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

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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 tumor antigen highly expressed in clear-cell renal cell carcinoma.
- We aimed to evaluate the sensitivity and specificity of [^{89}Zr]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

- ZIRCON - prospective, open-label, multicentre, phase 3 trial
- 36 research hospitals and practices across nine countries (the USA, Australia, Canada, the UK, Türkiye, Belgium, the Netherlands, Spain, and France).
- 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. Readers were three experienced individuals, masked to patient medical history and any previous histology results, who conducted central and independent PET–CT imaging analysis
- The coprimary endpoints, determined for each individual reader, were the sensitivity and specificity of [^{89}Zr]Zr-girentuximab PET–CT imaging to noninvasively detect clear-cell renal cell carcinoma in patients with cT1 indeterminate renal masses (≤7 cm) who underwent partial or radical nephrectomy.

Statistical analysis

- Sample size was estimated for sensitivity and specificity, and the larger of the two estimates determined sample size.
- For sensitivity, to ensure the study had 90% power to show that the lower limit of the two-sided 95% Wilson 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%.

- 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.
- 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.

Findings

- 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).

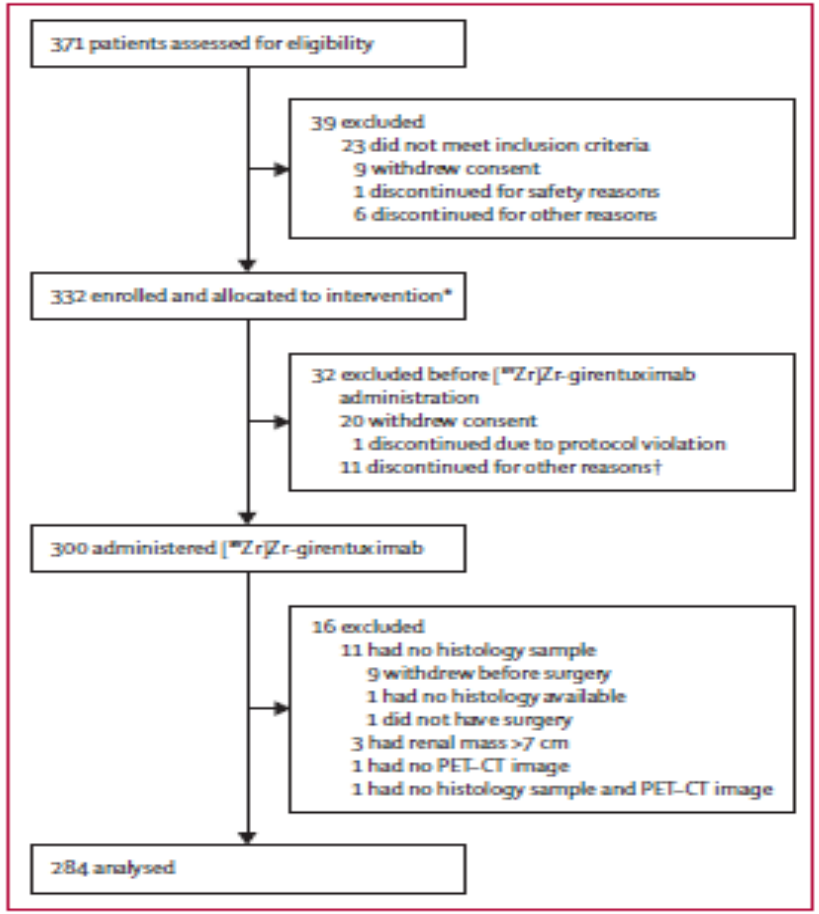


Figure 1: **Trial profile**

*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.

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

	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%)

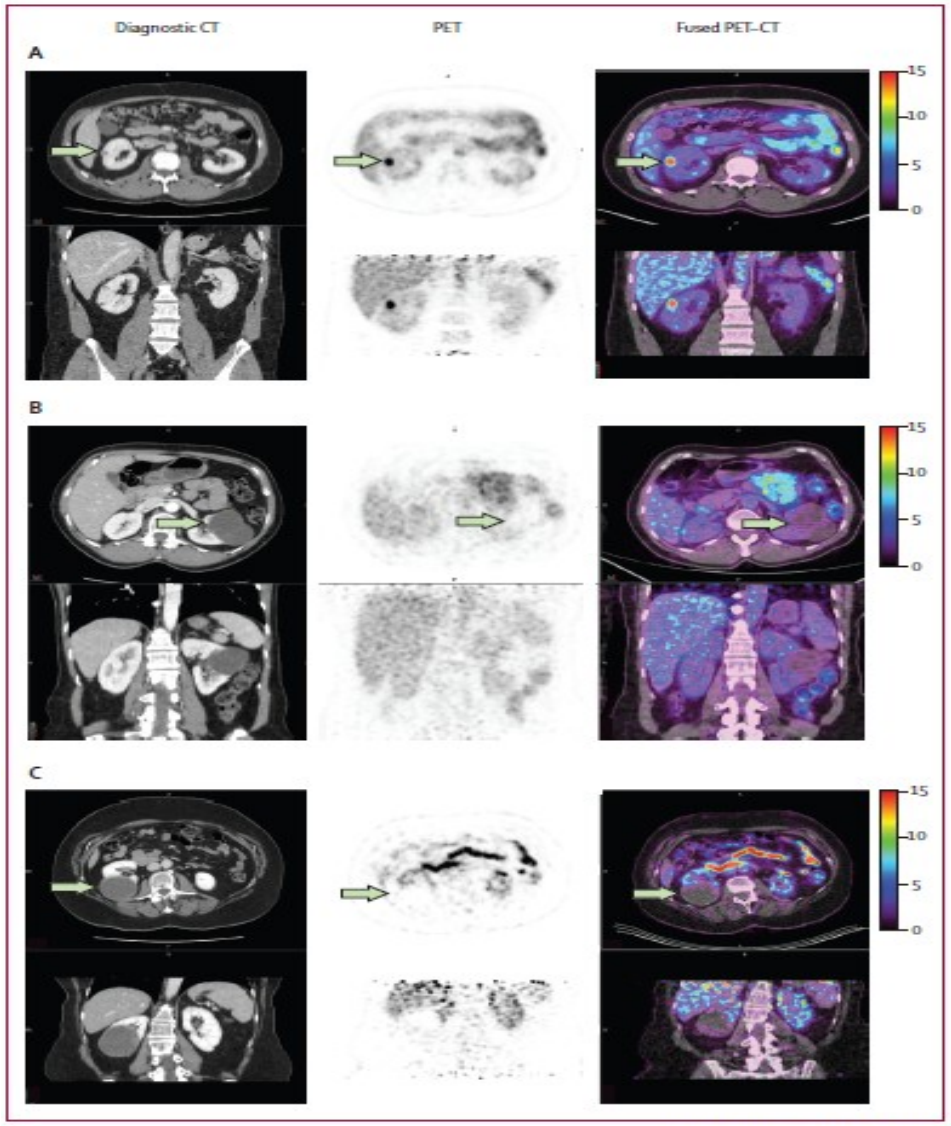
Data are median (range), mean (SD), or n (%). Baseline values were taken on day 0 (day of [⁸⁹Zr]Zr-girentuximab administration) before dose administration, and at screening for human antichimeric antibody and tumour location. *Included patients who reported their race as American Indian or Alaskan Native, 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.

