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Original Article

Efficacy of [^{177}Lu]Lu-PSMA-617 in Patients with Metastatic Clear-cell Renal Cell Carcinoma: The Multicentre, Single-arm, Phase 2 RENALUT Trial

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Abstract

Background and objective: Angiogenesis-targeting tyrosine kinase inhibitors (TKIs) and immune checkpoint inhibitors (ICIs) are standard treatments for metastatic clear-cell renal cell carcinoma (ccRCC). However, therapeutic options remain limited after progression on these agents. Prostate-specific membrane antigen (PSMA) is highly expressed on the surface of endothelial cells in ccRCC, making radioligand therapy with [^{177}Lu]Lu-PSMA-617 a promising approach.

Clinical trial design and timeframe: RENALUT (NCT06783348) is a single-arm, open-label, phase 2 trial investigating the safety and efficacy of [^{177}Lu]Lu-PSMA-617 in metastatic ccRCC after TKI and ICI failure. Eligible patients must have PSMA-positive lesions on PSMA positron emission tomography imaging. Patients will receive four cycles of [^{177}Lu]Lu-PSMA-617 every 6 wk, with up to two additional cycles in cases with stable disease or a partial response.

Endpoints: The primary endpoint is the objective response rate according to Response Evaluation Criteria in Solid Tumours version 1.1.

Data sources and statistical analysis plan: Assuming a PSMA negativity rate of 15%, a total of 56 patients will be screened to achieve the target enrolment of 48 patients. European centres from three countries (Belgium, France, and Spain) will participate. First patient enrolment is expected in September 2025.

Strengths and limitations: This is the first multicentre trial to assess PSMA-targeted radioligand therapy for patients with metastatic ccRCC selected on the basis of PSMA expression, which may be a potential biomarker in this setting.

Funding: RENALUT is funded by Novartis and is being conducted as a research collaboration trial. The trial is sponsored by the EORTC.

Ethics and trial registration: The trial has been approved by the ethics committee of the coordinating institution in the lead country (Belgium) and is registered on

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ClinicalTrials.gov as NCT06783348. Twelve centres across three countries will be participating. Regulatory submissions are ongoing at all participating sites in compliance with national requirements. Enrolment will begin only after all required approvals are in place.

Patient summary: This trial is looking at a new treatment, called [^{177}Lu]Lu-PSMA-617, for patients with advanced kidney cancer that has spread and no longer responds to standard inhibitor and immunotherapy treatments. [^{177}Lu]Lu-PSMA-617 is a radioactive agent that targets a molecule called PSMA (prostate-specific membrane antigen). Patients who have PSMA detected on a PET (positron emission tomography) scan will receive the treatment every 6 weeks for up to four cycles, with the possibility of two extra cycles if their cancer is stable or shrinking. The aim of the trial is to test a new treatment option for patients who have few remaining alternatives.

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1. Introduction

Clear-cell renal cell carcinoma (ccRCC) accounts for ~80% of all renal cancers. Unlike other subtypes, ccRCC is primarily driven by inactivation of the *VHL* gene, leading to accumulation of hypoxia-inducible factors and subsequent excessive angiogenesis. According to the 2025 European Association of Urology guidelines, two main therapeutic strategies are available for first-line treatment of metastatic ccRCC, guided by International Metastatic RCC Database Consortium (IMDC) risk stratification. The first approach involves a combination of a VEGFR-targeting tyrosine kinase inhibitor (TKI) and an immune checkpoint inhibitor (ICI) [1–5]. Objective response rates (ORRs) to VEGFR-TKI + ICI combinations such as axitinib + pembrolizumab, cabozantinib + nivolumab, and lenvatinib + pembrolizumab range from 46% to 71%, with median progression-free survival (PFS) of 15–23 mo across favourable, intermediate, and poor IMDC risk groups. CheckMate 214 originally demonstrated the benefit of dual checkpoint blockade with nivolumab + ipilimumab for patients with intermediate- or poor-risk disease, with an ORR of 42%, median PFS of 11.6 mo, and median overall survival (OS) of 47 mo [6,7]. Updated results after median follow-up of 67.7 mo showed a potential OS benefit in IMDC favourable-risk disease (hazard ratio 0.94, 95% CI 0.65–1.37), with a higher complete response rate (13% vs 6%) and a higher proportion of patients with a durable response (59% vs 52% at 5 yr) in comparison to sunitinib [8]. These findings led to updated guideline recommendations supporting nivolumab + ipilimumab for the IMDC favourable-risk population as well [9].

