risk, and detection of distant metastasis. Additional trials to further ascertain effects on patient management and clinical utility of [^{89}Zr]Zr-girentuximab PET–CT for other renal cancer subtypes are warranted.

with localised renal cell carcinoma have a 5-year relative survival rate of more than 90%.[9]

Treatment of renal masses is often based on abdominal CT, MRI, or renal mass biopsy results, which have major limitations.[10–12] CT and MRI cannot reliably differentiate between benign and malignant renal lesions, or provide information about disease biology.[4,6,12,13] PET or PET–CT imaging with available tracers have limited roles in the diagnosis and characterisation of renal tumours due to poor uptake, poor specificity and sensitivity, and excretion from the collecting system.[12,14] Renal mass biopsy is invasive, with a high non-diagnostic rate (up to 15%), poor negative predictive capability, and substantial discrepancies with definitive histology.[11,15,16] Sampling error or suboptimal sampling site can underestimate the tumour grade within heterogenous renal cell carcinomas.[17] Renal mass biopsy cannot show extrarenal spread, precise cancer location, or extent, and has risks of complications, including seeding of the biopsy tract.[15,18] Overtreatment of indeterminate renal masses, including small renal masses, might cause adverse health outcomes, with one trial reporting a 10% rate of surgical complications in patients with benign lesions who underwent elective partial nephrectomy for suspected renal cell carcinoma.[19] Up to 30% of small renal masses removed by partial nephrectomy are benign.[13]

Current challenges facing the diagnostic uncertainty of clear-cell renal cell carcinoma underscore an unmet need for a new, non-invasive technique that accurately detects and differentiates clear-cell renal cell carcinoma from other renal masses in patients to inform clinical decision making. Girentuximab, a chimeric monoclonal antibody targeting carbonic anhydrase 9 (CAIX), a tumour-associated antigen highly expressed in clear-cell renal cell carcinoma, might aid differentiating this tumour from other lesions.[20,21] In a phase 1 trial, [^{89}Zr]Zr-girentuximab showed a favourable safety profile, supporting its use in imaging of patients with suspected clear-cell renal cell carcinoma.[22] In the phase 1/2 ZIRDEE trial,[23] which included patients with localised renal masses, [^{89}Zr]Zr-girentuximab accurately confirmed the presence or absence of metastatic clear-cell renal cell carcinoma and differentiated non-clear-cell renal cell carcinoma cancers, which impacted clinical decision making in up to 86% of patients.[23]

We aimed to evaluate the sensitivity and specificity of [89Zr]Zr-girentuximab PET–CT imaging to non-invasively detect clear-cell renal cell carcinoma in patients with cT1 indeterminate renal masses (≤7 cm in diameter) who underwent nephrectomy, using central histological confirmation as standard of truth.

Methods

Study design and participants

ZIRCON was a prospective, open-label, multicentre, phase 3 trial conducted at 36 research hospitals and practices across nine countries (the USA, Australia, Canada, the UK, Türkiye, Belgium, the Netherlands, Spain, and France; appendix pp 2–3).

Eligible patients were aged 18 years or older, with evidence of a single, localised indeterminate renal mass 7 cm or smaller in the largest diameter that was suspicious for renal cell carcinoma. Imaging consisted of a contrast-enhanced CT or MRI performed within 90 days of trial start (day 0). Key exclusion criteria included renal mass known to be metastasis of another primary tumour; active non-renal malignancy requiring therapy during the timeframe of trial participation; chemotherapy, radiotherapy, or immunotherapy within 4 weeks before planned [89Zr]Zr-girentuximab administration; antineoplastic therapies planned between [89Zr]Zr-girentuximab administration and imaging; renal insufficiency with glomerular filtration rate 45 mL/min per 1·73 m² or less; or exposure to murine or chimeric antibodies within the past 5 years. Full details of eligibility criteria are in the appendix (p 7). Sex, race, and ethnicity were defined according to individual sites.

The trial was designed, conducted, interpreted, and reported as a collaboration between the lead investigators, trial sponsor, and independent contractors. This manuscript was drafted with the Standards for Reporting Diagnostic accuracy studies checklist.[24] The trial was conducted in accordance with the principles of the Declaration of Helsinki and International Conference on Harmonization guideline E6: Good Clinical Practice guidelines. All participants provided written informed consent. At each site, institutional review boards or ethics committees (appendix pp 4–6) approved the trial protocol, which is available in the appendix. An independent committee monitored safety throughout the trial. The conduct of this clinical trial met all local, legal, and regulatory requirements.

This trial was registered with ClinicalTrials.gov, NCT03849118, and EUDRA Clinical Trials Register, 2018-002773-21.

Procedures

Patients underwent formal screening with baseline examinations. Patients could withdraw at any time for any reason. Investigators could withdraw a patient for any of the following reasons: adverse event, non-compliance, protocol violation, pregnancy, or loss to follow-up. Once withdrawn, no follow-up was conducted.

Eligible patients received a single dose of [89Zr]Zr-girentuximab by slow intravenous injection over a minimum of 3 min (37 MBq ±10%; 10 mg girentuximab) on day 0, and then underwent abdominal PET–CT imaging on day 5 (±2 days). In patients with unexpected evidence for disseminated disease, PET–CT imaging could be extended to whole-body imaging (skull base to mid-thigh) at the discretion of the investigator. Patients were scheduled for partial or radical nephrectomy, based on the surgeon's preference for routine management, within 90 days of planned intravenous administration of [89Zr]Zr-girentuximab. Blinded central review, conducted by three independent readers, determined the histology from surgical samples. Readers were three experienced individuals, masked to patient medical history and any previous histology results, who conducted central and independent PET–CT imaging analysis. Each reader received training before the trial, and performance was checked via frequent monitoring. On day 42 (±7 days) after [89Zr]Zr-girentuximab injection, patients participated in a trial visit to assess potential formation of human antichimeric antibodies (HACAs) and review of safety parameters. Further details of trial visits and safety parameters are provided in the trial protocol (appendix).

