Results from phase 3 study of ^{89}Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma (ccRCC) ZIRCON study (NCT 03849118)

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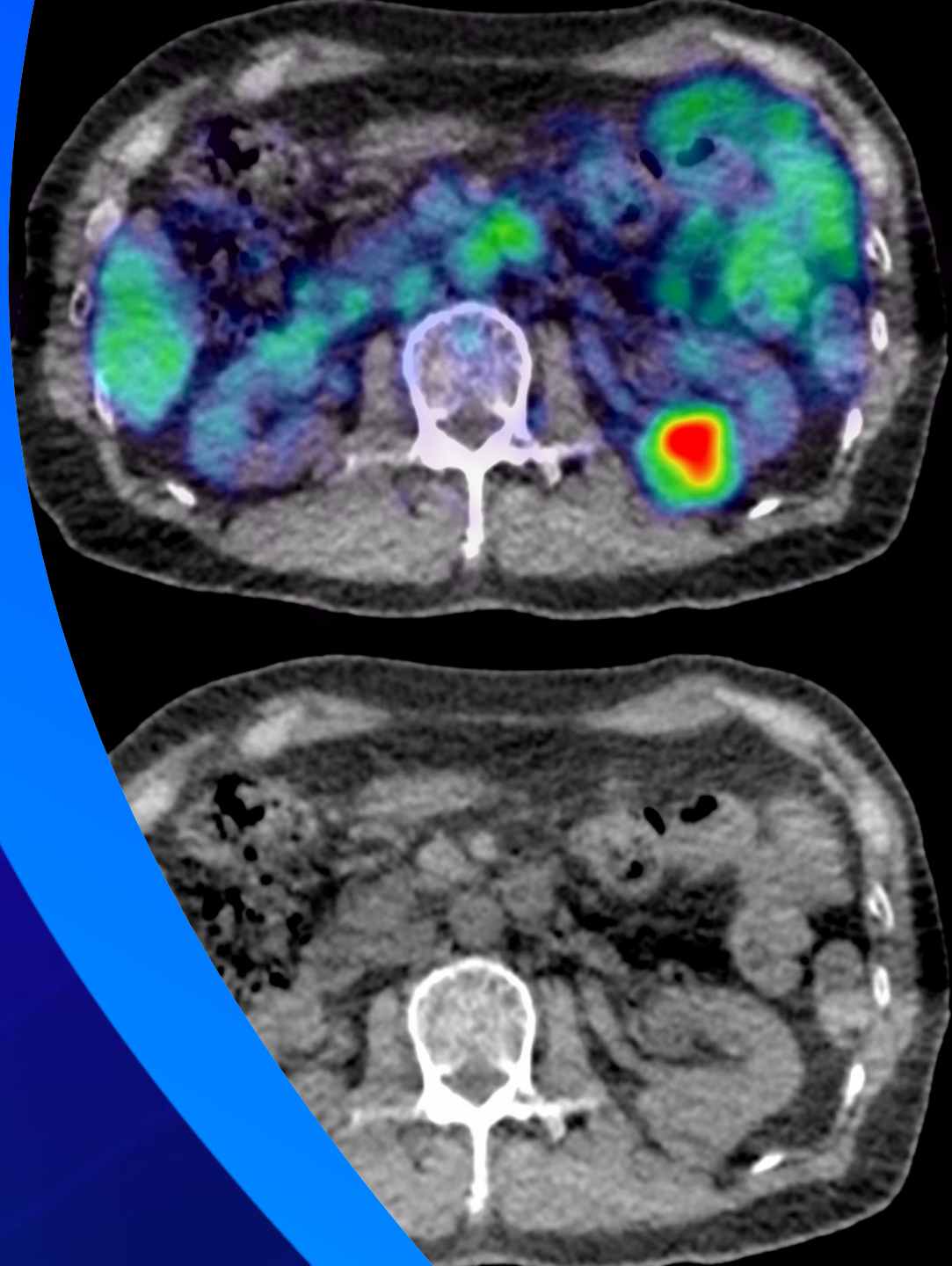

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This study was sponsored by Telix Pharmaceuticals

^{89}Zr-DFO-girentuximab is not currently approved in any jurisdiction

Presenter (Shuch) disclosures listed below

Company	Role
JNJ, Telix, BMS, Genetech, Merck, Veracyte	Consulting
Merck	Speaking
SWOG, Hope Foundation, DOD, KCA, Veracyte, Rebiotix, Allogene	Research Support
Histosonics, Telix	Travel