Management of patients after disease progression on these regimens remains challenging. Trials such as CONTACT-03 and TiNivo-2 failed to show a benefit of ICI rechallenge strategies, with no improvement in ORR, PFS, or OS when atezolizumab or nivolumab was added to cabozantinib or tivozanib, respectively [10,11]. As a result, guidelines no longer recommend PD-1/PD-L1–based rechallenge approaches. The most robust second-line data are for cabozantinib monotherapy. In the CaboPoint trial, the ORR to cabozantinib was 32% among patients progressing after nivolumab + ipilimumab (cohort A) and 25% for ICI-TKI combinations [12,13]. Similarly, in the phase 3 CONTACT-03 trial, cabozantinib ± atezolizumab resulted in an ORR of 41% in both arms, with median PFS of 10.6 mo and 10.8 mo, respectively [10]. For later lines, the phase 3 LITESPARK-005 trial demonstrated that belzutifan, a HIF2A inhibitor, was superior to everolimus in previously treated ccRCC, with PFS rates at 18 mo of 24% versus 8.3% ($p = 0.002$) and ORRs of 22% versus 3.5% [14]. These findings highlight the limited efficacy of therapies available after first-line treatment and reinforce the need for innovative strategies.

Prostate-specific membrane antigen (PSMA) is a transmembrane glycoprotein highly expressed on prostate cancer cells and in the neovasculature of ccRCC. PSMA overexpression is found in 86–100% of ccRCCs, whereas expression is significantly lower in non–clear-cell subtypes such as chromophobe RCC (30–61%) and papillary RCC (0–28%) [15,16]. This vascular expression pattern raises the possibility that PSMA participates in dynamic remodelling of the tumour-associated vasculature in ccRCC [17]. High PSMA expression in tumour vasculature in RCC was associated with tumour aggressiveness, metastatic potential, and shorter OS [18].

Prospective studies have provided strong evidence of the superior diagnostic performance of PSMA PET/CT over conventional imaging in metastatic ccRCC. In a study by Rowe et al [19], ^{18}F-DCFPyL PET/CT detected 28 metastatic lesions, compared to only 18 on conventional imaging, in a cohort of five patients, corresponding to a detection rate of 97% versus 62%, and sensitivity of 94.7% versus 78.9%. In a study involving 14 patients with presumed oligometastatic ccRCC, Meyer et al [20] found that PSMA PET/CT detected 29 of 33 metastatic lesions, in comparison to 21 lesions detected on conventional imaging, which translated to a detection rate of 87.9% versus 63.4%. In some cases, PSMA PET/CT findings led to reclassification of disease extent, shifting patients from an oligometastatic to a polymetastatic state [20]. These findings are corroborated by retrospective data. In a multicentre Australian study involving 61 patients undergoing PSMA PET/CT for renal cancer staging, 98% of ccRCC lesions showed PSMA ligand avidity. PET/CT identified more metastatic lesions than conventional imaging (195 vs 160) and led to a change in clinical management in 32% of cases (20% major, 12% minor) [21]. Interestingly, PSMA expression may be modulated by therapy. Recent observations by Seront et al [22,23] suggest that a decrease in PSMA

ligand uptake may be associated with a response to VEGFR-TKI and ICI combination therapy.

Administration of [^{177}Lu]Lu-PSMA-617, a radioligand therapeutic agent targeting PSMA, has shown efficacy in metastatic prostate cancer, as demonstrated in the phase 3 VISION trial, with improvements in the prostate-specific antigen response rate, radiographic PFS, and OS [24].

Given the high prevalence and dynamic regulation of PSMA expression in ccRCC vasculature, as well as the favourable safety profile of [^{177}Lu]Lu-PSMA-617, RENALUT was designed to evaluate the efficacy of PSMA-targeted radioligand therapy in patients with metastatic ccRCC who have progressed after treatment with at least one ICI and one VEGFR-TKI agent.