See Online for appendix

Outcomes

The coprimary endpoints, determined for each individual reader, were the sensitivity and specificity of [89Zr]Zr-girentuximab PET–CT imaging to non-invasively detect clear-cell renal cell carcinoma in patients with cT1 indeterminate renal masses (≤7 cm) who underwent partial or radical nephrectomy. Key secondary endpoints were the sensitivity and specificity of [89Zr]Zr-girentuximab PET–CT imaging to detect clear-cell renal cell carcinoma in the subgroup of patients with cT1a indeterminate renal masses (≤4 cm). Sensitivity was defined as the proportion of patients with a true-positive [89Zr]Zr-girentuximab PET–CT scan, relative to those with a positive clear-cell renal cell carcinoma histopathological diagnosis. Specificity was defined as the proportion of patients with a true-negative [89Zr]Zr-girentuximab PET–CT scan (no clear-cell renal cell carcinoma), relative to those with a negative histopathological diagnosis.

Other secondary endpoints were the positive predictive value, negative predictive value, and accuracy of [89Zr]Zr-girentuximab PET–CT imaging in patients with a cT1 indeterminate renal mass and patients with a cT1a indeterminate renal mass; standardised uptake value cutoff for [89Zr]Zr-girentuximab to discriminate clear-cell renal cell carcinoma from non-clear-cell renal cell carcinoma subtypes using receiver operating characteristics (ROCs); inter-reader and intrareader variability; safety; and sensitivity, specificity, positive predictive value, negative predictive value, and accuracy

of detecting clear-cell renal cell carcinoma in patients with indeterminate renal masses 3 cm or smaller and 2 cm or smaller, and Bosniak 3 and 4 lesions as determined by independent central readers. The per-protocol analysis of Bosniak 3 and 4 lesions was identified as not being clinically meaningful, as all solid lesions were included in the subgroup Bosniak 4: clearly malignant. Given the importance for clinically meaningful analysis of Bosniak lesions, an ongoing study is being conducted to differentiate solid versus cystic lesions using Bosniak categorisation 1–4 and will be reported in a later publication. The positive predictive value was defined as the probability that a positive histopathology diagnosis was obtained given a positive [^{89}Zr]Zr-girentuximab PET–CT scan result (detection of clear-cell renal cell carcinoma). The negative predictive value was defined as the probability that a negative histopathology diagnosis was obtained given a negative [^{89}Zr]Zr-girentuximab PET–CT scan (no detection of clear-cell renal cell carcinoma). The accuracy was defined as the probability that the [^{89}Zr]Zr-girentuximab PET–CT scan result was correct.

The mean standardised uptake value was then used to predict an optimal cutoff point for maximum, mean, and peak tumour to background ratio using ROC analysis as a post-hoc assessment.

PET positivity as qualitative [^{89}Zr]Zr-girentuximab tracer uptake in target lesion by visual reading (yes or no) and histopathological designation of clear-cell renal cell carcinoma-positive and non-clear-cell histology (standard of truth) were used to determine specificity and sensitivity. Standardised uptake value assessment was based on reader-defined volume of interest, which was based on tumour morphology. PET reading was performed with mintLesion (version 3.8.5; Mint Medical, Heidelberg, Germany).

The safety profile was assessed as adverse events as well as changes in laboratory parameters, vital signs, electrocardiogram, and HACA titres. Adverse events were recorded according to the Common Terminology Criteria for Adverse Events (version 5.0), and classified as related, possibly related, unlikely, not related, and not assessable based on likelihood that the event was caused by [^{89}Zr]Zr-girentuximab or trial conduct. Adverse events and concomitant medications were recorded continuously after [^{89}Zr]Zr-girentuximab administration until end of trial participation.

Statistical analysis

Sample size was estimated for sensitivity and specificity, and the larger of the two estimates determined sample size. Originally, assuming approximately 70% of patients with cT1a lesions and 30% of patients with cT1b lesions (>4 cm to ≤7 cm), and 34% non-clear-cell renal cell carcinoma in the cT1a subgroup, a minimum estimated sample size of 252 patients was considered sufficient. For sensitivity, to ensure the study had 90% power to show that the lower limit of the two-sided 95% Wilson CI for sensitivity was above the critical limit (or non-inferiority limit) of 70%, the minimum sample size required for the population of patients with cT1 lesions under the above assumption was 125, when assuming a true sensitivity of 83%. For specificity, to ensure the study had 90% power to show that the lower limit of the two-sided 95% Wilson CI for the specificity was above the critical limit (or non-inferiority limit) of 68%, the minimum sample size required for the population of patients with cT1 lesions under above assumptions was 252, when assuming a true specificity of 83%.

An independent data monitoring committee monitored patient accrual and histological results to ensure the trial was sufficiently powered. Due to the actual number of enrolled patients classified as positive or negative for clear-cell renal cell carcinoma, the protocol was amended on Sept 30, 2019, to increase sample size to 300 patients and extend trial duration to enable sufficient patient recruitment. Analyses were done on the full analysis set, defined as patients who had evaluable PET–CT imaging and confirmed histopathological diagnosis. Safety analyses were conducted on all patients who received [^{89}Zr]Zr-girentuximab. Patients were defined as not assessable if they did not have evaluable [^{89}Zr]Zr-girentuximab PET–CT images or confirmed histopathological diagnosis.

The trial was deemed successful if the lower bound of the 95% CI for sensitivity was greater than 70% and if the lower bound of the 95% CI for specificity was greater than 68%, in at least the same two of three independent readers. Wilson's binomial (score) CIs were used to compare the 95% CI lower boundary of each quantity with their prespecified threshold. Assuming the null hypothesis was rejected for both coprimary endpoints, formal statistical testing would proceed to key secondary endpoints, using the fixed-sequence method, assessing sensitivity first followed by specificity.

Standardised uptake values were determined for each tumour lesion. ROCs were analysed to identify a standardised uptake value cutoff most appropriate to discriminate between clear-cell renal cell carcinoma and non-clear-cell renal cell carcinoma as evidenced by central histology results.

Fleiss' κ statistics were used to determine inter-reader variability, with an intraclass κ of 0·70 or more considered an acceptable value. Cohen's κ statistics were used to determine intrareader variability, using a subset of 10% of randomly selected cases read twice per reader. Two-sided tests were used for the coprimary and key secondary endpoints. To account for multiplicity and control type 1 error under the paradigm of two coprimary endpoints, sensitivity and specificity were each estimated at a 5% significance level.

