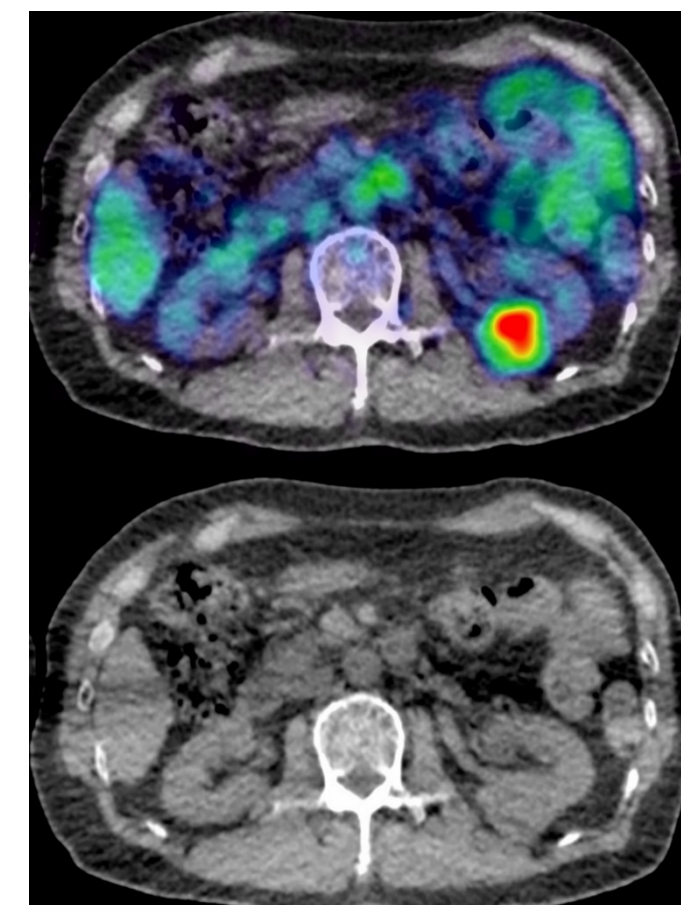


^{89}Zr -DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma

—
results from phase 3 ZIRCON study
(NCT 03849118)



Karolien Goffin, Peter Mulders, Brian M. Shuch, Allan J. Pantuck, Michael A. Morris, Viraj Master, Andrew Scott, Charles van Praet, Clement Bailly, Bulent Onal, Tamer Aksoy, Robin Merks, David M. Schuster, Sze Ting Lee, Neeta Pandit-Taskar, Alice Fan, Libuse Tauchmanova, Karl Schmidt, Phillip Allman, Kavita Vadali, Colin Hayward, Jean-Christophe Bernhard



Background

Increasing detection of renal masses presents a significant patient management challenge

Anatomic imaging cannot reliably differentiate 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 benign²

ccRCC is ~75% of RCC and causes ~90% of deaths^{3,4}
ccRCC progress more rapidly with active surveillance⁵

Unmet medical need in accurate non-invasive diagnosis and characterization of ccRCC in patients pre-treatment to help risk stratification and guide management

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 Urol*. 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

