BENCH TO BEDSIDE
URO-ONCOLOGY
GU CANCERS TRIAD

Proceedings From the 5th B2B Uro-Oncology: GU Cancers Triad Meeting

October 13, 2023

Kidney Cancer

SOCIÉTÉ INTERNATIONALE D'UROLOGIE SIU

www.siu-urology.org

#B2BGUCancersTriad

B2B: Kidney Cancer Summary

DOI: 10.48083/MPRU1397

Simon Tanguay,[1,a,b] Tarik Esen,[2] Patrick O. Richard,[3] Karima Oualla,[4] Christian Kollmannsberger,[5] Öner Sanli,[6] Tian Zhang,[7] Axel Bex,[8,9] Peter C. Black[10,b]

[1]Department of Surgery, Division of Urology, McGill University, Montreal, Canada [2]Department of Urology, Koç University School of Medicine, Istanbul, Türkiye [3]Department of Urology, Centre Hospitalier Universitaire de Sherbrooke and Centre de Recherche du CHUS, Sherbrooke, Canada [4]Medical Oncology Department, Hassan II University Hospital, Mohamed Ben Abdellah University, Fes, Morocco [5]Division of Medical Oncology BC Cancer Vancouver Cancer Centre & Department of Urologic Sciences/The Prostate Cancer Centre, University of British Columbia, Vancouver, Canada [6]Division of Urologic Oncology, Department of Urology, Istanbul Faculty of Medicine, Istanbul University, Istanbul, Türkiye [7]Department of Internal Medicine, University of Texas Southwestern Medical Center & Harold C. Simmons Comprehensive Cancer Center, Dallas, United States [8]The Royal Free London NHS Foundation Trust & UCL Division of Surgery and Interventional Science, London, United Kingdom [9]Department of Urology, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands [10]Department of Urologic Sciences, University of British Columbia, Vancouver, Canada

[a]Lead, Kidney Cancer, Scientific Programme Committee [b]Co-Chair, Scientific Programme Committee

The 5th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 43rd Annual Congress of the Société Internationale d'Urologie, was held on October 13th, 2023, at the Istanbul Lutfi Kirdar International Convention and Exhibition Centre in Istanbul, Türkiye, and transmitted live on the *SIU@U* virtual platform. The session on renal cell carcinoma (RCC) took place in the morning and was chaired by Dr. Simon Tanguay (Canada). This session started with presentations on the novel imaging approaches to predict histologic subtypes of RCC and how artificial intelligence (AI) can help improve characterization of complex renal cysts, followed by a debate on whether triple therapy is the optimal treatment for intermediate-risk metastatic RCC (mRCC). Next were presentations on the most important endpoint to select first-line regimen, optimal patient selection for adjuvant therapy post nephrectomy, and the use of belzutifan in sporadic and hereditary RCC. The session concluded with an update on key ongoing clinical trials in RCC.

Dr. Tarik Esen (Türkiye) discussed novel imaging options and how those can be used to predict histologic subtypes of small, solid renal masses[1]. Incidental detection of renal lesions increases every year. Nevertheless, between 20% and 30% of resected small renal masses are benign, with an estimated 5600 benign lesions unnecessarily resected in the United States alone every year[2,3].

The European Association of Urology (EAU) guidelines recommend the use of contrast-enhanced computed tomography (CT) or magnetic resonance imaging (MRI) to diagnose or differentiate between small renal masses. Biopsy is particularly recommended for patients undergoing active surveillance[4]. However, the histopathological classification of renal tumours has become increasingly complex with the description of new subtypes that ultimately make differential diagnosis more challenging.

There are several challenges for the differential diagnosis of small renal masses: first, the differentiation between a benign and a malignant tumour, such as the case of an oncocytoma vs. chromophobe RCC, a fat-poor angiomyolipoma vs. RCC, and a complicated cyst vs. papillary RCC; second, the discrimination between low-grade and high-grade RCC, which can be used to guide decisions for active surveillance management; and lastly, the differentiation between clear cell RCC (ccRCC) vs. non-ccRCC, which has important implications for systemic therapy selection in the metastatic setting. Renal mass biopsy might help the differential diagnosis; however, this is an invasive procedure, with a high nondiagnostic rate (10% to 15%). It often leads to erroneous diagnosis resulting from tumour

heterogeneity (10%) and is generally not feasible in challenging anatomical locations[5].

Conventional imaging has limited utility to characterize renal masses. Aside from detecting macroscopic fat, which leads to the diagnosis of angiomyolipoma, there is significant overlap of conventional imaging findings[6]. For instance, CT and MRI cannot achieve definitive diagnosis of renal lesions. In fact, oncocytoma, low-grade oncocytic tumour, and chromophobe RCC look very similar on conventional imaging alone. These limitations emphasize the need for superior imaging modalities to characterize renal masses.