For continuous variables, descriptive statistics included the number of patients, mean (SD), median (IQR), minimum, and maximum by analysis group. Frequencies and percentages were calculated for categorical data by

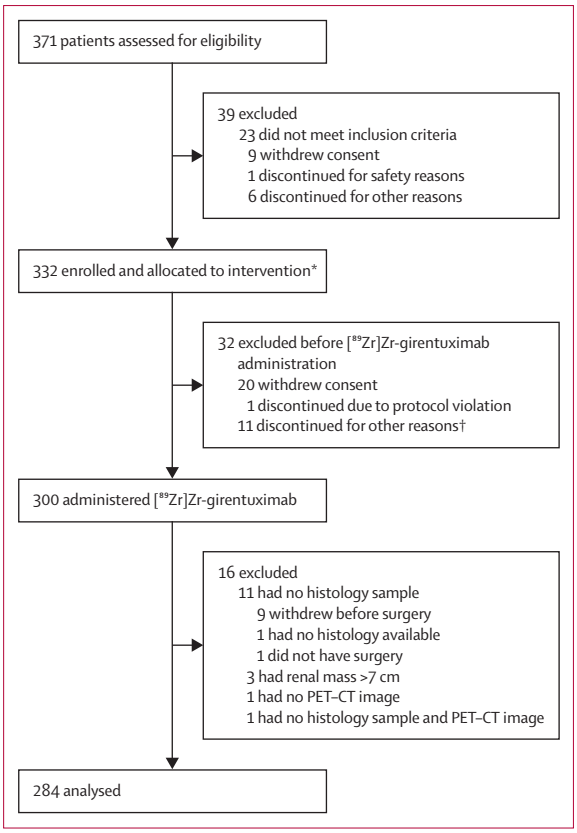


Figure 1: **Trial profile**
*Patients who met the eligibility criteria and were scheduled to receive a single dose of [89Zr]Zr-girentuximab, regardless of whether they took any trial drug. †Patients did not receive [89Zr]Zr-girentuximab due to shipment delay or related constraints; one patient had an illness before dose administration.

	All patients (n=300)
Age, years	
Mean	61 (12)
Median	62 (27–87)
Sex	
Female	86 (29%)
Male	214 (71%)
Race	
White	277 (92%)
Black or African American	13 (4%)
Asian	9 (3%)
Other*	0
Missing	1 (<1%)
Ethnicity	
Hispanic or Latino	28 (9%)
Not Hispanic or Latino	272 (91%)
Tumour location†	
Inferior left	47 (14%)
Inferior right	59 (18%)
Superior left	28 (8%)
Superior right	23 (7%)
Posterior left	25 (8%)
Posterior right	10 (3%)
Apical left	31 (9%)
Apical right	30 (9%)
Middle left	35 (11%)
Middle right	44 (13%)
Human anti-chimeric antibody‡	
Mean titre	86·7 (153·7)
Positive	16 (5%)
Negative	277 (95%)
Concomitant and previous medication use	258 (86%)

Data are median (range), mean (SD), or n (%). Baseline values were taken on day 0 (day of [89Zr]Zr-girentuximab administration) before dose administration, and at screening for human antichimeric antibody and tumour location. *Included patients who reported their race as American Indian or Alaskan Native, Native Hawaiian, or other Pacific Islander. †Calculated as a proportion of 332 patients who were enrolled and allocated to receive [89Zr]Zr-girentuximab. ‡n=293 patients with evaluable human anti-chimeric antibody samples. Seven patient samples excluded due to analysis outside protocol-specified timeframe. Percentage calculated as proportion of 293.

Table 1: **Patient demographics and characteristics at baseline**

analysis group and by dose administration or time, where applicable. Percentages by categories were based on the number of patients with no missing data.

Missing efficacy results were not imputed because missing data were not expected for outcomes that involve a standard of truth for positive or negative confirmation of readings. Statistical analysis was performed with SAS (version 9.4 or higher).

Role of the funding source

The funder of the study had oversight of all trial aspects including study design, data collection, data analysis, data interpretation, preparation and review of the manuscript, and the decision to submit the manuscript for publication.

Results

Between Aug 14, 2019, and July 8, 2022, 371 patients were screened for eligibility, 332 of whom were enrolled (figure 1). 300 patients received [89Zr]Zr-girentuximab. The mean age was 61 years (SD 12), 214 (71%) patients were male and 86 (29%) were female (table 1). Images were evaluable in 287 (96%) patients, three (1%) of whom had lesions larger than 7 cm and were therefore not eligible for inclusion in the full analysis set. Information on the representativeness of trial participants is in the appendix (p 8). 284 (95%) evaluable patients were included in the primary analysis (figure 1). Accordingly, less than 5% of data was missing, with no impact on overall study results, outcomes, or interpretation.

The performance parameters of [89Zr]Zr-girentuximab PET–CT imaging by individual readers are shown in table 2. Mean sensitivity was 85·5% (95% CI 81·5–89·6) and mean specificity was 87·0% (81·0–93·1). Sensitivity and specificity as determined by each reader exceeded prespecified thresholds. Mean positive predictive value,