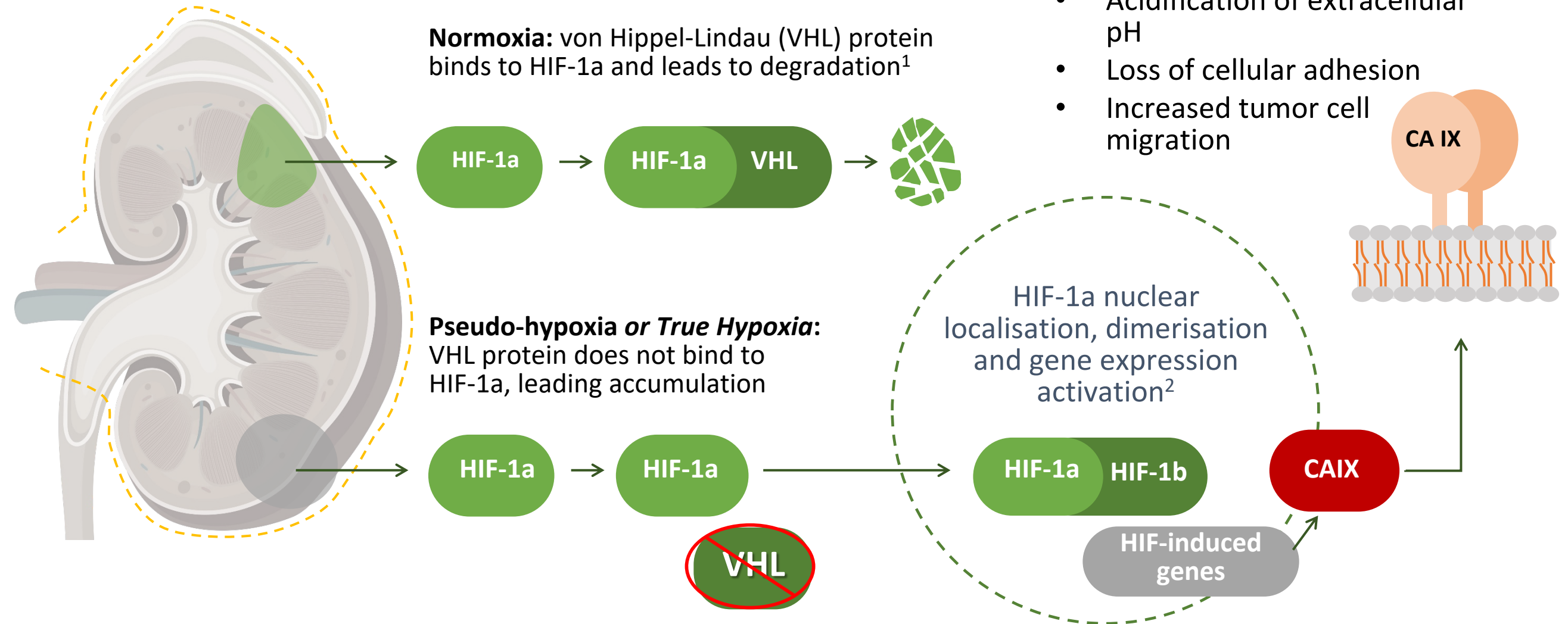


Illustration adapted from Stillebroer et al. 2010.

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

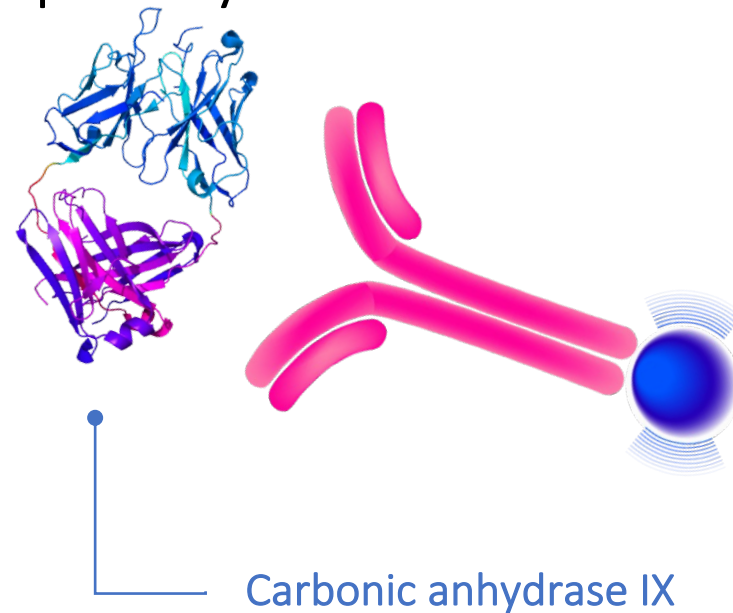
Antibody-based PET imaging agent targeting CAIX

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

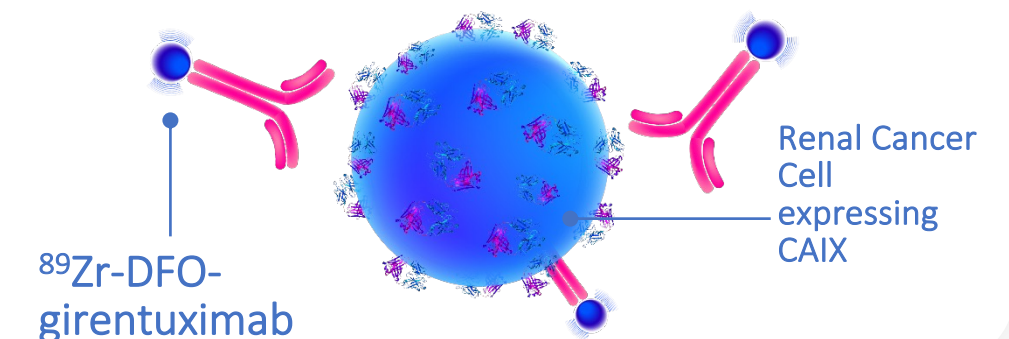
Payload: ^{89}Zr

- 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 administration³



ZIRCON study design

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
⁸⁹Zr-DFO-girentuximab PET/CT vs.
central histology (surgical resection)
in detection of ccRCC