Background

Unmet medical need in the non-invasive diagnosis and characterization of ccRCC in patients

Anatomic imaging cannot reliably distinguish between benign/malignant renal masses

Renal mass biopsy is invasive, performed infrequently (~15%), and often non-diagnostic (~20%)[1]

20-30% of resected small renal masses are ultimately found to be benign[2]

all forms of therapy may have morbidity

ccRCC is ~75% of RCC and causes ~90% of deaths[3,4]

ccRCC progress more rapidly with active surveillance[5]

There is need for accurate, noninvasive methods for pre-treatment risk stratification to help guide management

PSMA imaging has changed the way we view and manage prostate cancer

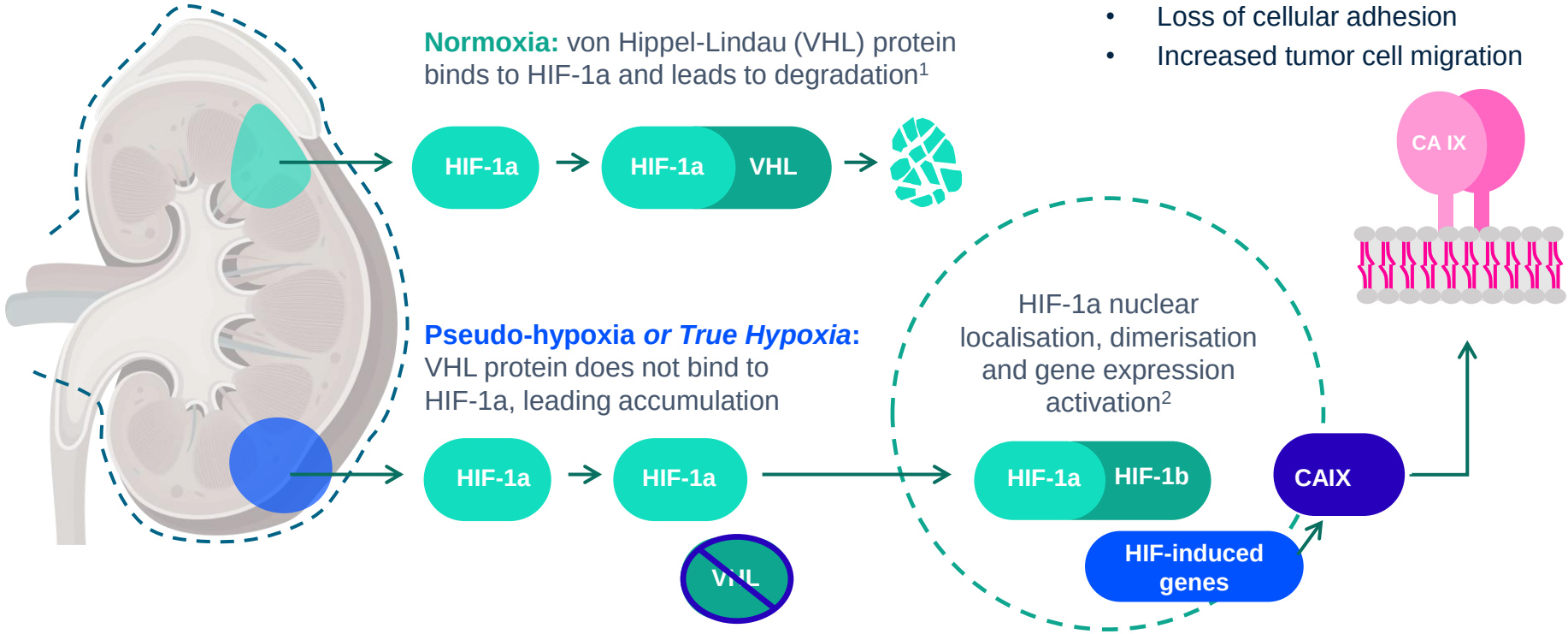
1. Patel et al. *J Urol.* 2016;195(5):1340-7.
2. Oei et al. *Imaging Med.* 2011;3:207-18.
3. Abu Haeyeh et al. *Bioengineering (Basel).* 2022;9:423.
4. Metin et al. *Medicina (Kaunas).* 2022;58:221.
5. Finelli et al. *Eur Uroll.* 2020;78,460-7.

Carbonic anhydrase IX (CAIX) in ccRCC

CAIX is a cell surface, transmembrane protein induced by hypoxia[1,2]

With hypoxia or VHL loss (~90% of ccRCC), CAIX is upregulated

CAIX is minimally expressed in normal tissue



CAIX upregulation may lead to:[1]

- Acidification of extracellular pH
- Loss of cellular adhesion
- Increased tumor cell migration

Illustration adapted from Stillebroer et al. 2010.