	Reader 1	Reader 2	Reader 3	Mean
All evaluable patients (n=284)				
Sensitivity	84·1% (78·2–88·7)	85·2% (79·4–89·6)	87·3% (81·8–91·3)	85·5% (81·5–89·6)
Specificity	88·4% (80·5–93·4)	88·4% (80·5–93·4)	84·2% (75·6–90·2)	87·0% (81·0–93·1)
Positive predictive value	93·5% (88·8–96·4)	93·6% (88·9–96·4)	91·7% (86·7–94·9)	92·9% (90·2–95·7)
Negative predictive value	73·7% (64·9–80·9)	75·0% (66·2–82·1)	76·9% (68·0–84·0)	75·2% (71·2–79·3)
Accuracy	85·6% (81·0–89·2)	86·3% (81·8–89·8)	86·3% (81·8–89·8)	86·0% (85·0–87·0)
Indeterminate renal mass ≤4 cm cT1a subgroup (n=145)				
Sensitivity	83·5% (74·6–89·8)	85·7% (77·1–91·5)	85·7% (77·1–91·5)	85·0% (81·8–88·1)
Specificity	90·7% (80·1–96·0)	90·7% (80·1–96·0)	87·0% (75·6–93·6)	89·5% (84·2–94·8)
Positive predictive value	93·8% (86·4–97·3)	94·0% (86·7–97·4)	91·8% (84·0–96·0)	93·2% (90·1–96·3)
Negative predictive value	76·6% (64·9–85·3)	79·0% (67·4–87·3)	78·3% (66·4–86·9)	78·0% (74·8–81·1)
Accuracy	86·2% (79·7–91·0)	87·6% (81·2–92·0)	86·2% (79·7–91·0)	86·7% (84·7–88·6)
Indeterminate renal mass ≤3 cm subgroup (n=76)				
Sensitivity	83·0% (69·9–91·1)	85·1% (72·3–92·6)	85·1% (72·3–92·6)	84·4% (81·4–87·5)
Specificity	93·1% (78·0–98·1)	89·7% (73·6–96·4)	89·7% (73·6–96·4)	90·8% (85·9–95·8)
Positive predictive value	95·1% (83·9–98·7)	93·0% (81·4–97·6)	93·0% (81·4–97·6)	93·7% (90·7–96·7)
Negative predictive value	77·1% (61·0–87·9)	78·8% (62·3–89·3)	78·8% (62·3–89·3)	78·2% (75·9–80·6)
Accuracy	86·8% (77·5–98·7)	86·8% (77·5–92·7)	86·8% (77·5–92·7)	86·8% (77·5–92·7)
Indeterminate renal mass ≤2 cm subgroup (n=20)				
Sensitivity	100·0% (72·3–100·0)	100·0% (72·3–100·0)	90·0% (59·6–98·2)	96·7% (82·3–100·0)
Specificity	100·0% (72·3–100·0)	100·0% (72·3–100·0)	90·0% (59·6–98·2)	96·7% (82·3–100·0)
Positive predictive value	100·0% (72·3 –100·0)	100·0% (72·3–100·0)	90·0% (59·6–98·2)	96·7% (82·3–100·0)
Negative predictive value	100·0% (72·3–100·0)	100·0% (72·3–100·0)	90·0% (59·6–98·2)	96·7% (82·3–100·0)
Accuracy	100·0% (83·9–100·0)	100·0% (83·9–100·0)	90·0% (69·9–97·2)	96·7% (82·3–100·0)

Data are % (95% CI). The means and corresponding 95% CIs were calculated from the three reader results. The 95% CIs were calculated based only on the mean sensitivity, specificity, positive predictive value, negative predictive value, and accuracy and not on the proportions of sensitivity, specificity, positive predictive value, negative predictive value, and accuracy. Therefore, no inference can be made from these CIs in reference to the ZIRCON trial. N represents the number of patients included in the analysis (patients had evaluable PET–CT imaging and a confirmed histopathology diagnosis). Of 284 evaluable patients, 189 patients had histologically verified clear-cell renal cell carcinoma and 95 evaluable patients had non-clear-cell renal cell carcinoma (other histology).

Table 2: **Performance parameters of [^{89}Zr]Zr-girentuximab PET–CT imaging by reader**

	Reader 1	Reader 2	Reader 3	Mean
Maximum standardised uptake value				
Cutoff point	25·2	25·2	24·1	24·09
Sensitivity	80·8%	80·2%	81·8%	80·8%
Specificity	96·7%	94·6%	96·7%	95·7%
Youden index	77·5	74·8	78·5	76·4
Euclidean distance	0·2	0·2	0·2	0·2
Mean standardised uptake value				
Cutoff point	12·6	13·6	12·3	11·8
Sensitivity	79·1%	81·9%	81·2%	83·5%
Specificity	92·4%	92·4%	90·1%	89·1%
Youden index	71·5	74·3	71·3	72·7
Euclidean distance	0·2	0·2	0·2	0·2
Peak standardised uptake value				
Cutoff point	15·5	16·2	16·6	16·3
Sensitivity	85·2%	84·1%	82·3%	83·0%
Specificity	90·2%	92·4%	94·5%	94·6%
Youden index	75·4	76·5	76·8	77·5
Euclidean distance	0·2	0·2	0·2	0·2

Optimal standardised uptake value threshold is where Youden index is maximum. Standardised uptake value was calculated using digital imaging and communications in medicine weight, therefore not validated and not used in standardised uptake value statistics.

Table 3: **Standardised uptake value cutoff for [^{89}Zr]Zr-girentuximab to discriminate clear-cell renal cell carcinoma from non-clear-cell renal cell carcinoma for all patients (n=300)**

negative predictive value, and accuracy are shown in table 2.

Of 284 evaluable patients, 145 patients (51%) had cT1a lesions (≤4 cm) assessed by central review. Mean sensitivity and specificity in detecting cT1a lesions are shown in table 2. Sensitivity and specificity as determined by each reader exceeded prespecified thresholds. Mean positive predictive value, negative predictive value, and accuracy for the cT1a subgroup are shown in table 2.

76 (27%) of 284 patients had indeterminate renal masses 3 cm or smaller, and 20 (7%) patients had indeterminate renal masses 2 cm or smaller assessed by central review (table 2). Mean sensitivity, specificity, positive predictive value, negative predictive value, and accuracy for both subgroups are shown in table 2.

The mean cutoff points to discriminate clear-cell renal cell carcinoma from non-clear-cell renal cell carcinoma lesions are shown in table 3. Results of the post-hoc analysis of tumour-to-background ratio cutoff points are reported in the appendix (pp 9–10). The Fleiss' κ statistic for inter-reader variability was 91·1% (95% CI 87·1–95·1), and the Cohen's κ statistic for intrareader variability was 100·0% for each reader.

Central histology subtypes for PET-positive and PET-negative patients are in the appendix (p 11). There were 11 non-clear-cell renal cell carcinoma PET-positive lesions, of which eight (73%) were papillary carcinoma, one (9%) was an indeterminable subtype (mixed histology), one (9%) was sarcoma, and one (9%) was oncocytoma with sarcomatous component. All PET-positive lesions were malignant. 11 false-negatives were recorded by reader 1, 11 by reader 2, and 15 by reader 3. Representative images of a clear-cell renal cell carcinoma lesion, benign lesions, and a false-negative clear-cell renal cell carcinoma lesion are in figure 2.