Key secondary endpoints

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



⁸⁹Zr-girentuximab administration

Initial sample size: n=252
Adapted size: n=300

Day 0



Abdominal PET/CT imaging^a
Blinded central image review*

5 ± 2 days
post-administration



Partial/Radical Nephrectomy
Central histology review*

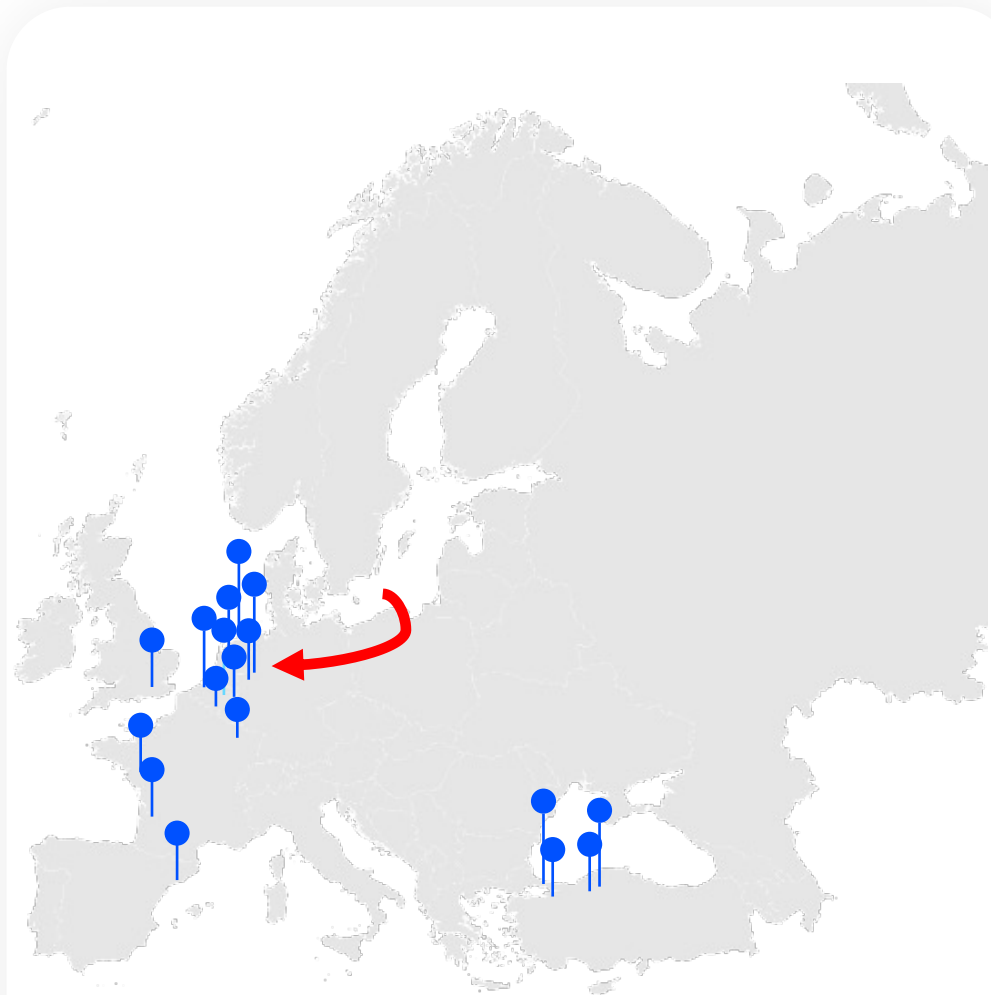
Within 90 days
post-administration

^a PET/CT imaging 20 mins single bed position - may be extended, at the discretion of the investigator, to whole-body imaging
Qualitative visual analysis, using histological results as standard of truth