Abbreviations: CAIX, carbonic anhydrase IX; ccRCC, clear cell renal cell carcinoma; HIF, hypoxia-inducible factor; VHL, von Hippel-Lindau.

1. Aldera and Govender. *J Clin Pathol.* 2021;74:350-4.
2. Pastorekova and Gillies. *Cancer Metastasis Rev*. 2019;38:65-77.
3. Stillebroer et al. *Eur Urol.* 2010;58:75-83.

CAIX detection with ^{89}Zr-DFO-girentuximab

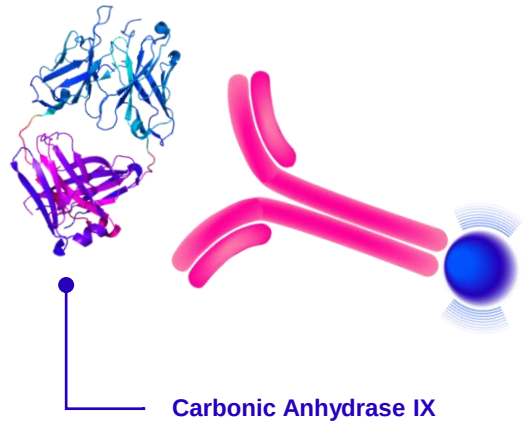
Antibody-based PET imaging agent targeting CAIX

Girentuximab

- IgG1 kappa light chain chimeric monoclonal antibody
- Girentuximab binds with high specificity to CAIX and is internalized
- Extensive safety experience with girentuximab in prior imaging and therapeutic studies
- Hepato-biliary excretion allows optimal renal visualisation

Payload: ^{89}Zr

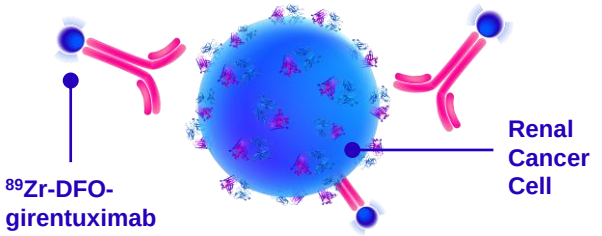
- Positron emitter
- $T_{1/2}$ 3.3 days
- Suited for antibody-based imaging
- Hepatically cleared



^{89}Zr-DFO-girentuximab in CAIX expressing tumors

- Previous studies show feasibility imaging CAIX positive tumors (SPECT & PET)[1,2]

- ^{89}Zr-DFO-girentuximab (37 MBq [1 mCi] / 10 mg) was previously shown safe and allowed PET/CT imaging of ccRCC at 4-7 days after administration[3]



1. Oosterwijk-Wakka et al. *Int J Mol Sci*. 2013;14(6):11402-23.
2. Kulterer et al. *J Nucl Med.* 2021;62(3):360-5.
3. Merkx et al. *Eur J Nucl Med Mol Imaging.* 2021;48(10)3277-85.

ZIRCON study design

^{89}Zr-girentuximab administration
Initial sample size: n=252
Adapted size: n=300

Day 0

Abdominal PET/CT imaging[a]
Blinded central image review*

Performed 5 ± 2 days post-administration

Partial/Radical Nephrectomy
Central histology review*

Within 90 days post-^{89}Zr-DFO-girentuximab administration

Eligibility

Single indeterminate renal mass ≤7 cm (cT1) in diameter on CT or MRI suspicious for ccRCC

Scheduled for surgical removal

Endpoints

Co-primary endpoints

Sensitivity and specificity of ^{89}Zr-DFO-girentuximab PET/CT vs. central histology (surgical resection) in detection of ccRCC