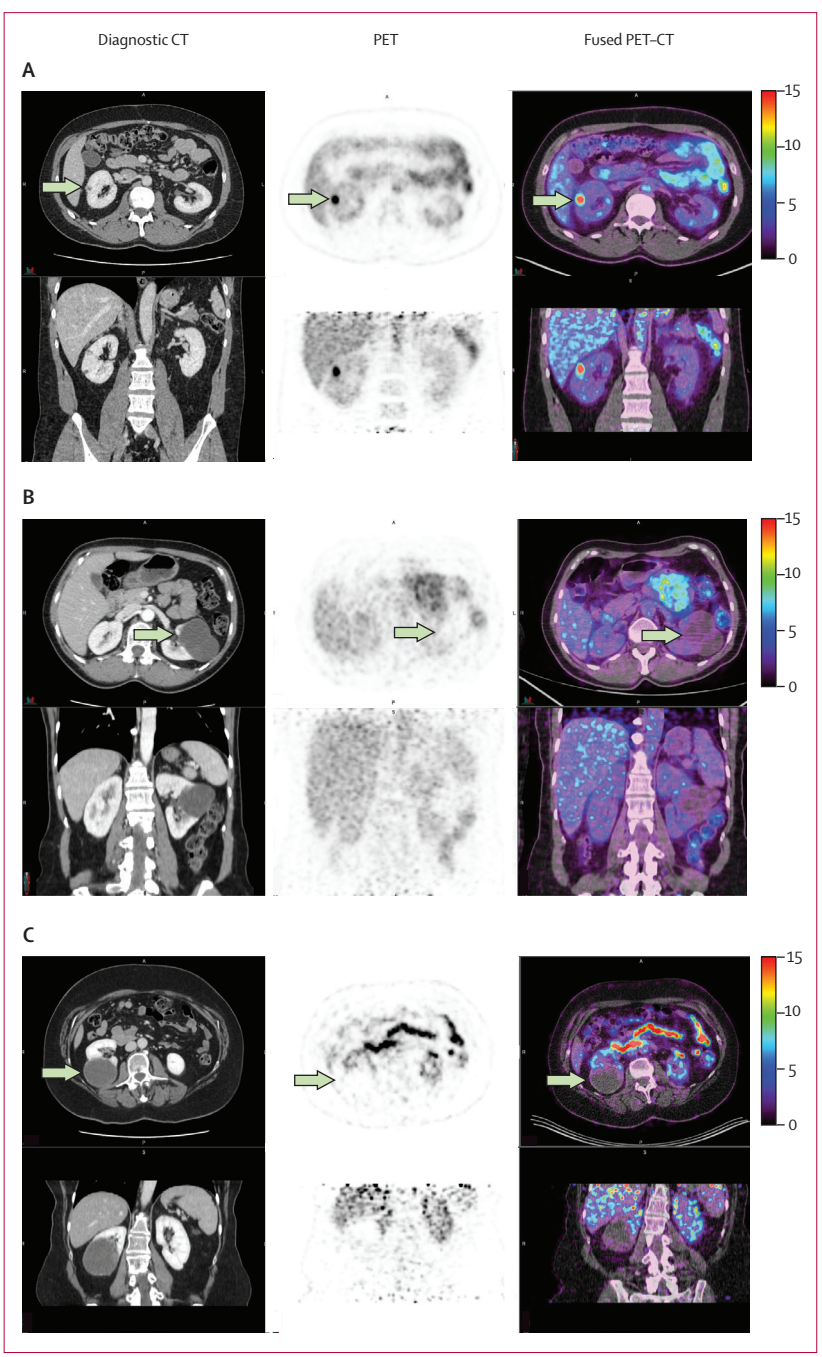
Among the 300 patients who received [89Zr]Zr-girentuximab, the mean calculated radiation activity per patient was 37·3 MBq (SD 2·3; appendix p 12). Overall, 261 adverse events were reported in 122 (41%) of 300 patients (table 4). 193 (74%) adverse events occurred during or after surgery, and 146 (56%) of these adverse events were mild in intensity. The most common adverse events, each with one event per person, that were considered severe (grade ≥3) were post-procedural haemorrhage (in six [2%] patients), urinary retention (three [1%]), and hypertension (three [1%]). 246 (94%) adverse events were not related or unlikely to be related to [89Zr]Zr-girentuximab, with two additional events not having an assessable causality. 13 (5%) adverse events were considered possibly or definitely related to [89Zr]Zr-girentuximab and were reported in eight (3%) patients (diarrhoea, abdominal pain, fatigue [two events], asthenia, pyrexia, hypoaesthesia, back pain, urinary retention [two events], dysuria, night sweats, and increased urine output). In 25 (8%) of 300 patients, 52 serious adverse events were reported, of which 51 (98%) occurred after surgery. Only one (2%) serious adverse event (urinary retention) was considered possibly related to [89Zr]Zr-girentuximab. Three (1%) adverse events that were not related to [89Zr]Zr-girentuximab led to discontinuation from the trial (two deaths and one stroke). One death occurred 4 days after surgery due to an unknown cause, and one death occurred 6 weeks after surgery due to surgical complications following hepatic artery incision. Neither of these deaths was considered related to [89Zr]Zr-girentuximab or PET procedure.

Relevant laboratory changes (mean eosinophils and leukocytes, platelets, erythocytes, haemoglobin, haematocrit, alkaline phosphatase, amylase, creatinine, gamma glutamyl transferase, eGFR, and lipase) did not occur directly after [89Zr]Zr-girentuximab administration but were reported between day 5 and the end of the trial (appendix pp 13–14). None of the laboratory changes reported as adverse events were considered related to [89Zr]Zr-girentuximab. 16 (5%) of 293 patients were HACA-positive at baseline and 277 (95%) patients were HACA-negative at baseline. The number of positive patients increased to 50 (17%) at day 42 (appendix p 12). Mean HACA concentration titres increased from 86·7 (SD 153·7) at baseline to 112·7 (170·9) at day 42.