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

300

Dosed with
⁸⁹Zr-DFO-girentuximab

Safety analysis set - demographics

Patient characteristic	Total (N = 300)
Age, years	
Median (range)	62 (27-87)
Mean ± SD	61 ± 12
Male, n (%) Female, n (%)	214 (71) 76 (29)

Analysis set	Definition	Number of patients
Safety analysis set	All patients who received ⁸⁹ Zr-TLX250	300
Full analysis set (FAS)	All patients with evaluable PET/CT imaging and confirmed histopathological diagnosis (ccRCC/no ccRCC)	284
Patients with cT1a lesions (≤ 4 cm of max diameter)	FAS criteria	148

- * All patients who received ⁸⁹Zr-DFO-girentuximab
- ** All patients with evaluable PET/CT imaging and confirmed histopathology (ccRCC/no ccRCC)



Population characteristics

Patients with evaluable histology on 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 (> 4 -7 cm), n (%)	109 (38)
lesions ≤ 2 cm (# local and ## central reading)	39 (13.5) [#] 21 (7) ^{##}

Central histology	Total (N = 288)
ccRCC, n (%)	193 (67) 
other renal lesions, n (%)	95 (33)
malignant lesions	
pRCC	44 (15.3)
cRCC	22 (8)
spindle cell	4 (1.4)
sarcoma	2 (<1)
Other (mixed, rare,...)	14 (5)
benign lesions	
oncocytomas	9 (3)



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, %	84.1	85.2	87.3	85.5
Lowest bounds, Wilson 95% CI	78.2	79.4	81.8	(79.8, 89.8)
Specificity, %	88.4	88.4	84.2	87.0
Lowest bounds, Wilson 95% CI	80.5	80.5	75.6	(78.8, 92.3)
Positive predictive value**, %	93.5	93.6	91.7	93.0 (88.0, 96.0)
Negative predictive value**, %	73.7	75.0	76.9	75.0 (66.0, 82.0)
Accuracy**, %	85.6	86.3	86.3	86.0 (81.5, 89.6)



Key secondary endpoints: cT1a (≤ 4 cm) lesions

Sensitivity and specificity thresholds exceeded by all 3 independent readers

	Reader 1	Reader 2	Reader 3	Overall % (95% CI)
Sensitivity, %	84.1	86.2	86.2	85.5
Lowest bounds, Wilson 95% CI	75.3	77.8	77.8	(77.0, 91.2)
Specificity, %	90.7	90.7	87.0	89.5
Lowest bounds, Wilson 95% CI	80.1	80.1	75.6	(78.6, 95.2)
Positive predictive value, %	94.1	94.2	92.1	93.4 (86.1, 97.0)
Negative predictive value, %	76.6	79.0	78.3	78.0 (66.2, 86.5)
Accuracy, %	86.5	87.8	86.5	87.0 (80.6, 91.4)

Abbreviations: CI, confidence interval.



Safety - known safety & tolerability profile confirmed



263 TEAEs recorded in 124 patients; **very few** AEs considered possible or related to ^{89}Zr -DFO-girentuximab



Most AEs were mild; only 18 patients (6%) had a $\geq$ Grade 3 TEAE



AE pattern consistent with post-surgical complications **related to the nephrectomy**