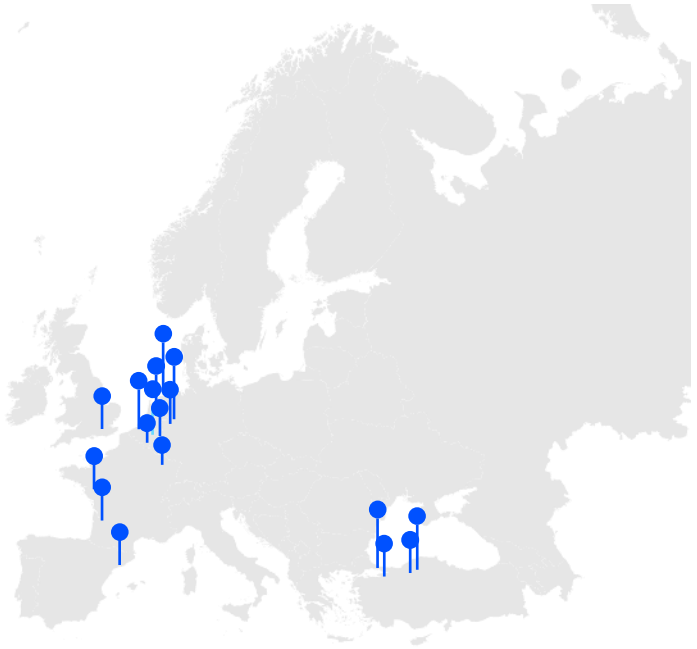
Key secondary endpoints

Sensitivity and specificity of ^{89}Zr-DFO-girentuximab PET/CT in cT1a (≤4 cm) subgroup

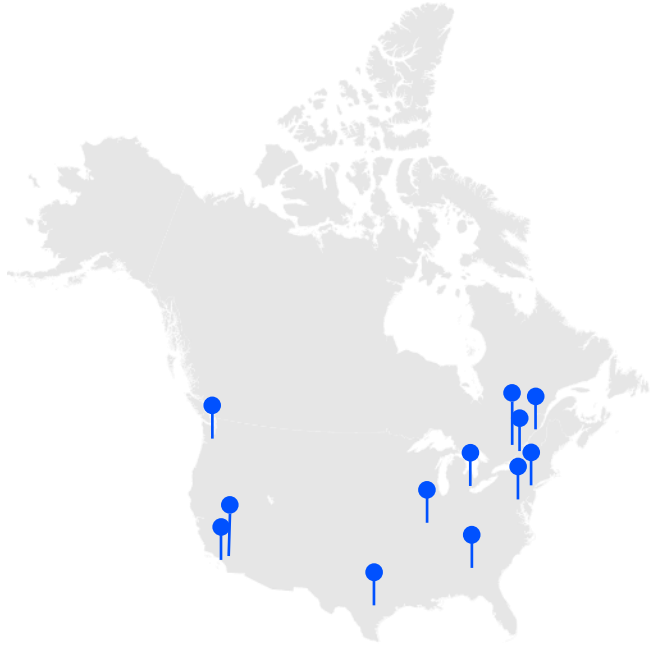
[a] PET/CT imaging 20 mins single bed position - may be extended, at the discretion of the investigator, to whole-body imaging

Global study participation

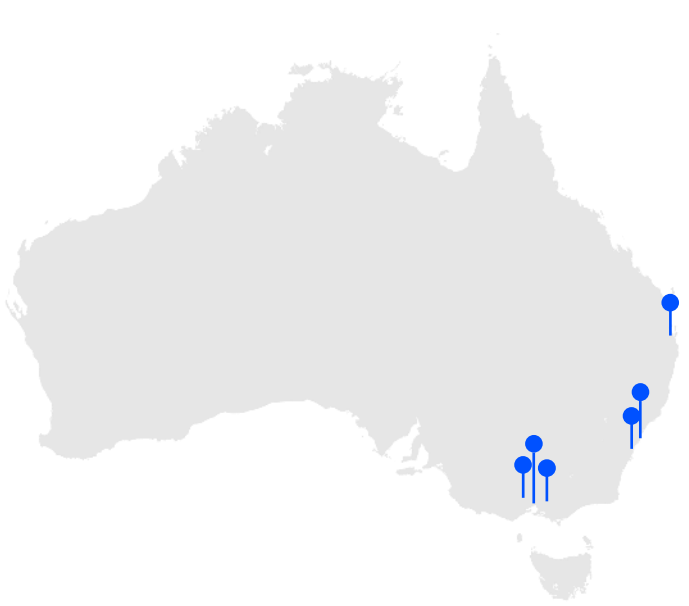
300 subjects enrolled between Aug 2019-Aug 2022 | 36 sites | 9 countries