Over the years, new imaging modalities have been developed and employed in the diagnosis of renal masses. Contrast-enhanced ultrasound (CEUS) is a non-invasive approach that was shown to perform at least as well as or better than contrast-enhanced CT and MRI, both in sensitivity as well as specificity, in a meta-analysis of 16 studies[7]. Multiparametric MRI (mpMRI) of the kidney, although not as frequently used as in prostate cancer, has relatively high diagnostic power to predict ccRCC (85% sensitivity, 76% specificity) and papillary RCC (80% sensitivity, 94% specificity)[8].

One approach that harnessed interest in the last few years is technetium-99m (^{99m}Tc)-sestamibi single-photon emission CT (SPECT)/CT. ^{99m}Tc-sestamibi is a lipophilic cation that accumulates by affinity in cells with high density of mitochondria, such as oncocytoma. ccRCC, by contrast, has low density of mitochondria; because of low affinity, there is no intracellular accumulation of ^{99m}Tc-sestamibi, which is pumped out of the cell by multidrug resistance pumps[9]. The first study reporting on the diagnostic performance of ^{99m}Tc-sestamibi SPECT/CT included 50 patients with a solid cT1 renal mass. Overall, the observed sensitivity was 87.5% and specificity was 95.2%, with only 2 false positives identified on ^{99m}Tc-sestamibi SPECT/CT[10]. Relative uptake of ^{99m}Tc-sestamibi was higher in oncocytomas and hybrid oncocytic/chromophobe tumours than in RCC. The diagnostic accuracy of ^{99m}Tc-sestamibi SPECT/CT was reviewed systematically across 4 studies with a total of 117 renal lesions. The meta-analysis demonstrated superior performance of this approach in diagnosing oncocytoma compared to other renal lesions[11]. In a cost effectivity analysis of competing management strategies for a small, asymptomatic renal mass, ^{99m}Tc-sestamibi SPECT/CT followed by confirmatory biopsy had very low risk of untreated malignant tumours (0.2%), the highest probability of leaving a benign tumour untreated (84.4%), and the lowest cost-effectiveness ratio ($18 812 US/quality-adjusted life years)[12].

Another approach explored for imaging in ccRCC is carbonic anhydrase IX (CAIX), which becomes upregulated in hypoxic conditions. Loss or inactivation of the *VHL* gene also results in hypoxia-inducible factor (HIF) increase, which upregulates CAIX[13]. CAIX is upregulated in 95% of ccRCC. Girentuximab (previously termed G250) is a chimeric monoclonal antibody that binds to CAIX with high affinity. Initial investigation of girentuximab bound to the radionuclide iodine-124 (^{124}I-girentuximab) as a radiotracer for positron-emission tomography (PET)/CT in small renal masses was reported in a pilot study of 26 patients[14]. ^{124}I-girentuximab PET/CT performed before surgical resection was able to accurately identify 15/16 ccRCC. All 9 non-ccRCC were negative for the tracer. For ccRCC, the tracer performed with sensitivity of 94%, specificity of 100%, positive predictive value (PPV) of 100%, and negative predictive value (NPV) of 90%. In the REDECT trial, the diagnostic performance of ^{124}I-girentuximab PET/CT was compared with contrast-enhanced CT in 195 patients[15]. ^{124}I-girentuximab PET/CT vs. contrast-enhanced CT had greater sensitivity (86.2% vs. 75.5%; $P = 0.23$) and specificity (85.9% vs. 46.8%; $P = 0.005$) to detect ccRCC. More recently, another radiotracer zirconium-89 (^{89}Zr)-girentuximab was evaluated in the multicentre phase 3 ZIRCON trial, which enrolled 300 patients. In the full analysis set (n = 284), the sensitivity, specificity, PPV, NPV, and accuracy of ^{89}Zr-girentuximab PET/CT were 85.5%, 87%, 93%, 75%, and 86%, respectively[16]. Similar diagnostic performance was seen in small renal masses (cT1a). Most adverse events were mild, and only 18 (6%) of cases were grade ≥ 3. Other radiotracers, such as fluorine-18-fluodeoxyglucose (^{18}F-FDG) and prostate-specific membrane antigen (PSMA) have limited sensitivity and are not used routinely for histologic subtyping of renal masses[17,18].