No unexpected safety signals were observed

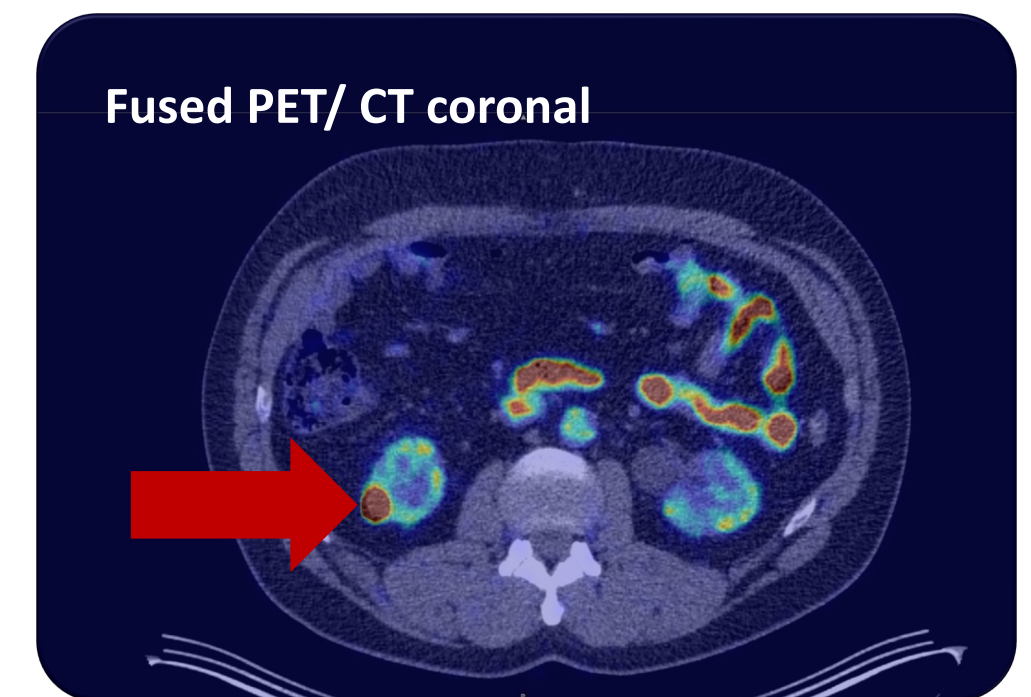
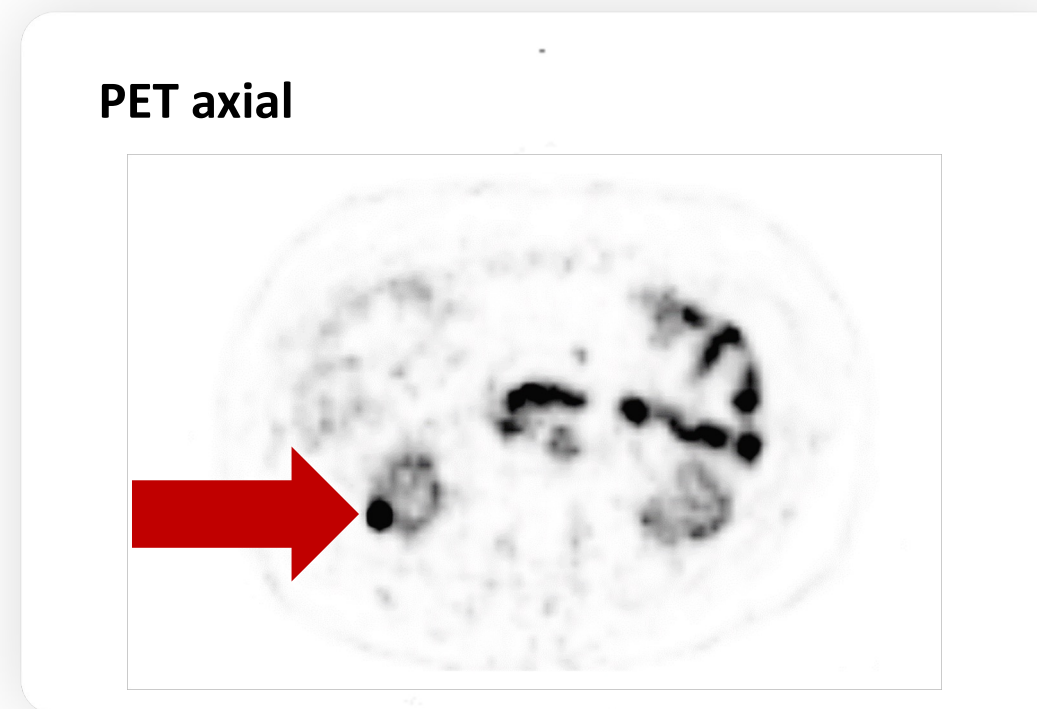
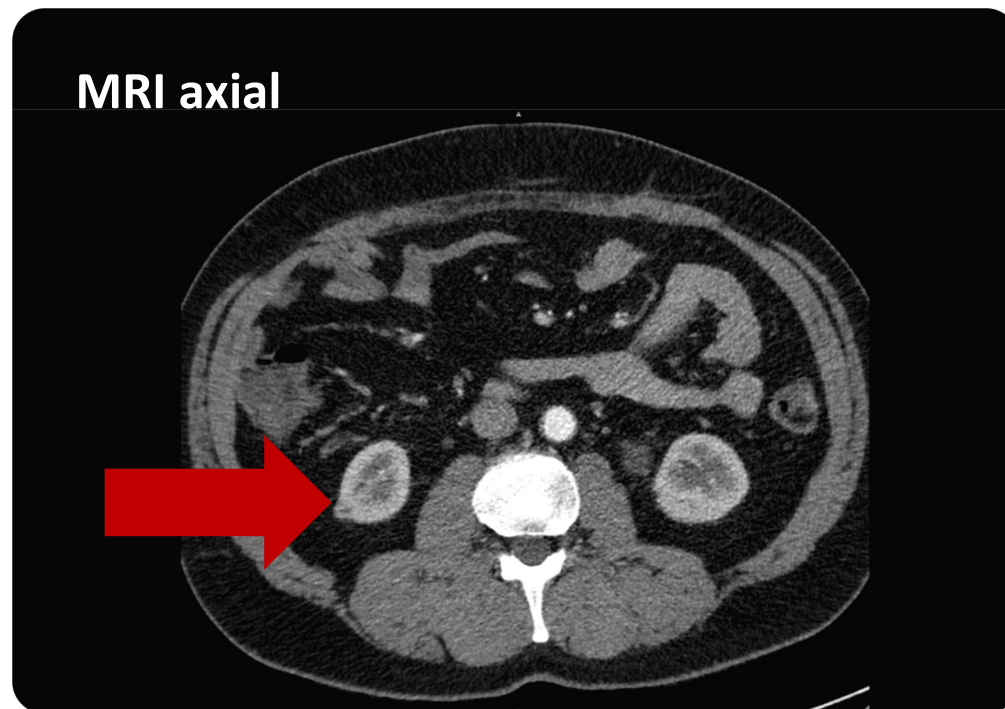