Europe | 17 sites



North America | 13 sites



Australia | 6 sites

Patient disposition

371

Screened

332

Enrolled

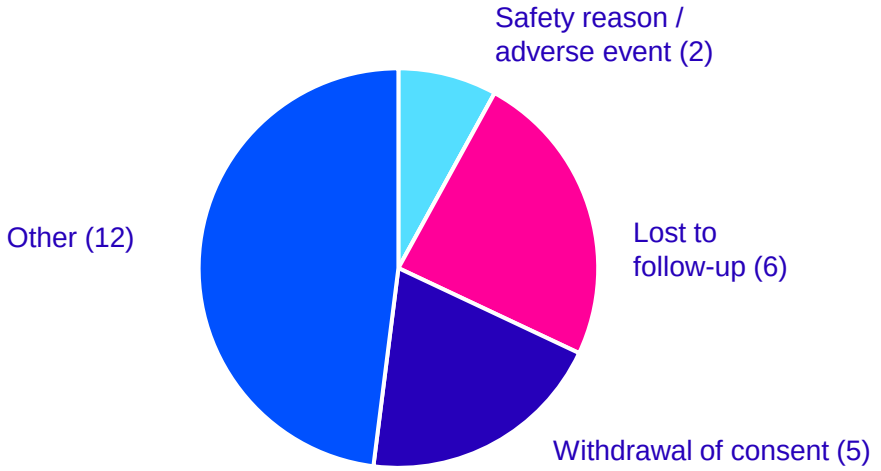
Safety analysis set*, n (%) | 300 (100)
Full analysis set**, n (%) | 284 (94.7)

Early withdrawal

8.3%

25 patients

Reason for early withdrawal



* All patients who received ^{89}Zr-DFO-girentuximab

** All patients with evaluable PET/CT imaging and confirmed histopathology (ccRCC/no ccRCC)

Population demographics

Safety analysis set

Patient characteristic	Total (N = 300)
Age, years	
Median (range)	62 (27-87)
Mean ± SD	61 ± 12
Male, n (%)	214 (71.3%)