2. Patients and methods

2.1. Clinical trial design

RENALUT is a phase 2 interventional trial designed to prospectively evaluate the efficacy and safety of [^{177}Lu]Lu-PSMA-617 in patients with metastatic ccRCC who have progressed after treatment with a VEGR-TKI and ICI administered either sequentially or in combination. This multicentre trial will involve at least ten European centres in Belgium, France, and Spain.

The primary endpoint is the ORR, defined as the proportion of patients with a confirmed complete response or partial response (PR) according to Response Evaluation Criteria in Solid Tumours version 1.1 for conventional imaging (computed tomography [CT] scan or magnetic resonance imaging). Secondary endpoints include safety, the 6-mo disease control rate (DCR), time to the start of next systemic treatment (TTNT), PFS, and OS. The trial has financial support from Novartis, a pharmaceutical company that is also supplying the investigational drug. The company has been granted a license by the European Organisation for Research and Treatment of Cancer (EORTC) to access and use a copy of the study data after the end of the trial.

2.2. Study population

Eligible patients must have histologically confirmed metastatic ccRCC that has progressed on or after VEGR-TKI and ICI agents administered sequentially or in combination, meaning that patients may be enrolled in the trial at the second- or third-line stage. Patients may have received an ICI-ICI combination followed by a VEGFR-TKI; a VEGFR-TKI followed by an ICI; a VEGFR-TKI + ICI combination; or a VEGFR-TKI + ICI combination followed by a VEGFR-TKI. Patients must have at least one PSMA-positive metastatic lesion on PET/CT imaging, defined as tracer uptake greater than physiological liver uptake on visual analysis. Patients must have predominantly PSMA-positive lesions, provided that PSMA-negative lesions (defined as PSMA ligand uptake on PET/CT equal to or lower than that in liver parenchyma) are not clinically significant (short axis <15 mm in any lymph node lesion, short axis <10 mm in any metastatic solid-organ or bone lesion). The handling of lesions without PSMA ligand avidity will be documented.

Patients with ccRCC who have a solitary kidney and those with an estimated glomerular filtration rate of <40 ml/min will be excluded.

2.3. Procedures

During the screening period, patients will undergo PSMA PET/CT imaging to confirm the presence of PMSA-positive disease. Patients meeting the eligibility criteria will receive [^{177}Lu]Lu-PSMA-617 at standard activity of 7.4 GBq every 6 wk for four initial cycles. In cases with PR or stable disease on conventional imaging after four [^{177}Lu]Lu-PSMA-617 cycles, two additional cycles can be administered. The timeline is described in Figure 1.

Post-treatment single-photon emission CT/CT imaging will be conducted at least on the day after [^{177}Lu]Lu-PSMA-617 administration to ensure that disease sites have been adequately targeted.

A PSMA PET/CT scan will be performed after cycles 2 and 4 of [^{177}Lu]Lu-PSMA-617. Conventional imaging will be conducted every 12 wk after initiation of [^{177}Lu]Lu-PSMA-617 treatment for 12 mo, or earlier if symptoms arise, in accordance with standard practice.

2.4. Statistical considerations

Given the lack of prospective studies evaluating [^{177}Lu]Lu-PSMA-617 in ccRCC, this benchmark trial is based on best available data from second-line cabozantinib studies and may need validation in future randomised trials. Imaging assessments are scheduled up to 12 mo after treatment initiation, and will be continued thereafter according to clinical practice. The primary endpoint, ORR, is defined as the radiological response observed during this period.

Patients without a follow-up scan during this period will be considered as failure to respond.

A one-stage A'Hern design will be used to test the null hypothesis for the primary endpoint. Secondary endpoints (TTNT, PFS, and OS) will be estimated using the Kaplan-Meier method. Two-sided 95% confidence interval for the median will be calculated using the Brookmeyer-Crowley method.

Patients will be censored at the date of last contact or last available disease assessment (for PFS). Missing scans will be addressed according to standard censoring rules (eg, censoring at the last radiologically evaluable time point if progression is not confirmed).