B2B: Kidney Cancer Summary

Lastly, radiomics combined with AI has become the focus of new developments for the histologic diagnosis of small renal masses. Radiomics is able to identify hidden textural information in a tissue that is imperceptible to the human eye[19]. This approach has been implemented to differentiate fat-poor angiomyolipoma from ccRCC using both CT[20,21] as well as MRI texture analysis[22]. In fact, a systematic review and meta-analysis of 113 studies demonstrated significant log odds ratio of radiomics for distinguishing RCC from angiomyolipoma (2.89, 95% confidence interval [CI] 2.40 to 3.39; $P < 0.001$), oncocytoma (3.08; 95% CI, 2.09 to 4.06, $P < 0.001$), and unspecified renal tumours (3.57; 95% CI, 2.69 to 4.45, $P < 0.001$)[19]. Machine learning integrating ^{99m}Tc-sestamibi SPECT/CT and radiomics has also demonstrated potential for characterization of renal masses. In a prospective study of 54 renal tumours, ^{99m}Tc-sestamibi SPECT/CT combined with radiomics had better performance than radiomics alone in oncocytomas from RCC (area under the curve [AUC] = 98.3% vs. 75%, respectively)[23].

While further validation is required, new molecular imaging approaches and AI show great promise to overcome the clinical challenges in the differential diagnosis of small solid renal masses, which could have a positive impact on surgical decision-making in clinical practice.

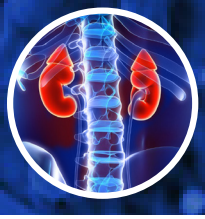
During the Q&A, Dr. Esen discussed whether new molecular imaging, such as ^{89}Zr-girentuximab PET/CT, would be able to replace renal biopsy to guide clinical decisions regarding surgery or active surveillance. While biopsy may still be required in select cases, ^{89}Zr-girentuximab PET/CT shows great promise as a novel diagnostic approach, especially in highly suspicious cases where a diagnosis is necessary before surgery. Furthermore, he pointed out that the ZIRCON trial could be the first step for a possible theranostic use of girentuximab bound to radioligands (e.g., lutetium-177) to manage metastatic ccRCC and to downsize renal tumour burden.

Next, Dr. Patrick O. Richard (Canada) highlighted how AI will help improve characterization of complex renal cysts. Kidney cancer is a prevalent malignancy with a rapidly growing incidence of 1% to 2% yearly. This increase in incidence is associated with greater incidental detection of tumours through imaging[24]. Despite an increase in surgery, kidney cancer–associated mortality has remained predominantly stable for the last 40 years.

Why is there a discordance between incidence and mortality? First, nearly 50% of all newly diagnosed renal lesions are small renal masses[25]. Of those, 20% to 30% will be benign[26–28]. Even for malignant lesions, the vast majority will be indolent, with slow growth and low metastatic potential[26,27]. Second, 5% to 10% of lesions will be complex renal cysts, of which up to 50% are benign[29]. Even if malignant, stage for stage, malignant complex cysts have a better prognosis than solid RCCs[30]. Lastly, with average age of diagnosis from 65 to 70, the majority of patients have comorbidities that put them more at risk of death by other causes than from kidney cancer[31]. If patients with a renal lesion continue to be managed by surgery, it is likely that many will be overtreated. Per definition, overtreatment consists of an intervention that does not benefit the patient or where the risk of harm from the intervention is likely to outweigh any benefit the patient would receive.

One of the reasons why most patients are overtreated is the limitations of conventional imaging (CT and MRI) to distinguish between a benign vs. a malignant tumour. In a systematic review including 3036 complex renal cysts categorized with the Bosniak classification system, the estimated surgical number needed to treat to prevent metastatic disease of Bosniak III and IV cysts was 140 and 40, respectively[32]. This highlights the low effectiveness of the Bosniak classification for complex renal cysts category III. In recognition of the impact of overtreatment, the Canadian Urological Association has recently published guidelines on the management of cystic renal lesions, emphasizing the role of active surveillance[29].

Radiomics is a technique that extracts quantitative features from conventional imaging (e.g., CT, MRI, PET) that are invisible to the naked eye. According to the Image Biomarker Standardisation Initiative (IBSI), these can be classified into 79 nontextural features, such as tumour morphology and pixel intensity, and 94 textural features, such as pixel organization in the tumour area. To perform radiomics, it is necessary to



identify the area of interest, which is done in most studies by manual segmentation: the lesion is delineated manually, usually on each slice of the CT scan or MRI. This process is laborious and time consuming, especially for large lesions.

Machine learning and AI can be used to facilitate this process by automating the segmentation computationally, as seen in several studies, which may streamline the process and make the use of radiomics feasible in daily practice. Several studies investigating AI-automated segmentation have shown an AUC of approximately 0.80[33–36], demonstrating that this approach can be further improved. Machine learning can also be used to develop predictive models and be applied to evaluate benign vs. malignant tumours, RCC subtypes, RCC aggressiveness, and even help to evaluate response to treatment in the metastatic setting. In studies of machine learning model–based radiomics to discriminate between benign vs. malignant solid renal lesions, the AUC ranged from 0.68 to 0.84[37,38], highlighting potential for improvement. Importantly, a meta-analysis has demonstrated a 3-fold detection improvement of benign lesions in patients who underwent CT- or MRI-based radiomics investigation[19]. Another interesting future avenue is the development of radiogenomics, the combination of radiomics features with genomic data, which may help clinicians to better define stratification risk, guide treatment selection and follow-up strategy, as well as better determine disease prognosis[39].