Consistent with experience of girentuximab in previous therapeutic and imaging studies



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 $\rightarrow$ 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 sensitivity and specificity targets**
- The study **met its key secondary endpoint of sensitivity and specificity in small masses (cT1a $\leq 4\text{cm}$)**
- **The favorable safety and tolerability profile** of ^{89}Zr -DFO-girentuximab was confirmed
- 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*

UZ Leuven	Institut Jules Bordet	OLV Ziekenhuis Aalst	Radboud UMC	Leiden UMC
Macquarie University Hospital	Urology San Antonio	MSKCC	Cabrini Hospital	CHRU de Nancy – Hôpitaux de Brabois
Royal Free, UK	Royal North Shore Hospital	Peter MacCallum Cancer Centre	Austin Health	Princess Alexandra Hospital
University of California Los Angeles	Nantes University Hospital Hotel-Dieu	City of Hope	Advanced Molecular Imaging and Therapy	CHU de Bordeaux, Groupe Hospitalier
Hacettepe University Erişkin Hospital, Ankara	Emory	Ankara University Medical Faculty	Jewish General Hospital	Netherlands Cancer Medical Centre
Hospital Sant Pau	Washington Univ, St. Louis	Johns Hopkins	Isala Hospital, Zwolle	Seattle Cancer Alliance
Istanbul University, Cerrahpasa Medical	CHU de Québec-Université Laval (CHU)	Centre De Recherche Centre hospitalier de l/Universite de Montreal (CrCHUM)	Urology San Antonio	Istanbul Health Science University