The sample size consideration is based on a null hypothesis of an ORR $\leq$30% (based on cabozantinib efficacy in the interim CaboPoint analysis) versus the alternative hypothesis that ORR >30%. The power and sample size were computed under the alternative hypothesis that ORR = 50%. The type I and type II error constraints are set to 5% and 20%, respectively, corresponding to power of 80%. Under these assumptions, the minimal number of evaluable patients that guarantees 80% power is 43. Success is defined as a response in $\geq$18 patients from a cohort of 43 evaluable patients. Under these assumptions, we expect a type I error rate of 3.4% and a type II error rate of 18.0%.

A screening success rate of 85% is anticipated, considering that approximately 15% of screened patients may have

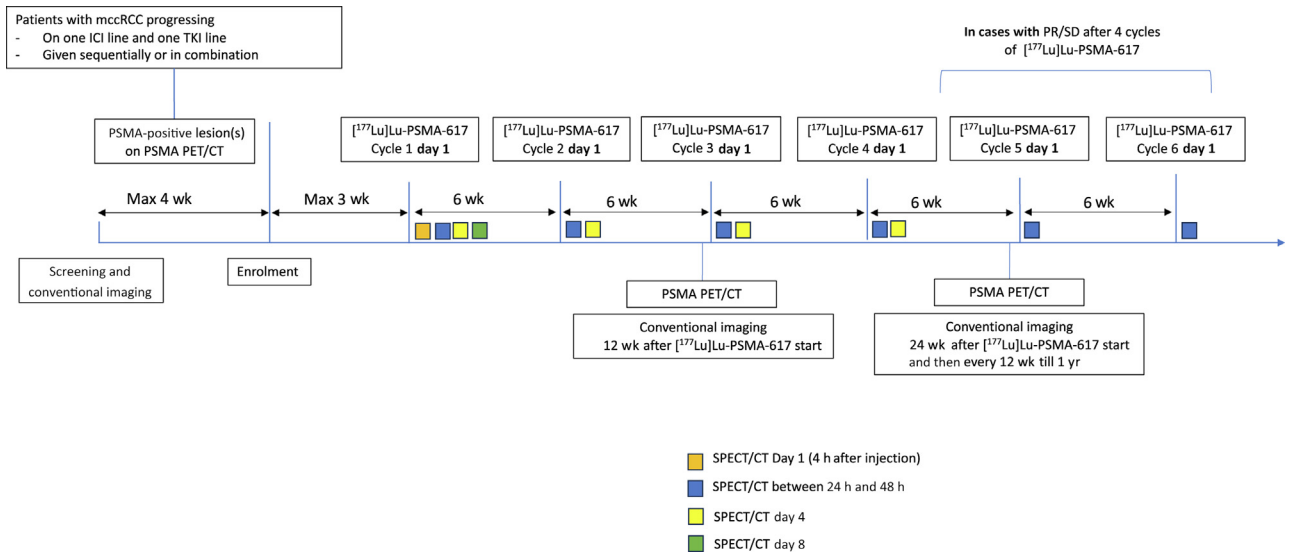

Figure 1 – Timeline for the RENALUT trial. Conventional imaging is magnetic resonance imaging of the thorax and abdomen/bone scan. Assessment of treatment responses on conventional imaging is based on Response Evaluation Criteria in Solid Tumours version 1.1. mccRCC = metastatic clear-cell renal cell carcinoma; ICI = immune checkpoint inhibitor; TKI = VEGF-targeted tyrosine kinase inhibitor; PET = positron emission tomography; CT = computed tomography; Max = maximum; PSMA = prostate-specific membrane antigen; PR = partial response; SD = stable disease; SPECT = single-photon emission CT.

PSMA-negative disease or other disqualifying factors, and up to 10% of patients may be excluded from the study analysis because of ineligibility.

This brings the total number of patients for screening to $43 \div 0.90 \div 0.85 \approx 56$, with 48 patients expected to be enrolled in the study.

The estimated accrual time is 18 mo from inclusion of the first participant. The primary ORR analysis will be performed approximately 9 mo (end of six treatment cycles) after inclusion of the last patient. Given the relatively short follow-up, it is not anticipated that median OS will be reached, but estimates of early PFS and TTNT results may be informative and will help in guiding the design of future randomised trials.