Discussion

[89Zr]Zr-girentuximab PET–CT imaging accurately detected clear-cell renal cell carcinoma in patients with cT1 indeterminate renal masses (≤7 cm), with a mean sensitivity of 85·5% (95% CI 81·5–89·6) and a mean specificity of 87·0% (81·0–93·1). [89Zr]Zr-girentuximab PET–CT imaging performance was consistent in patients irrespective of smaller size of indeterminate renal mass. The primary and secondary endpoints were met by all three readers and exceeded prespecified thresholds. Inter-reader variability showed robust agreement among the readers and intrareader variability was 100%.

No safety concerns associated with the administration of [89Zr]Zr-girentuximab were observed, consistent with published literature.[22,23,25] For example, in the ARISER trial,[25] with patients with renal cell carcinoma who received up to 50 mg of unconjugated girentuximab in



(Figure 2 continues on next page)

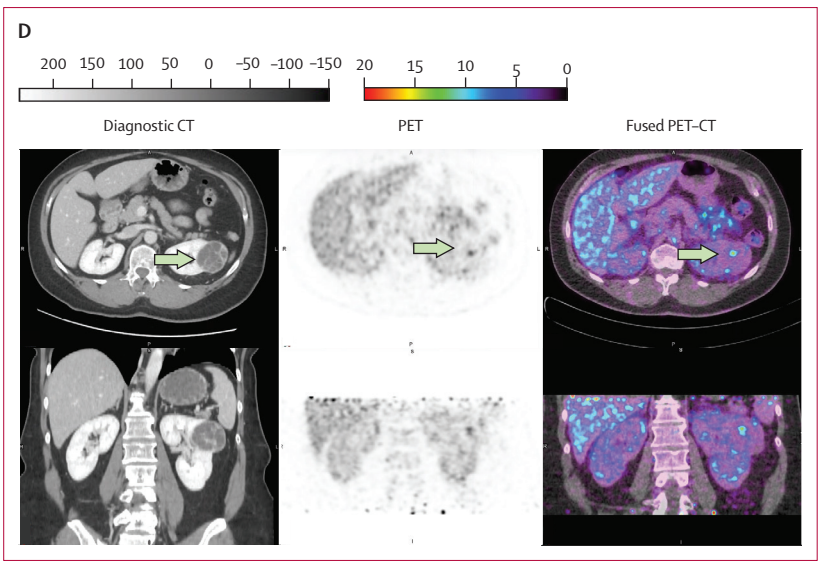


Figure 2: **Representative imaging with [^{89}Zr]Zr-girentuximab**
(A) A 40-year-old male with 12 mm lesion in superior right kidney showing positive [^{89}Zr]Zr-girentuximab PET and histologically confirmed clear-cell renal cell carcinoma. (B) A 53-year-old female with 62 mm lesion in middle-left kidney with negative [^{89}Zr]Zr-girentuximab PET and histologically confirmed benign lesion. (C) A 63-year-old female with 62 mm lesion in middle right kidney with negative [^{89}Zr]Zr-girentuximab PET and histologically confirmed papillary renal cell carcinoma. (D) A 59-year-old female with 57·5 mm left kidney lesion with negative [^{89}Zr]Zr-girentuximab PET and histologically confirmed clear-cell renal cell carcinoma. Arrows indicate lesion locations.

week 1 (five times the dose in this trial) followed by weekly infusions of 20 mg over 24 weeks, no differences in adverse events were observed versus placebo.

Girentuximab, a monoclonal antibody, has a longer uptake and clearance time than small molecules. Radiolabelling with ^{89}Zr, which has a long physical half-life (78·4 h) compared with ^{18}F (half-life 110 min),[26] allows for optimal imaging with monoclonal antibodies. Merkx and colleagues[22] found that differentiation of clear-cell renal cell carcinoma from non-clear-cell renal cell carcinoma lesions was achieved sufficiently with administration of approximately 37 MBq of [^{89}Zr]Zr-girentuximab. The longer half-life allows administration of a lower dose while providing clear images with excellent tumour to background ratio and high standardised uptake value (for positive scans) following clearance of background radiolabel from the sera.[27,28] Our results support previous findings that imaging performed 5 days (±2 days) after approximately 37 MBq [^{89}Zr]Zr-girentuximab administration is sufficient to visualise and assess clear-cell renal cell carcinoma lesions.[22]

The flexible timeframe (5 days [±2 days]) between [^{89}Zr]Zr-girentuximab administration and PET–CT imaging has several advantages. First, patients can return home during this period, provided they follow minor safety measures (eg, avoiding crowded spaces and limiting close contact with others). Imaging can be scheduled according to the patient and imaging facility needs. Second, imaging can be scheduled in the morning when other patients might be undergoing injections of other imaging agents (eg, prostate-specific membrane antigen radiotracers) and waiting for sufficient uptake, thus optimising patient workflow and scanner time. Ultimately, this process optimisation will allow a greater number of patients to be imaged per day and enhance patient workflow efficiency.

In the REDECT trial,[29] [^{124}I]girentuximab PET–CT imaging showed significantly higher average sensitivity (86·2% *vs* 75·5%) and specificity (85·9% *vs* 46·8%) compared with standard-of-care CT imaging for detection of clear-cell renal cell carcinoma in patients scheduled for resection. PET–CT imaging accuracy (86·2% for average sensitivity and 85·9% for average specificity in lesions ranging from 0·2 cm to 22 cm) and safety results were similar to those reported here.[29] However, [^{124}I]girentuximab has the potential to dehalogenate with a higher rate of tumour clearance and renal excretion of iodine atoms.[28] [^{89}Zr]Zr-girentuximab offers advantages of superior image quality compared with [^{124}I]girentuximab due to greater tumour to background ratio and lesion retention, low urinary excretion, and hepatic clearance, enabling differentiation of renal masses, including smaller lesions, and resultantly clear PET–CT images. Rapid renal excretion of iodine for [^{124}I]girentuximab, due to residualisation of iodinated antibodies, can impair imaging performance for clear-cell renal cell carcinoma.[22,28,30] In our trial, the optimal maximum standardised uptake value cutoff was 24·1–25·2; however, PET readers relied only on qualitative information to assign clear-cell renal cell carcinoma-positive or clear-cell renal cell carcinoma-negative scans. Although accuracy and specificity are already high, performance could be further optimised by supportive software tools and comparison of maximum standardised uptake value of a reader-defined volume of interest with a predefined maximum standardised uptake value cutoff point. For patients with newly diagnosed renal lesions that cannot be adequately characterised by conventional imaging (ie, distinguishing clear-cell renal cell carcinoma from other histologies or subtypes or benign tumours), [^{89}Zr]Zr-girentuximab might contribute to improved clinical decision making. [^{89}Zr]Zr-girentuximab imaging might have the potential to help identify benign lesions, and ultimately avoid unnecessary surgical interventions or support a more conservative invasive treatment such active surveillance or ablation.