Compared to solid renal masses, the role of radiomics on cystic renal lesions has not been as well explored. One study of 150 patients examined a CT-based radiomics nomogram to identify malignant and benign Bosniak IIF lesions. The radiomics nomogram performed with an accuracy of 0.935[40]. A limitation of this study was the number of malignant Bosniak IIF lesions (> 20%) in the cohort, which is much higher than seen in clinical practice (usually < 5%). It is also important to note that the Bosniak classification system is subject to inter-reader variability.

A more relevant approach moving forward is using radiomics instead of the Bosniak system to predict malignancy. This approach was employed in a study led by Dr. Caroline Reinhold at McGill University. The study included 149 cystic renal lesions in the training dataset and 50 cystic renal lesions in the testing dataset. In both datasets, the radiomics model had excellent performance, with sensitivity of 88% and specificity of 97% in the testing dataset[41]. The radiomics model was then built into a clinical decision algorithm to determine appropriate management (no follow-up, active surveillance, or surgery). Using radiomics combined with a clinical decision algorithm, the authors were able to reliably predict management. This decision algorithm is promising but must be prospectively validated in a multicentre study including Bosniak IIF, III, and IV lesions.

Additionally, different mathematical formulae can be used to extract quantitative features from images. In another study, the use of a fusion feature–based classifier machine learning algorithm demonstrated excellent diagnostic performance to accurately distinguish malignant and benign cystic renal lesions, outperforming the Bosniak-2019 version classification with improved utility in clinical decision-making[42].

There is an ongoing need for noninvasive approaches to decrease the overtreatment of renal lesions. Radiomics holds promise as a new clinical decision tool. Some needed improvements to this tool include further development of automated segmentation, as well as larger and higher-quality studies, particularly for cystic renal lesions, to validate the role of radiomics in clinical practice.

During a Q&A, Dr. Richard further delved into the limitations of AI and radiomics in the kidney cancer practice. He believes that the main limiting factor is the manual segmentation of conventional imaging. So far, no studies have been able to use automated segmentation reliably, i.e., use AI to identify the region of interest, and make the segmentation process faster. Several groups are looking into strategies to improve segmentation. He also added that there are studies investigating MRI-based radiomics, but those have not been superior to radiomics based on CT scans.

Following was a debate on whether triple therapy is the best treatment option for patients with intermediate-risk RCC according to the International mRCC

B2B: Kidney Cancer Summary

Database Consortium (IMDC) classification. Dr. Karima Oualla (Morocco) presented the pros, whereas Dr. Christian Kollmannsberger (Canada) presented the cons of this approach.

Dr. Oualla started by highlighting the evolution of the treatment landscape in mRCC in the last 2 decades, progressing from very few therapeutic options with limited survival benefit to contemporary treatments with immunotherapy-immunotherapy (IO-IO) and immunotherapy-tyrosine kinase inhibitor (IO-TKI) and combinations. Such advances have contributed to meaningful improvements in overall survival (OS) for patients in the advanced setting.

Ipilimumab-nivolumab is the only first-line IO-IO combination therapy available for mRCC. This combination demonstrated improved OS and progression-free survival (PFS) against sunitinib in the randomized phase 3 CheckMate 214 trial in patients with intermediate- and poor-risk mRCC[43]. Five-year follow-up data demonstrated continued benefit of ipilimumab-nivolumab combination vs. sunitinib[44].

Available IO-TKI options are pembrolizumab-axitinib (KEYNOTE-426)[45], nivolumab-cabozantinib (CheckMate 9ER)[46], and pembrolizumab-lenvatinib (CLEAR)[47]. All available IO-TKI combinations have demonstrated improved objective response rate (ORR), PFS, and OS compared to sunitinib in the respective phase 3 trials. Median OS for avelumab-axitinib (JAVELIN Renal 101) has not been reached[48].

There are certain advantages to each treatment combination strategy, in addition to improved OS. IO-IO combination has the most mature follow-up data demonstrating durable responses and long-term survival. IO-TKI combinations, on the other hand, have demonstrated high ORR, long PFS, and lower rate of immune-related adverse events. With the advantages of each combination, would it be possible to achieve an additive effect of an IO-IO-TKI combination?