3. Strengths and limitations

The RENALUT trial has several notable strengths. First, PSMA radioligands selectively target the tumour vasculature in RCC, which is an essential driver of ccRCC pathophysiology, and [^{177}Lu]Lu-PSMA-617 administration represents a novel and innovative antiangiogenic strategy in metastatic ccRCC. Second, RENALUT is the first European multicentre prospective trial investigating [^{177}Lu]Lu-PSMA-617 in patients with metastatic ccRCC. Furthermore, patient selection is based on PSMA PET imaging using real-world tracers (^{68}Ga-PSMA-11 and ^{18}F-PSMA-11), which enhances the external validity of the trial and reflects routine clinical practice. The protocol has a flexible treatment design with a 4 + 2 schedule that allows two extra cycles in responding patients, which may improve clinical outcomes.

However, some limitations should be acknowledged. PSMA is expressed directly on tumour cells in prostate cancer, so direct radioligand targeting is possible, but PSMA in ccRCC is predominantly expressed in the tumour neovasculature, so there may be potential differences in efficacy because of an indirect targeting mechanism, heterogeneous radioligand uptake, and undefined retention and rapid washout of the radioligand. The single-arm design without a control group limits the ability to make direct comparisons with standard therapies. Furthermore, the inclusion of patients with minor PSMA-negative lesions, while justified, may introduce heterogeneity in treatment responses.

4. Discussion and conclusions

RENALUT is exploring the safety and efficacy of [^{177}Lu]Lu-PSMA-617 in patients with PSMA-positive metastatic ccRCC. Another ongoing trial, PraDR, is also investigating [^{177}Lu]Lu-PSMA-1 in the ccRCC setting [25]. However, our trial differs from PraDR in several aspects.

- While the primary endpoint in PraDR is DCR at 24 wk, the endpoint in RENALUT is ORR for better assessment of the antitumour activity of [^{177}Lu]Lu-PSMA-617.
- RENALUT includes PSMA PET/CT imaging after cycles 2 and 4 of [^{177}Lu]Lu-PSMA-617 to collect data for correlative analysis of outcomes.
- While PraDR is enrolling only patients with PSMA-expressing tumours, RENALUT allows the inclusion of patients with not clinically significant PSMA-negative lesions; this broader inclusion is particularly relevant given that one of our secondary endpoints is TTNT, a critical consideration when alternative therapeutic options are limited.
- Whereas PraDR is exclusively using gallium-based PSMA PET imaging, RENALUT allows the use of ^{68}Ga-PSMA-11 and ^{18}F-PSMA-11, which will better reflect real-world practice across multiple countries [10].
- PraDR is investigating [^{177}Lu]Lu-PSMA-1, which is a radioligand that is less commonly used with distinct pharmacokinetic properties, so further indirect comparison with [^{177}Lu]Lu-PSMA-617 will be possible.
- While both trials involve initial administration of four treatment cycles, the RENALUT protocol offers up to two addi-

tional cycles for patients with controlled but residual disease, a "4 + 2" regimen.

If RENALUT demonstrates clinical activity of [^{177}Lu]Lu-PSMA-617 in metastatic ccRCC, this could mark a paradigm shift in the management of patients who have exhausted standard VEGFR-TKI and ICI regimens. Given the high unmet need in this setting and the absence of effective rechallenge options, radioligand therapy could provide a novel, imaging-guided, biomarker-driven treatment strategy. Integration of PSMA PET imaging into RCC management algorithms would allow for refined patient selection, with the potential to personalise therapy beyond conventional histology- or risk-based stratification. A positive signal from RENALUT would justify the development of randomised phase 3 trials comparing [^{177}Lu]Lu-PSMA-617 to current second- or third-line standards such as cabozantinib and belzutifan. It might also open the door for investigation of combination approaches, particularly the addition of immunotherapy to enhance antitumour responses and overcome limitations related to heterogeneous PSMA expression.

The correlative imaging and exploratory biomarker analyses in RENALUT might inform new assessment criteria for treatment responses to theranostic agents, and could help in identifying the patients who are most likely to benefit.

RENALUT is investigating a potential paradigm shift in treatment for metastatic ccRCC. If successful, the study could open the door to future therapeutic innovations and significantly improve the management of this challenging disease.