A high unmet need exists for diagnostic tools that can accurately classify tumour subtypes, support staging, and help risk stratify patients earlier without unnecessary and invasive procedures. The accurate detection of clear-cell renal cell carcinoma from non-clear-cell renal cell carcinoma in this trial suggests that [^{89}Zr]Zr-girentuximab PET–CT imaging is a reliable imaging modality to identify patients with clear-cell renal cell carcinoma. The non-invasive nature of this technique might be especially beneficial to those with a risk of complications with renal

	Grade 1–2	Grade 3	Grade 4	Grade 5
Gastrointestinal disorders				
Nausea	11 (4%)	1 (<1%)	0	0
Vomiting	6 (2%)	1 (<1%)	0	0
Abdominal pain	5 (2%)	1 (<1%)	0	0
Haemoperitoneum	0	1 (<1%)	0	0
Retroperitoneal effusion	0	1 (<1%)	0	0
General disorders and administration site conditions				
Asthenia	4 (1%)	1 (<1%)	0	0
Death	0	0	0	1 (<1%)
Multiple organ dysfunction syndrome	0	0	1 (<1%)	0
Injury, poisoning, and procedural complications				
Procedural pain	11 (4%)	1 (<1%)	0	0
Post-procedural haemorrhage	1 (<1%)	6 (2%)	0	0
Arterial injury	0	0	0	1 (<1%)
Post-procedural bile leak	0	1 (<1%)	0	0
Post-procedural complication	0	1 (<1%)	0	0
Post-procedural haematuria	0	1 (<1%)	0	0
Post-procedural hypotension	0	1 (<1%)	0	0
Postoperative renal failure	0	1 (<1%)	0	0
Procedural pneumothorax	0	1 (<1%)	0	0
Nervous system disorders				
Syncope	0	2 (1%)	0	0
Cerebrovascular accident	0	1 (<1%)	0	0
Infections and infestations				
Urinary tract infection	6 (2%)	1 (<1%)	0	0
Pyelonephritis	0	2 (1%)	0	0
Haematoma infection	0	1 (<1%)	0	0
Infection	0	1 (<1%)	0	0
Pneumonia	0	1 (<1%)	0	0
Sepsis	0	1 (<1%)	0	0
Musculoskeletal and connective tissue disorders				
Haematoma muscle	0	1 (<1%)	0	0
(Table 4 continues in next column)				

	Grade 1–2	Grade 3	Grade 4	Grade 5
(Continued from previous column)				
Respiratory, thoracic, and mediastinal disorders				
Pulmonary embolism	0	1 (<1%)	1 (<1%)	0
Pleural effusion	0	1 (<1%)	0	0
Pneumothorax	0	1 (<1%)	0	0
Vascular disorders				
Hypertension	3 (1%)	3 (1%)	0	0
Hypotension	2 (1%)	1 (<1%)	0	0
Metabolism and nutrition disorders				
Dehydration	1 (<1%)	1 (<1%)	0	0
Hypovolaemia	0	1 (<1%)	0	0
Renal and urinary disorders				
Urinary retention	1 (<1%)	3 (1%)	0	0
Acute kidney injury	0	1 (<1%)	0	0
Renal impairment	0	0	1 (<1%)	0
Urinoma	0	1 (<1%)	0	0
Skin and subcutaneous tissue disorders				
Subcutaneous emphysema	0	1 (<1%)	0	0
Investigations				
C-reactive protein increased	1 (<1%)	1 (<1%)	0	0
Cardiac disorders				
Tachycardia	1 (<1%)	1 (<1%)	0	0
Blood and lymphatic system disorders				
Anaemia	1 (<1%)	2 (1%)	0	0
Hepatobiliary disorders				
Ischaemic hepatitis	0	0	1 (<1%)	0

Data are n (%). Treatment-emergent adverse events are defined as all adverse events that started after the patient received [^{89}Zr]Zr-girentuximab. If a patient had more than one of the same treatment-emergent adverse event, only the event with the highest severity was counted. All grade 3 or worse treatment-emergent adverse events are reported.

Table 4: **Treatment-emergent adverse events**

mass biopsy. In addition, the results observed with indeterminate renal masses with diameters up to 2, 3, and 4 cm suggest that [^{89}Zr]Zr-girentuximab PET–CT imaging could improve detection of very small lesions. A high-quality scan for small lesions allows an earlier diagnosis of clear-cell renal cell carcinoma and could potentially improve outcomes and impact patient management.

We enrolled presurgical patients with suspected clear-cell renal cell carcinoma and histology results provided the standard of truth. Accordingly, we anticipate the negative predictive value to be higher in the real-world setting. The ZIRDEE trial[23] enrolled 16 patients with primary renal masses who did not have a history of clear-cell renal cell carcinoma and were not scheduled for surgery. In these patients, [^{89}Zr]Zr-girentuximab PET–CT successfully diagnosed clear-cell renal cell carcinoma and guided clinical decision making (surgery or active surveillance).[23] The utility of [^{89}Zr]Zr-girentuximab in clinical practice will be to provide accurate and non-invasive diagnosis of renal masses in patients without surgery. However, histopathological characterisation of indeterminate renal masses is the current standard reference in diagnostic imaging studies, and therefore also a strength of this trial. The number of patients with false-negative results identified in this trial might be explained by the low CAIX expression compared with patients with true-positive results. Expression of CAIX by other non-clear-cell renal cell carcinoma renal lesions might explain observed false-positive results. Up to 20% of papillary renal cell carcinomas express CAIX.[31] Finally, [^{89}Zr]Zr-girentuximab PET–CT does not allow the characterisation of benign lesions, which will require further differentiation to aid in clinical decision making. Additional trials to ascertain the clinical use of [^{89}Zr]Zr-girentuximab PET–CT in

other renal cancer subtypes are also warranted. A limitation of our trial was the limited racial diversity, which is representative of current global challenges in clinical research and access. This trial serves as seminal work for the unmet medical need for the characterisation of clear-cell renal cell carcinoma.