The phase 3 COSMIC-313 trial examined this strategy as first-line treatment in mRCC. Patients were randomized to receive ipilimumab + nivolumab + cabozantinib in the treatment arm vs. ipilimumab + nivolumab + placebo in the control arm. Ipilimumab was stopped in both arms after the fourth cycle. Patients received maintenance nivolumab for up to 2 years. The trial met its primary endpoint of improved median PFS with the triplet combination (hazard ratio [HR] = 0.73; 95% CI, 0.57 to 0.94, P = 0.01)[49]. Interestingly, the PFS and ORR benefits with the triplet combination were observed only in IMDC intermediate-risk patients, but not in poor-risk patients. Early separation of curves was seen in intermediate-risk patients, indicating an early effect of the triplet combination. In this group, triplet therapy resulted in 32% reduction of the risk of progression or death[50]. Despite the differences in PFS benefit, Dr. Oualla noted that ipilimumab + nivolumab + cabozantinib resulted in high disease control rate (DCR) and low progressive disease rate, even in the poor-risk population. However, higher rates of adverse events and treatment discontinuations were seen with the triplet therapy compared to ipilimumab + nivolumab.

COSMIC-313 represents an important milestone for the treatment of mRCC, as this is the first randomized controlled trial in this space to have a contemporary doublet control arm (i.e., not sunitinib). This is the first positive trial evaluating a triplet therapy. It demonstrates not only early response to treatment but also maintenance of the PFS benefit and suggests potential advantages of combining the IO-IO and IO-TKI treatment strategies. OS data are highly anticipated. However, there are several limitations to the current results. It is still unclear why no benefit was seen with the triplet combination in poor-risk patients, who have more aggressive disease. Toxicity was higher with the triplet than the doublet therapy, as expected. It is thus important to better select patients who may benefit from an intensified treatment through a risk-adapted approach. Biomarker studies may support these treatment decisions. Other ongoing trials are investigating triplet combinations (LITESPARK-012, NCT04736706) and a risk-adapted approach (PDIGREE, NCT03793166) for the treatment of mRCC.

Dr. Kollmannsberger started by explaining that *optimal therapy* is therapy that maximizes the benefit and minimizes the risk. While this definition is subjective, there is a general agreement that benefit can be defined by tumour shrinkage, disease control, and/

or extension of survival. Risk, on the other hand, can be defined as type, timing, and duration of treatment toxicity, inconvenience of treatment, and/or financial toxicity.

In the COSMIC-313 trial, after a median follow-up of 17.7 months, PFS benefit with the triplet combination was seen in the IMDC intermediate-risk group (HR = 0.68; 95% CI, 0.54 to 0.86) but not in the poor-risk group (HR = 0.93; 95% CI, 0.64 to 1.35)[50]. This analysis by IMDC risk group appears to be an exploratory subgroup analysis that was not adjusted for multiplicity. This adjustment is important because it potentially inflates the risk for a type 1 error, i.e., there is an increased risk of reporting a false positive result. Therefore, these results should be interpreted with caution.

Compared with the doublet, the triplet combination in the intermediate-risk group resulted in higher ORR (45% vs. 36%), higher DCR (88% vs. 74%), and lower progressive disease (7% vs. 20%)[50]. However, it is important to examine the distribution of responses to properly interpret the data. In the intermediate-risk triplet therapy group, there were more responses and less progressive disease, but lower depth of response compared to the doublet therapy group[51]. This is particularly relevant because the depth of response correlates with survival and duration of response (DoR) [52–54].

Another issue with the triplet combination investigated in COSMIC-313 is the overlapping toxicity between IOs and TKIs, such as rash, diarrhea, hepatitis, and hypothyroidism. These toxicities may become more pronounced depending on the TKI. Cabozantinib has the longest half-life (~99 h) among TKIs approved for the treatment of mRCC[55], which has important implications for the safety results from the trial. Hepatotoxicity was the main overlapping adverse event observed and had a pronounced impact on treatment exposure and discontinuation. Patients in the triplet arm received a lower average daily dose of cabozantinib and fewer doses of ipilimumab, had more frequent dose reductions and treatment breaks, and discontinued a therapy component or all therapy more frequently. A higher proportion of patients in the triplet arm needed high-dose steroids compared with patients in the doublet arm (60% vs. 37%) to manage toxicities[50], which may be partly explained by the long half-life of cabozantinib. Likely, patients received steroids before it was possible to distinguish whether the hepatitis was caused by cabozantinib or IO. Steroids may also reduce the efficacy of IO, ultimately impacting outcomes.