5. Clinical trial in context

RENALUT is addressing a significant therapeutic gap in the management of metastatic ccRCC after TKI and ICI failure. There are currently no approved treatment options that exploit PSMA expression in ccRCC, despite consistent findings of high PSMA uptake in the tumour neovasculature. The open-label, single-arm, multicentre phase 2 RENALUT trial is evaluating the efficacy and safety of [^{177}Lu]Lu-PSMA-617 in patients with PSMA-positive metastatic ccRCC. Patients will receive four cycles of treatment, with the option for two additional cycles, depending on treatment responses. The design allows the use of both ^{68}Ga-PSMA and ^{18}F-PSMA PET tracers, which reflects real-world clinical practice. If successful, RENALUT could provide a rationale for further development of radioligand therapy as a treatment strategy in advanced ccRCC and support the potential role of PSMA ligand uptake on PET as a biomarker for patient selection. It would also pave the way for subsequent randomised studies comparing this novel approach to existing standard therapies.

Author contributions: Emmanuel Seront had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Seront, Tombal, Goffin.
Acquisition of data: Seront, Bsilat.
Analysis and interpretation of data: Seront, Bsilat, Goffin, Govaerts.
Drafting of the manuscript: Seront, Bsilat, Goffin, Govaerts.
Critical revision of the manuscript for important intellectual content: Seront, Bsilat, Goffin, Govaerts, Litière, Cabrieto, Dhondt, Tombal, Albiges.
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Appendix A. Supplementary data

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References

[1] Choueiri TK, Powles T, Burotto M, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2021;384:829–41. https://doi.org/10.1056/NEJMoa2026982.
[2] Rini BI, Plimack ER, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. N Engl J Med 2019;380:1116–27. https://doi.org/10.1056/NEJMoa1816714.
[3] Motzer R, Alekseev B, Rha SY, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. N Engl J Med 2021;384:1289–300. https://doi.org/10.1056/NEJMoa2035716.
[4] Plimack ER, Powles T, Stus V, et al. Pembrolizumab plus axitinib versus sunitinib as first-line treatment of advanced renal cell carcinoma: 43-month follow-up of the phase 3 KEYNOTE-426 study. Eur Urol 2023;84:449–54. https://doi.org/10.1016/j.eururo.2023.06.006.