A negative [^{89}Zr]Zr-girentuximab PET–CT result typically indicates a benign mass or indolent renal cell carcinoma. Following a negative [^{89}Zr]Zr-girentuximab PET–CT result, additional imaging (eg, contrast-enhanced CT or multiparametric MRI) might be recommended to confirm a diagnosis of indolent renal cell carcinoma or benign mass. Patients should be treated according to standard of care, taking into consideration the specific diagnosis and patient risk profiles. If confirmed by additional standard-of-care imaging, physicians will have confidence to consider active surveillance, while avoiding unnecessary treatment. Given that a benign or indolent mass is the most likely outcome, more time for confirmatory follow-up is afforded.

In conclusion, [^{89}Zr]Zr-girentuximab PET–CT imaging accurately identified clear-cell renal cell carcinoma in patients with a cT1 indeterminate renal masses (≤7 cm), with a favourable safety profile. These results establish the value of [^{89}Zr]Zr-girentuximab PET–CT imaging as a new standard, non-invasive tool for the diagnosis and detection, characterisation, and differentiation of clear-cell renal cell carcinoma from other renal and extrarenal lesions in clinical practice, minimising the risk of unnecessary invasive interventions. As PET–CT imaging with prostate-specific membrane antigen revolutionised the management of prostate cancer, imaging using [^{89}Zr]Zr-girentuximab has the potential to change clinical practice in renal cell carcinoma, including staging and monitoring patients at high risk and detection of distant metastasis.

Contributors

All authors contributed to the study conception and design and data interpretation. CRWH and LT were responsible for medical oversight of the study. BS, PA, and LT accessed and verified all raw data. All authors read and commented on previous versions of the manuscript and approved the final manuscript. All authors assume responsibility for the accuracy and completeness of data and analyses, and fidelity of the trial to the protocol. All authors had access to all the data and had final responsibility for the decision to submit for publication.

Declaration of interests

BS has served as a consultant for Telix Pharmaceuticals, Veracyte, Merck, and Johnson & Johnson; has served as a speaker for Merck; and received travel support from Histosonics. AJP has received institutional funding and medical writing support from Telix Pharmaceuticals for this trial. J-CB has served as a consultant or advisor, and received honoraria and research funding from Bristol Myers Squibb, Conmed, Ipsen Pharmaceuticals, Merck Sharp and Dohme, Pfizer, and Intuitive Surgical. MAM has received institutional funding from Telix Pharmaceuticals; served as a board member for Oranomed, RayzeBio, Fusion, Advanced Molecular Imaging and Therapy, American College of Nuclear Medicine, and Society for Nuclear Medicine and Molecular Imaging; and holds stock or stock options from Advanced Molecular Imaging and Therapy, Gentem Health, and SoftThread. VM has received honoraria from Ethicon and Exelixis. AMS has received institutional research funding from Telix Pharmaceuticals, National Health and Medical Research Council, National Imaging Facility, National Breast Cancer Foundation, Medical Research Future Fund, Australian Cancer Research Foundation, and Victorian Cancer Agency; holds intellectual property licensing with Humanigen, AbbVie, and Life Science Pharmaceuticals; served as an advisory board member and consultant for ImmunOs and Imagion Bio; served as a board member, committee member, or chair for Fusion, Telix Pharmaceuticals, Australian and New Zealand Society of Nuclear Medicine, Australian and New Zealand Urogenital and Prostate Cancer trials group, Cooperative Trials Group for Neuro-Oncology, National Imaging Facility Molecular Imaging Theme, Australian Academy of Health and Medical Sciences, Melbourne Academic Centre for Health Molecular Imaging Theme, World Federation of Nuclear Medicine and Biology, Victorian Comprehensive Cancer Centre, Australian Nuclear Science and Technology Organisation External Advisory Board, and International Centers for Precision Oncology Foundation. CvP has served as consultant or advisor for Astellas and Merck; received honoraria from Astellas; and received travel funding from Ipsen. CBa has served as a data safety monitoring board or advisory board member for Telix Pharmaceuticals. BO has received research funding from Telix Pharmaceuticals. TA has received honoraria and research funding from Telix Pharmaceuticals. RM has received research funding from Telix Pharmaceuticals. DMS has received institutional research funding from Telix Pharmaceuticals; served as a consultant for Global Medical Solutions Taiwan, Progenics Pharmaceuticals, Heidelberg University, and DuChemBio; received payments or honoraria from the School of Breast Oncology, PrecisCa, and US Department of Justice; and served as an associate chair of Society for Nuclear Medicine and Molecular Imaging Scientific Program Committee. STL has received research funding from Telix Pharmaceuticals. NP-T has received honoraria from Actinium Pharmaceuticals; served as a consultant and advisor for Illumina, Imaginab, Actinium, and Progenics/Lantheus; a speaker for Actinium Pharmaceuticals and Telix Pharmaceuticals; and received institutional research funding from Actinium Pharmaceuticals, Imaginab, Regeneron Pharmaceuticals, Bristol Myers Squibb, Janssen, Clarity, Bayer Health, Telix Pharmaceuticals, and Ymabs. ACF is a board member of Molecular Decisions; a consultant or advisor for Verily; has received research funding from Earli, Filtricine, MagARRAY, and Calithera; and holds founders stock at Molecular Decisions, ACF's spouse is an employee or owner of Silverado Hospice and Antelope Valley Hospice. PA is an employee of Premier Research, and a consultant for Premier Research. KS is an employee of ABX-CRO advanced pharmaceutical services Forschungsgesellschaft. LT is an employee of Telix Pharmaceuticals and holds stock from Novartis. MW is an employee and holds patents and stock from Telix Pharmaceuticals. CBe is an employee of Telix Pharmaceuticals. CRWH was an employee of Telix Pharmaceuticals at the time of the trial. PM has received research funding from Telix Pharmaceuticals.

Data sharing

The de-identified patient dataset pertaining to results reported in this manuscript will be made available upon reasonable request to the corresponding author (bshuch@mednet.ucla.edu) after the intervention and indication is approved by both the US Food and Drug Administration and European Medicines Agency, or 18 months after publication, whichever is latest.

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