Additionally, the probability of a tumour response increases with the mean daily exposure to a TKI. This means that a higher drug exposure is associated with an increased tumour response[56]. Therefore, dose reductions potentially have a negative effect on efficacy. This rationale may also apply to ipilimumab induction. For instance, the initial immune system stimulation by an ipilimumab induction phase appears important to achieving a good response to IO, as seen in studies in melanoma[57,58]. Moreover, a higher cumulative ipilimumab dose and shorter induction interval (every 3 weeks) appears superior to other regimens[59]. This is likely to also be the case in RCC.

In summary, the present data indicate that triplet therapy improves PFS and ORR without an OS benefit and at the cost of substantial toxicity. Theoretically, triplets should combine the benefits of both strategies, IO-IO and IO-TKI, in terms of early as well as durable responses. It is unlikely, however, that triplets will be effective in unselected patients, as the associated toxicity limits drug delivery. Also, there is a lack of clinically useful or validated biomarkers upon which therapy can be individualized or optimized. Until these limitations have been addressed, Dr. Kollmannsberger stressed, IO-based doublets should remain the initial standard of care for IMDC intermediate-risk mRCC.

During the Q&A, Dr. Tanguay pointed out that there are limited mechanisms of action of the treatment options in mRCC. He enquired what the ideal magnitude of benefit would need to be to make triplet combinations feasible in clinical practice. Dr. Kollmannsberger highlighted that triplet therapies have rarely performed better than doublets in the history of medical oncology. Currently, the PFS and ORR

benefit observed in the triplet comes at the cost of high toxicity and, likely, DoR. The situation could change if there was a clear OS benefit. Dr. Oualla added that risk stratification is presently based on archaic criteria. She stressed the need to develop biomarkers to more accurately stratify patients for treatment.

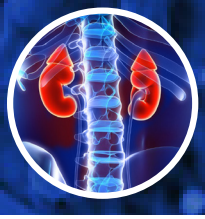
Next, the panel addressed the criteria for having pre-specified patient-reported outcomes data, such as quality of life (QoL), in phase 3 clinical trials and how these may help inform the benefit/risk ratio of treatment. Dr. Kollmannsberger finds it difficult to include patient-reported outcomes in clinical trial design. First, the current tools are not validated for specific diseases, such as kidney cancer, as the questions are not relevant for specific patient populations. Second, the patient experience is influenced by several factors, some of which may not be related to the treatment or the disease. Third, the time of assessment of toxicity may impact the outcomes reported. For these reasons, patient-reported outcomes are subjective and, therefore, difficult to base a statistical clinical trial design on.

Lastly, the debaters discussed the reason behind the lack of response in the poor-risk group, even though that group was expected to benefit from treatment intensification with triplet therapy. Dr. Oualla commented that there is high heterogeneity in the poor-risk group, which could explain why no benefit was observed. Further analysis could help identify certain characteristics in the poor-risk patients that may be associated with response to the triplet combination. Dr. Kollmannsberger added that, even though there were no differences in treatment delivery between the 2 risk groups, the reduced treatment exposure may have had a greater impact on the poor-risk group. Dr. Oualla noted that, despite the limitations, COSMIC-313 represents an important landmark in clinical trials in mRCC on which future trials can improve.

Next, Dr. Kollmannsberger discussed which clinical trial endpoint (PFS, ORR, or OS) is the most important for selecting first-line therapy in mRCC. Endpoints may be classified as traditional endpoints (ORR, PFS, OS), nontraditional endpoints (DoR, landmark PFS, long-term OS, treatment-free survival), early endpoints (ORR, PFS, early OS), and late endpoints (DoR, landmark PFS, long-term OS, treatment-free survival). How endpoints are structured hierarchically has an impact on treatment choice. However, patient presentation, such as the presence of comorbidities and the benefit seen with a specific regimen (short term vs. long term) may impact the hierarchy of endpoints as well.

An ideal treatment regimen would decrease the risk of early treatment failure and increase the chance of achieving a durable response. Across the different IO-IO and IO-TKI combinations available, there is little variation in the HR for OS (0.70 to 0.84)[60–63], which makes it a challenge for clinicians to discern between different treatments based on OS alone. Generally, IO-TKI regimens show significant benefits in terms of early endpoints, such as lower primary progressive disease rate and higher DCR[64–66] relative to IO-IO combination[60]. With respect to PFS, a plateau has been observed after a 24-month follow-up with IO-IO combination, and approximately 30% of patients remain progression-free 5 years after follow-up[60], whereas the development of a plateau has not been observed to the same degree with IO-TKI combinations. Similarly, the median DoR with IO-IO has not been reached even after a median follow-up of 6 years[67]. The majority of patients who achieved remission remain in remission, with a significant proportion of these patients being completely off treatment. IO-IO combination has also demonstrated durable and persistent long-term outcomes in terms of PFS, OS, and best observed response of complete response (CR)[60]. For the IO-TKI combinations, the median DoR has been reached and ranges from 21.5 to 27 months[64,65,68].