[5] Powles T, Burotto M, Escudier B, et al. Nivolumab plus cabozantinib versus sunitinib for first-line treatment of advanced renal cell carcinoma: extended follow-up from the phase III randomised CheckMate 9ER trial. ESMO Open 2024;9:102994. https://doi.org/10.1016/j.esmoop.2024.102994.
[6] Motzer RJ, Tannir NM, McDermott DF, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. N Engl J Med 2018;378:1277–90. https://doi.org/10.1056/NEJMoa1712126.
[7] Choueiri TK, Escudier B, McDermott DF, et al. Nivolumab plus ipilimumab vs sunitinib for first-line treatment of advanced renal cell carcinoma: final analysis from the phase 3 CheckMate 214 trial. J Clin Oncol 2025;43(16 Suppl):4505. https://doi.org/10.1200/JCO.2025.43.16_suppl.4505.
[8] Motzer RJ, McDermott DF, Escudier B, et al. Conditional survival and long-term efficacy with nivolumab plus ipilimumab versus sunitinib in patients with advanced renal cell carcinoma. Cancer 2022;128:2085–97. https://doi.org/10.1002/cncr.34180.
[9] Bex A, Ghanem YA, Albiges L, et al. European Association of Urology guidelines on renal cell carcinoma: the 2025 update. Eur Urol 2025;87:683–96. https://doi.org/10.1016/j.eururo.2025.02.020.
[10] Pal SK, Albiges L, Tomczak P, et al. Atezolizumab plus cabozantinib versus cabozantinib monotherapy for patients with renal cell carcinoma after progression with previous immune checkpoint inhibitor treatment (CONTACT-03): a multicentre, randomised, open-label, phase 3 trial. Lancet 2023;402:185–95. https://doi.org/10.1016/S0140-6736(23)00922-4.
[11] Choueiri TK, Albiges L, Barthélémy P, et al. Tivozanib plus nivolumab versus tivozanib monotherapy in patients with renal cell carcinoma following an immune checkpoint inhibitor: results of the phase 3 TiNivo-2 study. Lancet 2024;404:1309–20. https://doi.org/10.1016/S0140-6736(24)01758-6.
[12] Albiges L, Schmidinger M, Taguieva-Pioger N, Perol D, Grünwald V, Guemas E. CaboPoint: a phase II study of cabozantinib as second-line treatment in patients with metastatic renal cell carcinoma. Future Oncol 2022;18:915–26. https://doi.org/10.2217/fon-2021-1006.
[13] Albiges L, Powles T, Sharma A, et al. CaboPoint: interim results from a phase 2 study of cabozantinib after checkpoint inhibitor (CPI) therapy in patients with advanced renal cell carcinoma (RCC). J Clin Oncol 2023;41(6 Suppl):606. https://doi.org/10.1200/JCO.2023.41.6_suppl.606.
[14] Choueiri TK, Powles T, Peltola K, et al. Belzutifan versus everolimus for advanced renal-cell carcinoma. N Engl J Med 2024;391:710–21. https://doi.org/10.1056/NEJMoa2313906.
[15] Baccala A, Sercia L, Li J, Heston W, Zhou M. Expression of prostate-specific membrane antigen in tumor-associated neovasculature of renal neoplasms. Urology 2007;70:385–90. https://doi.org/10.1016/j.urology.2007.03.025.
[16] Chang SS, Reuter VE, Heston WD, Gaudin PB. Metastatic renal cell carcinoma neovasculature expresses prostate-specific membrane antigen. Urology 2001;57:801–5. https://doi.org/10.1016/s0090-4295(00)01094-3.
[17] Watanabe R, Kagimoto K, Chosei M, et al. Vesicles secreted by renal cell carcinoma cells cause vascular endothelial cells to express PSMA and drive tumor progression. Cells 2025;14:165. https://doi.org/10.3390/cells14030165.
[18] Spatz S, Tolkach Y, Jung K, et al. Comprehensive evaluation of prostate specific membrane antigen expression in the vasculature of renal tumors: implications for imaging studies and prognostic role. J Urol 2018;199:370–7. https://doi.org/10.1016/j.juro.2017.08.079.
[19] Rowe SP, Gorin MA, Hammers HJ, et al. Imaging of metastatic clear cell renal cell carcinoma with PSMA-targeted ^{18}F-DCFPyL PET/CT. Ann Nucl Med 2015;29:877–82. https://doi.org/10.1007/s12149-015-1017-z.
[20] Meyer AR, Carducci MA, Denmeade SR, et al. Improved identification of patients with oligometastatic clear cell renal cell carcinoma with PSMA-targeted ^{18}F-DCFPyL PET/CT. Ann Nucl Med 2019;33:617–23. https://doi.org/10.1007/s12149-019-01371-8.
[21] Tariq A, Pearce A, Rhee H, et al. The role of prostate-specific membrane antigen positron emission tomography/computed tomography in primary staging of selected renal tumours: initial experience in a multicentre cohort. Eur Urol Focus 2024;10:770–8. https://doi.org/10.1016/j.euf.2023.12.004.
[22] Seront E, Lhommel R, Tombal B. Case report: early ^{68}Ga-PSMA-PET metabolic assessment and response to systemic treatment for first-line metastatic clear cell renal cell carcinoma; about two clinical cases. Front Oncol 2021;11:782166. https://doi.org/10.3389/fonc.2021.782166.
[23] Seront E, Reichel C, Lhommel R, Tombal B. A case series study of the role of prostate-specific membrane antigen positron emission tomography/computed tomography in early evaluation of the response to systemic therapy in metastatic renal cancer. Eur Urol Oncol 2024;7:1147–9. https://doi.org/10.1016/j.euo.2024.02.006.
[24] Sartor O, de Bono J, Chi KN, et al. Lutetium-177-PSMA-617 for metastatic castration-resistant prostate cancer. N Engl J Med 2021;385:1091–103. https://doi.org/10.1056/NEJMoa2107322.
[25] Kryza D, Vinceneux A, Bidaux AS, et al. A multicentric, single arm, open-label, phase I/II study evaluating PSMA targeted radionuclide therapy in adult patients with metastatic clear cell renal cancer (PRadR). BMC Cancer 2024;24:163. https://doi.org/10.1186/s12885-023-11702-8.