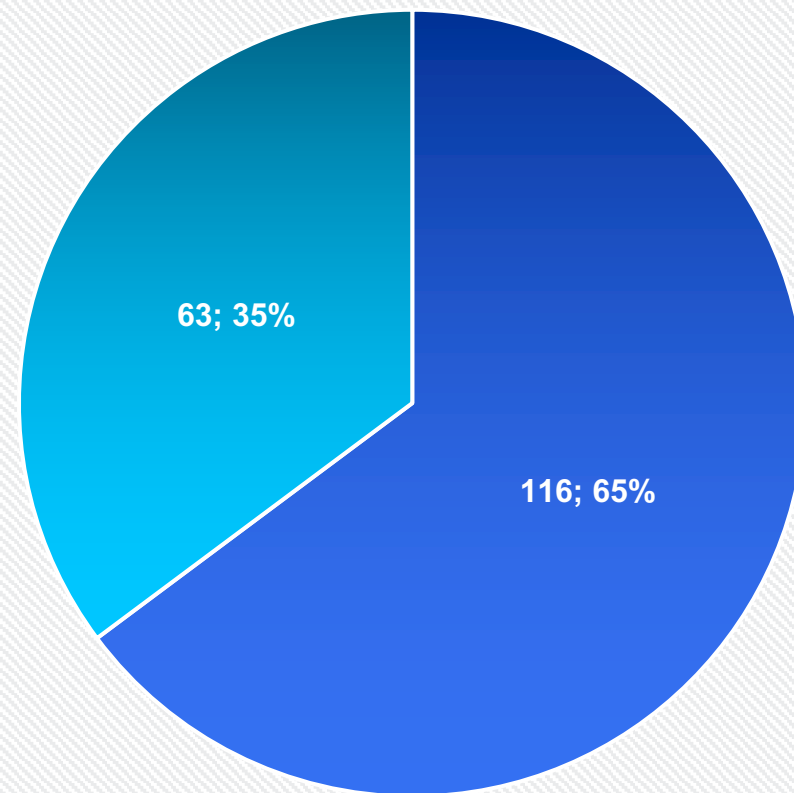
Radboud Translational Medicine, Isologic Innovative Radiopharmaceuticals, Cardinal Health, Eczacıbaşı Monrol Nuclear Products Co., MLM Medical Labs, Targos Molecular Pathology (Discovery Life Sciences), ABX-CRO advanced pharmaceutical services, Accelagen Pty Ltd, TMC Pharma Services, Mene Health Group, Translational Drug Development