One critical aspect to consider is what endpoints are important to patients. In a recent survey developed by the Kidney Cancer Research Alliance (KCCure), it was observed that most patients want to aim for cure, the chance of eliminating all evidence of disease, as well as durability[69]. Therefore, patients appear to favour durable endpoints, such as DoR and long-term survival, rather than short-term benefits.



B2B: Kidney Cancer Summary

Dr. Kollmannsberger shared his strategy for selecting first-line therapy after a thorough discussion with the patient. When the goal is achieving CR or a chance for long-term survival (or cure), then he aims to maximize a chance of long-term survival with an IO-IO combination, in which long-term benefit is more robust. In this context, patients are willing to favour efficacy over toxicity for the potential benefit of long-term survival. Alternatively, in patients who are highly symptomatic, who show wide-spread disease, and in whom second-line therapy is unlikely, response rate becomes more important to minimize the risk of primary progression.

Comorbidities also have an impact on the first-line choice for mRCC. IO-IO combination should be avoided when the patient has a pre-existing autoimmune disease or other conditions that prevent the administration of high-dose steroids, such as diabetes or decreased mobility. If the patient lives in a rural setting with limited access to resources, that may also prevent access to high-dose steroids. On the other hand, IO-TKI combinations should be avoided in patients who have uncontrolled hypertension, posterior reversible encephalopathy syndrome, recent stroke or myocardial infarction, poor kidney function, and/or recent bleeding episodes.

Defining which endpoint to favour when selecting first-line therapy (i.e., the hierarchy of endpoints) depends on a number of factors, including patient preference and patient presentation. Overall, patients prefer long-term outcomes over short-term outcomes, toxicity, and cost. Importantly, physicians should thoroughly discuss the goals of treatment with their patients because the physician and patient view on the importance of outcome parameters may differ. When the primary goal of treatment is response rate and tumour control, physicians may favour IO-TKI combinations given their strong early benefit for high tumour control and improved PFS. Alternatively, if the goal of treatment is long-term survival, then IO-IO combination retains a greater advantage in terms of long-term benefit observed from a PFS plateau, DoR, long-term OS, and conditional survival. Ultimately, OS remains the most important endpoint for selecting treatment. However, if there are several treatment options with similar OS, physicians should examine other endpoints in conjunction with the goal of treatment and patient preference to guide decision-making.

During a Q&A session, Dr. Kollmannsberger discussed whether the lack of plateau for IO-TKI combinations may derive from a suboptimal TKI dosing regimen compared to the TKI monotherapy. He agrees that the TKI dosing in the combination would require adjustment to optimize efficacy, as seen with single-agent TKI regimens. However, he is uncertain whether the lower TKI dose in the IO-TKI may explain the lack of a long-term plateau. This is because the number of long-term survivors in single-agent TKI studies is low, suggesting that TKIs are not the main driver of long-term outcomes with IO-TKI combinations.

The next talk, by Dr. Öner Sanli (Türkiye), covered optimal patient selection for adjuvant therapy post nephrectomy. Around 30% of patients with ccRCC will progress within the first 5 years after surgery[70]. Progression may be associated with higher tumour grade (independent of stage), stage ≥ T3, sarcomatoid differentiation, and lymph node metastasis of up to 80%[71]. In this setting, adjuvant therapy is vital in eliminating residual, undetectable, microscopic disease after curative resection. Of several targeted agents evaluated for adjuvant treatment, sunitinib is the only TKI that demonstrated disease-free survival (DFS) improvement compared to placebo, as seen in the phase 3 S-TRAC trial[72]. More recently, the adjuvant treatment with the immune checkpoint inhibitor pembrolizumab demonstrated significant DFS improvement compared to placebo based on results of the phase 3 KEYNOTE-564 trial[73].

Optimal patient selection for adjuvant therapy will depend on certain criteria. It is important to understand which patients may be at higher risk for progression, which treatment should be selected, if there are any biomarkers available to guide decision-making (e.g., programmed cell death ligand-1 [PD-L1] status), and if the patient can tolerate treatment.

Five prognostic models are supported by EAU guidelines to assess the risk of progression after

B2B: Kidney Cancer Summary

surgery: UISS, Leibovich 2003, Leibovich 2018, VENUSS, and GRANT[4]. In a head-to-head comparison of prognostic models to predict clinical progression and cancer-specific mortality, models demonstrated different prognostic performance according to RCC subtype: Leibovich 2018 was more accurate in predicting ccRCC outcomes, whereas VENUSS and UISS had better prognostic accuracy for papillary and chromophobe RCC, respectively[74]. In different studies of adjuvant therapy post nephrectomy, different prognostic models were used and the investigators often modified those. This makes inferences on risk stratification across clinical trials more challenging. Given its simplicity, Dr. Sanli prefers to use the American Urological Association (AUA) guideline on renal mass and localized renal cancer for risk stratification after surgery in his practice[75].