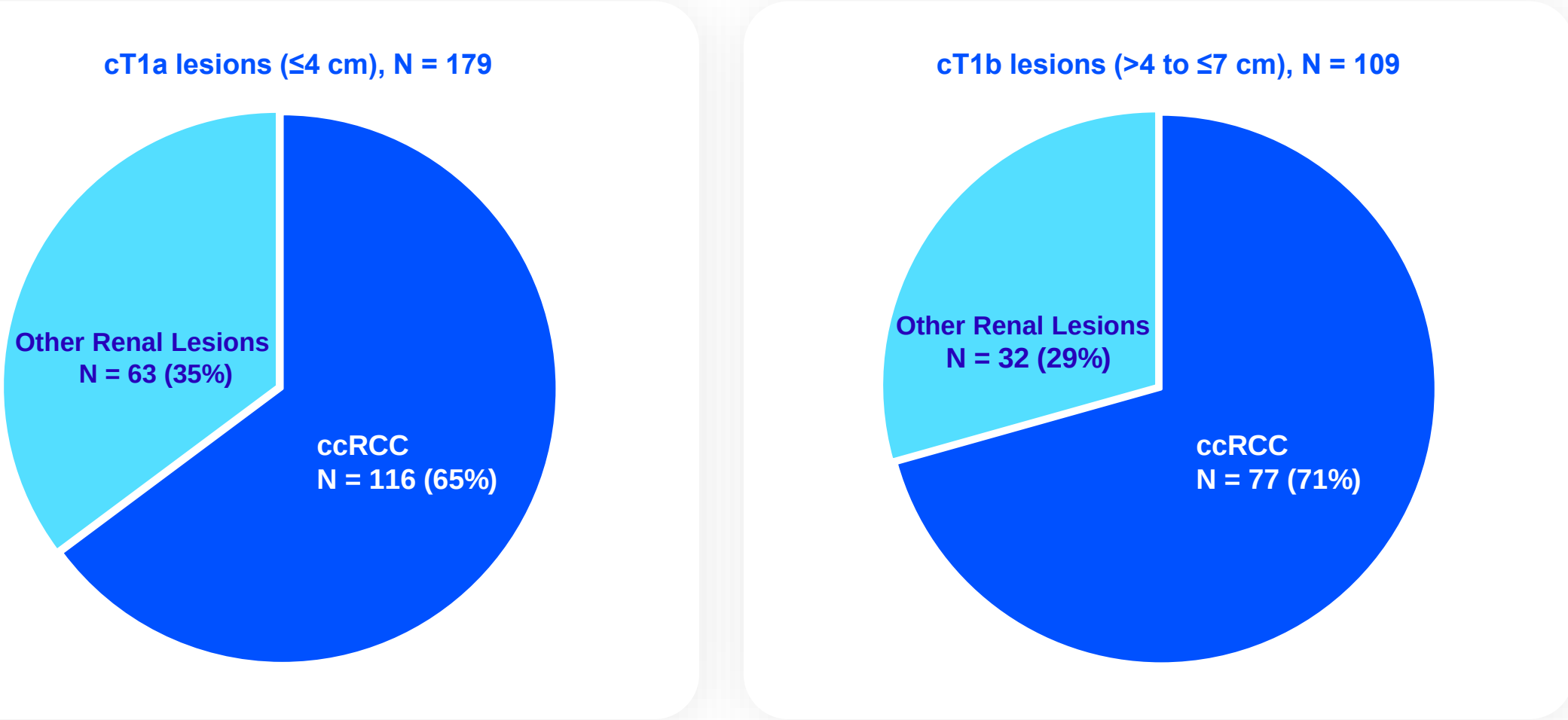
Evaluable surgical samples

Lesion characteristic	Total (N = 288)
Lesion median size, range (cm)	3.7 (0.9-7.7)
cT1a (≤ 4 cm) lesions, n (%)	179 (62%)
cT1b lesions, n (%)	109 (38%)
Lesions ≤ 2 cm	39 (13.5%)
Central histology	
ccRCC, n (%)	193 (67%)
Other Renal Lesions, n (%)	95 (33%)
pRCC	44 (15.3%)
cRCC	22 (8%)
Oncocytoma	9 (3%)
Spindle cell	4 (1.4%)
Sarcoma	2 (<1%)
Other (mixed, rare,….)	14 (5%)

* All patients who received ^{89}Zr-DFO-girentuximab

** All patients with evaluable PET/CT imaging and confirmed histopathology (ccRCC/no ccRCC)

ccRCC - slightly more frequent in larger lesions



* All patients who received ^{89}Zr-DFO-girentuximab

** All patients with evaluable PET/CT imaging and confirmed histopathology (ccRCC/no ccRCC)

Co-primary endpoints (Full Analysis Set, N = 284)

Sensitivity and specificity thresholds exceeded by all 3 independent readers*

	Reader 1	Reader 2	Reader 3	Overall % (95% CI)
Sensitivity, %	84.13	85.19	87.30	**85.5** (79.8, 89.8)
Lowest bounds, Wilson 95% CI	78.24	79.42	81.80	
Specificity, %	88.42	88.42	84.21	**87** (78.8, 92.3)
Lowest bounds, Wilson 95% CI	80.45	80.45	75.57	
Positive predictive value, %**	93.53	93.60	91.67	**93** (88, 96)
Negative predictive value, %**	73.68	75.00	76.92	**75** (66, 82)
Accuracy, %**	85.56	86.27	86.27	**86** (81.5, 89.6)

* 95% CI had to be > 0.7 for sensitivity and > 0.68 for specificity, for ≥ 2 independent readers to declare the study positive

** Secondary objectives

Abbreviations: CI, confidence interval.

Key secondary endpoints: cT1a (≤4 cm) Cohort

Sensitivity and specificity thresholds exceeded by all 3 independent readers (FAS)

	Reader 1	Reader 2	Reader 3	Overall % (95% CI)
Sensitivity, %	84.05	86.17	86.17	**85.5**
Lowest bounds, Wilson 95% CI	*75.33*	*77.76*	*77.76*	(77, 91.2)
Specificity, %	90.74	90.74	87.04	**89.5**
Lowest bounds, Wilson 95% CI	*80.09*	*80.09*	*75.58*	(78.6, 95.2)
Positive predictive value, %	94.05	94.19	92.05	**93.4** (86.1, 97)
Negative predictive value, %	76.56	79.03	78.33	**78** (66.2, 86.5)
Accuracy, %	86.5	87.8	86.5	**87** (80.6, 91.4)

Abbreviations: CI, confidence interval; FAS, full analysis set.

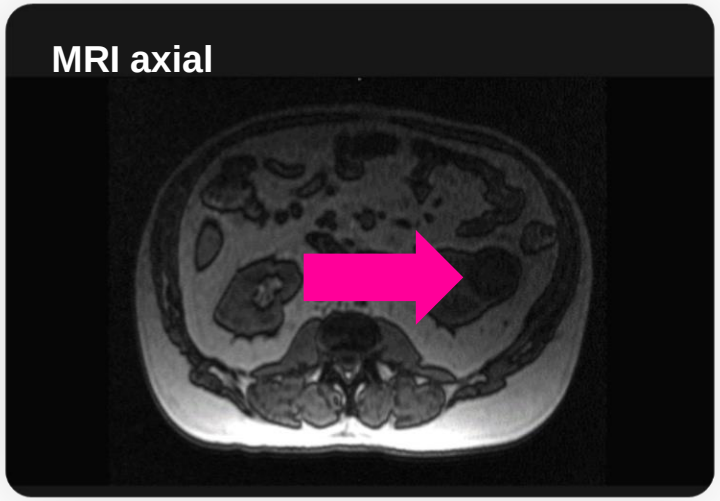
ZIRCON study confirms prior safety and tolerability profile