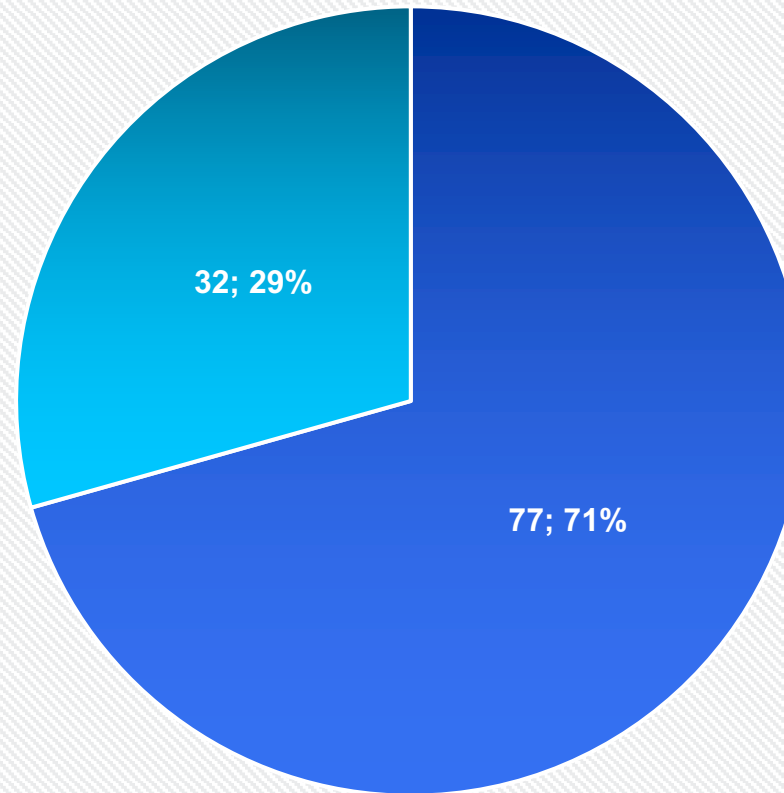


ccRCC proportion in cT1a, cT1b and ≤ 2 cm lesions

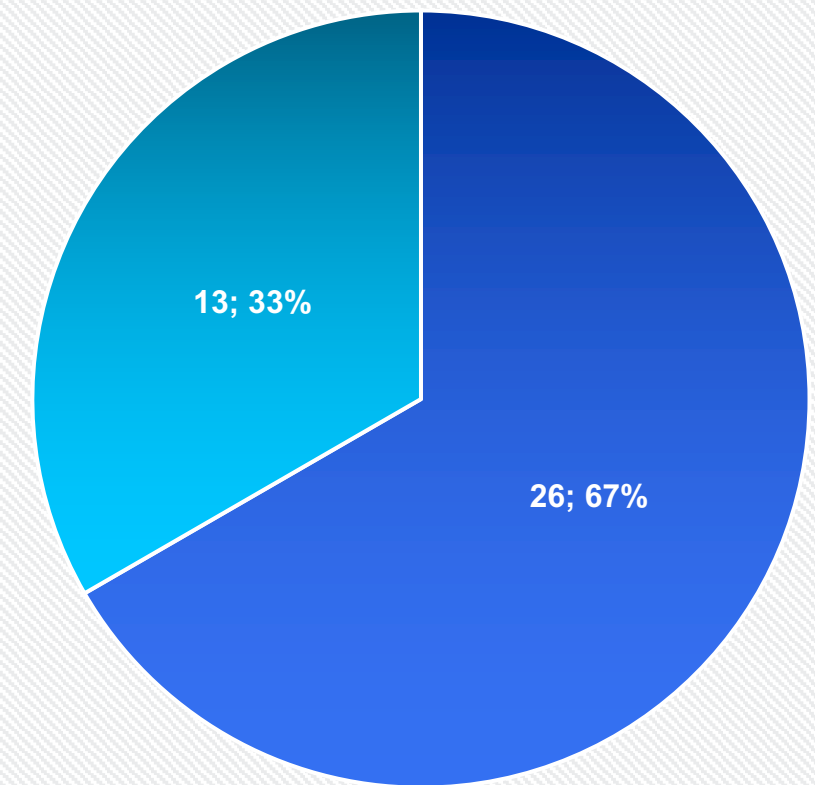
cT1a lesions, N = 179



cT1b lesions, N = 109



Lesions ≤ 2 cm, N = 39



■ ccRCC ■ non-ccRCC



Higher CAIX expression in patients with PET+ ccRCC (TP) than in PET- ccRCC (FN) patients



	N samples	CAIX H-Score		P-value (Wilcoxon)
		Mean ± SD	Median	
Reader 1				
ccRCC PET+	152	214 ± 95	242	0.032
ccRCC PET-	27	129 ±137	55	
Reader 2				
ccRCC PET+	154	214 ± 96	249	0.004
ccRCC PET-	25	122 ± 131	55	
Reader 3				
ccRCC PET+	157	215 ± 96	250	<0.001
ccRCC PET-	22	102 ± 127	8	

Note: The H-Score was assessed by immunostaining and was calculated:
 $H\text{-Score} = (0 \times [\% \text{ cat. } 0]) + (1 \times [\% \text{ cat. } 1]) + (2 \times [\% \text{ cat. } 2]) + (3 \times [\% \text{ cat. } 3])$.

False positive lesions identified on ⁸⁹Zr-DFO-girentuximab PET images:

- 9 pRCC
- 1 undefined cancer
- 1 oncocytoma
- 1 sarcomatoid / spindle cell cancer)



Types of RCC

- Clear cell. This is the most common type of RCC. The cancer cells look pale or clear.
- Papillary. This is the second most common type of RCC. This type of tumor has tiny fingerlike growths.
- Chromophobe. This is a rare form of RCC. The cells are larger than other types of RCC.
- Collecting duct. This is also a rare form of RCC. The cancer cells look like irregular tubes.
- Unclassified. This includes tumors that have cells from more than 1 type of cancer. It also includes tumors with cells that don't fit into the other categories.



T-classification of ccRCC

- **T_x**: tumor cannot be assessed
- **T₀**: tumor not seen
- **T₁**
 - **T_{1a}**: tumor confined to kidney, <4 cm
 - **T_{1b}**: tumor confined to kidney, >4 cm but <7 cm
- **T₂**: limited to kidney >7 cm
 - **T_{2a}**: tumor confined to kidney, >7 cm but not >10 cm
 - **T_{2b}**: tumor confined to kidney, >10 cm
- **T₃**: tumor extension into major veins or perinephric tissues, but not into ipsilateral adrenal gland or beyond [Gerota's fascia](#)
 - **T_{3a}**: tumor grossly extends into the renal vein or its segmental (muscle-containing) branches, or tumor invades perirenal and/or renal sinus fat but not beyond the Gerota fascia
 - **T_{3b}**: spread to infra diaphragmatic IVC
 - **T_{3c}**: spread to supra diaphragmatic IVC or invades the wall of the IVC
- **T₄**: involves ipsilateral adrenal gland or invades beyond [Gerota's fascia](#)



Acquisition protocol

- 37 MBq – 18 mSv by tracer (+ 1 mSv low dose CT kidneys; +3 mSv whole body)
- 1 BP of 20 min over kidneys
 - Optional WB acquisition with 10 min / BP
- 20 min / BP