	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**

- All PET-positive lesions were malignant.
- 11 false-negatives were recorded by reader 1, 11 by reader 2, and 15 by reader 3.



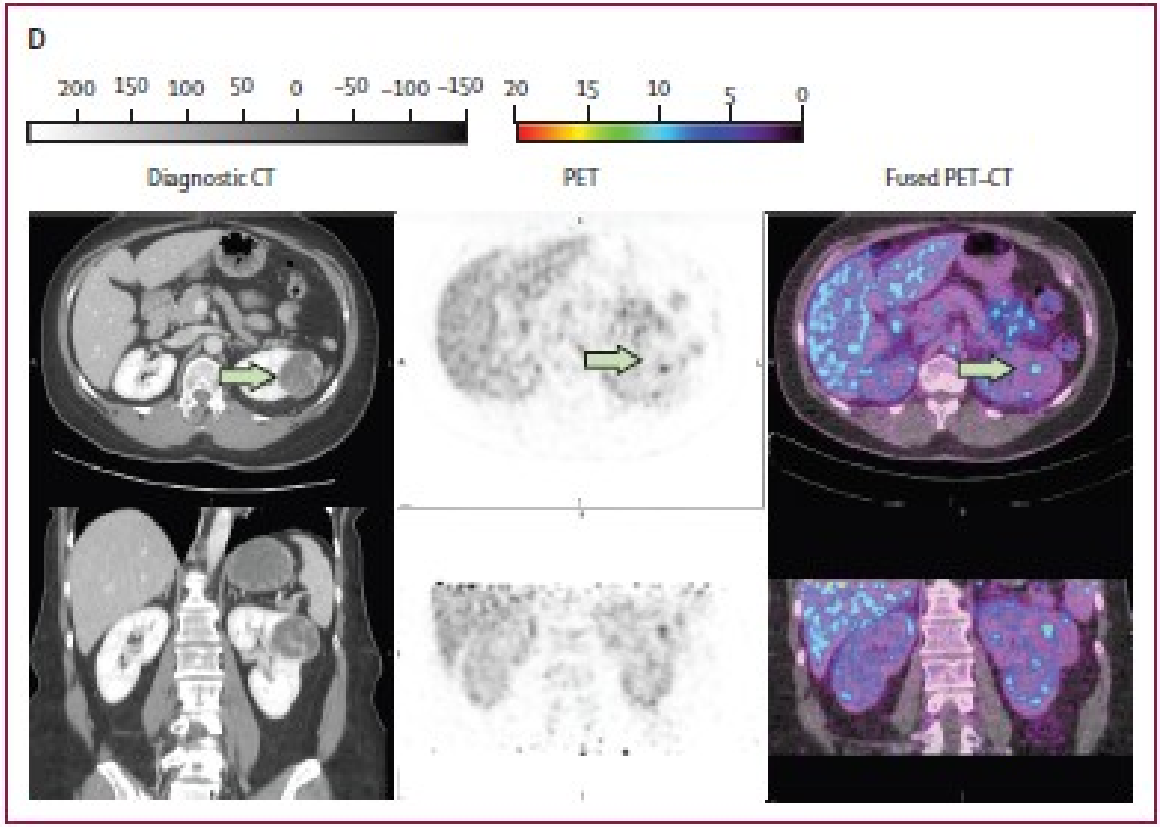


Figure 2: Representative imaging with [^{89}Zr]Zr-girentuximab

(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.

- 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

- [^{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. .

Take Home

- Strength of trial- prospective, multicentre, phase 3 trial
- Indeterminate renal masses cT1 – positive Zr Girentuximab – no details about biology of disease on pathology- is it really worth having the information to guide decision making
- False negative
- Cost
- Further studies