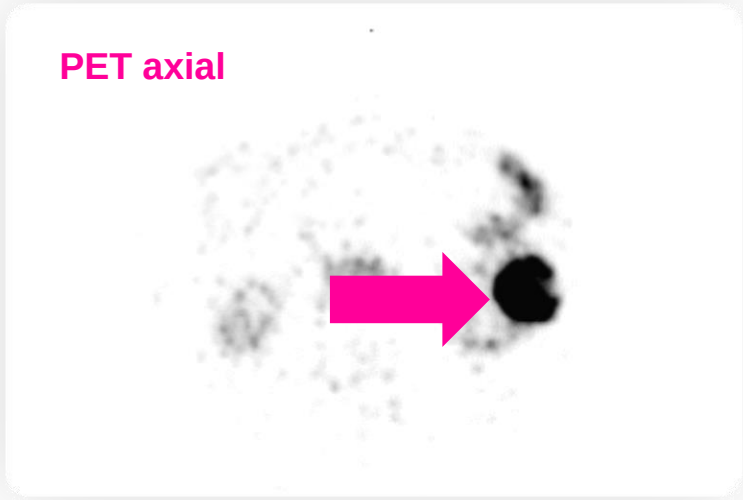
- **Very few AEs** considered possible or related to ^{89}Zr-DFO-girentuximab
- **Most AEs were mild**; only 18 patients (6%) had a ≥ Grade 3 TEAE
- AE pattern consistent with post-surgical complications **related to the nephrectomy**
- **No unexpected safety signals** were observed
- **Consistent** with experience of girentuximab in previous therapeutic and imaging studies

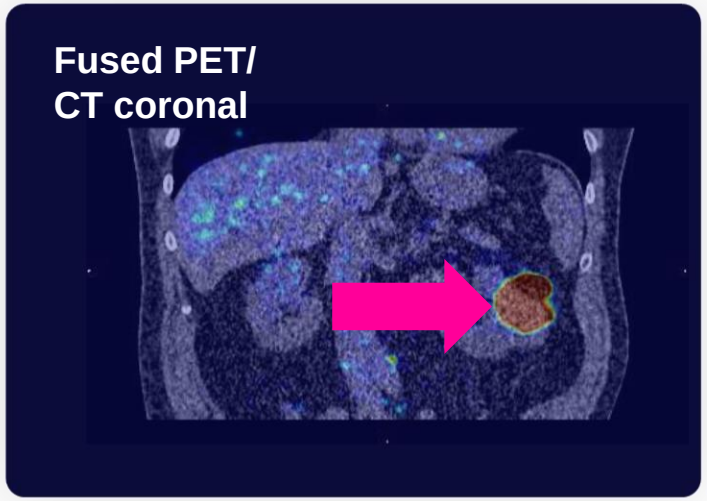
Abbreviations: AE, adverse event.

ZIRCON clinical case in a complex cyst

Potential support for clinical decision making







Diagnostic challenge:

- 42 yr male
- 3.1 cm (cT1a) left kidney mass
- ^{89}Zr-girentuximab PET scan clearly positive→ ccRCC highly likely

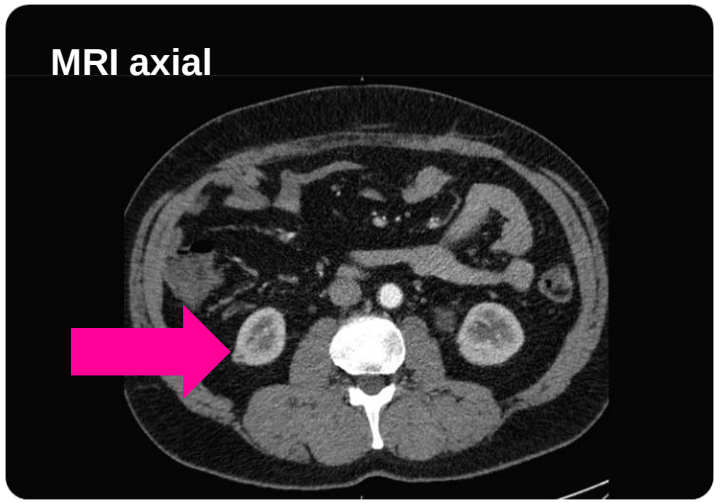
Clinical management:

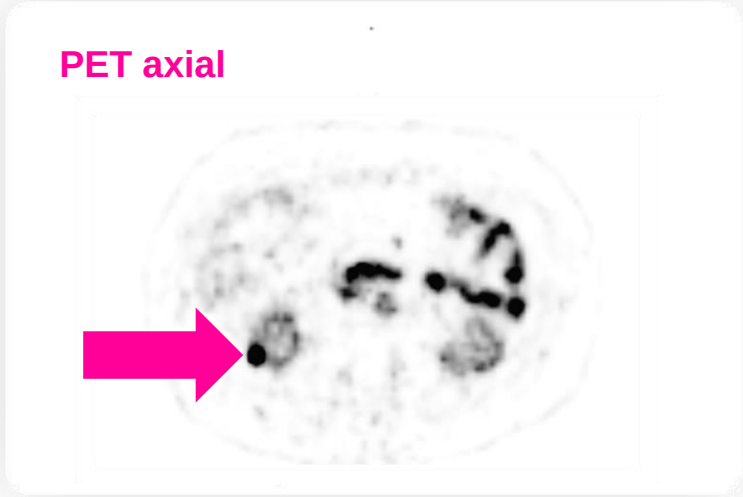
- Surgery - radical nephrectomy
- ccRCC confirmed by central pathology
- Low/Focal CAIX expression by IHC

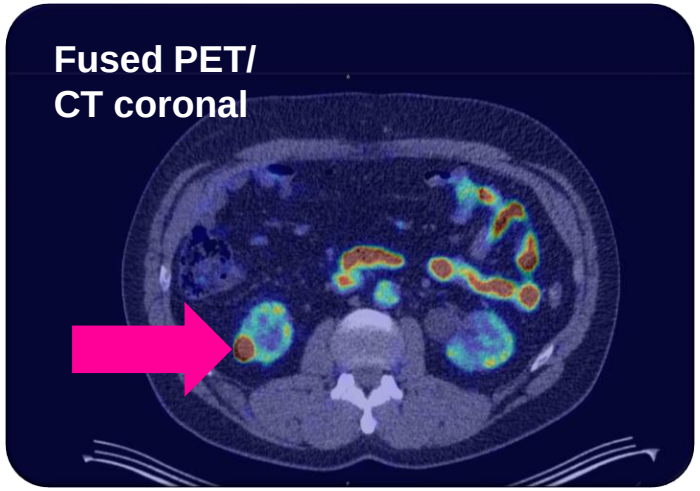
Note: representative patient response only, may not be representative for all patients.

ZIRCON clinical case in a 1 cm mass

Potential support for clinical decision making







Diagnostic challenge:

- 57 yr male with 1 cm lesion found incidentally in right kidney
- Management dilemma – active surveillance?
- ^{89}Zr-DFO-girentuximab PET clearly positive→ ccRCC highly likely

Clinical management:

- Partial nephrectomy
- ccRCC confirmed by central pathology

Note: representative patient response only, may not be representative for all patients.

Summary of ZIRCON results

ZIRCON Phase III pivotal study with ^{89}Zr-DFO-girentuximab has met its primary endpoint, **exceeding the sensitivity and specificity targets**

The study **met its key secondary endpoint of sensitivity and specificity in small masses (cT1a ≤4cm)**

The favorable safety and tolerability profile of ^{89}Zr-DFO-girentuximab was confirmed

Summary of ZIRCON results

These positive results suggest that ^{89}Zr-DFO-girentuximab improves identification of primary ccRCC compared to cross-sectional imaging

^{89}Zr-DFO-girentuximab has the potential to improve management by aiding risk stratification, selecting appropriate patients for treatment or suggesting where further imaging/biopsy could be indicated

^{89}Zr-DFO-girentuximab holds promise to improve staging in ccRCC, therapeutic target (radiopharmaceuticals), or image other solid tumors (true hypoxia) all of which are ongoing initiatives

Thank you for your attention!

We would like to acknowledge the invaluable contributions from participating patients, sites, and partners

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Austin Health

Peter MacCallum Cancer Centre

City of Hope

Macquarie University Hospital

Urology San Antonio

CHRU de Nancy – Hôpitaux de Brabois

Jewish General Hospital

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