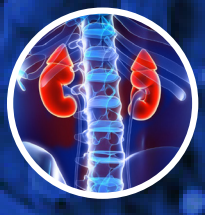
The choice of treatment may also vary from patient to patient. In the S-TRAC trial, subgroup analysis suggested a greater DFS benefit of adjuvant sunitinib in patients who were younger (< 45 years of age), had normal weight, good performance status, neutrophil-to-lymphocyte ratio ≤ 3, Fuhrman grade 3/4, and were high risk[72]. In KEYNOTE-564, subgroup analysis indicated a superior DFS benefit in M1 patients with no evidence of disease and those who presented with sarcomatoid features[73]. Other trials are ongoing in the adjuvant setting, such as RAMPART (durvalumab ± tremelimumab, NCT03288432) and LITESPARK-022 (pembrolizumab + belzutifan, NCT05239728), that may provide a better understanding of which patients may derive more benefit from adjuvant therapy. Dr. Sanli also noted that while DFS has been used as an early clinical surrogate for OS, its adoption is controversial. In a meta-analysis of 13 studies in the adjuvant setting, there was no correlation between 5-year DFS and 5-year OS rates, suggesting the need for an alternative early endpoint that better reflects clinical outcomes[76]. Median OS has not been reported for KEYNOTE-564.

Regarding biomarkers, PD-L1 expression and tumour mutational burden are predicted in response to immune checkpoint inhibitors in many immunogenic tumours, such as bladder cancer and melanoma. However, RCC responds to immune checkpoint inhibitor therapy irrespective of PD-L1 expression levels, as seen in KEYNOTE-564[73] and IMmotion010[77]. Additionally, higher expression of PD-L1 may not uniformly correlate with improved outcomes. In recent years, there have been several efforts to identify genomic biomarkers to optimize risk stratification in RCC. One example is ClearCode34, a 34-gene classifier-based model shown to improve upon established algorithms for assessing the risk of recurrence and death for nonmetastatic ccRCC[78]. Another study has identified a 16-gene expression panel associated with risk stratification for recurrences[79]. More recently, several studies have investigated liquid biomarkers in urine, serum, and plasma, although none have yet been validated for use in clinical practice[80].

Lastly, Dr. Sanli examined the tolerability of adjuvant treatment. In KEYNOTE-564, improved DFS was seen in patients younger than 65 years and those who had performance status ≤ 1[73]. However, the benefit observed in clinical trials may differ from that seen in the daily clinic. As seen in a study of 1459 patients, those who were included in clinical trials were generally younger, healthier, and had better estimated outcomes than patients in the real-world population[81]. Moreover, while patient-reported outcomes suggest no compromise to QoL with adjuvant pembrolizumab[82], physicians in daily practice will likely see patients who are generally older and frailer. An adequate management plan involving multiple specialties, such as geriatrics and medical oncology, should be developed.

Currently, data on adjuvant treatment of RCC post nephrectomy are limited. While the benefit observed with adjuvant pembrolizumab is presently based on DFS, OS data are required to guide decision-making. Optimal patient selection for adjuvant treatment requires adequate risk stratification and evaluation of performance status.

During a Q&A, Dr. Sanli examined whether he sees promise in combining genomic classifiers with current prognostic models to improve risk stratification and treatment selection. Despite the recent efforts in developing genomic classifiers for RCC, those are still



in early stages. Further development will be required before RCC genomic classifiers can be implemented in clinical practice.

The following presentation was by Dr. Tian Zhang (United States), who discussed treatment with belzutifan in sporadic and hereditary RCC. Von Hippel-Lindau (VHL) syndrome is a disease caused by germline pathogenic variants in the *VHL* gene. The syndrome is associated with an increased risk for the development of benign and malignant tumours in multiple organs and systems, such as the pancreas, central nervous system, and the retina, as well as the kidneys, where it manifests as ccRCC[83].

The VHL protein plays an important role in cellular oxygen sensing. Under normal oxygen conditions, the HIFα transcription factor hydroxylates and interacts with VHL, which is an E3 ligase allowing ubiquitination of HIFα and subsequent proteasomal degradation. Conversely, under hypoxic conditions, HIFα is not hydroxylated and does not bind to VHL. Instead, it dimerizes with an aryl hydrocarbon receptor nuclear translocator (ARNT) and translocates to the nucleus, where the HIFα-ARNT complex acts as a transcription factor for downstream expression of several genes, such as *EPO, TGFβ*, *PDGF*, and *VEGF*, which are involved in erythropoiesis, metabolism, and angiogenesis. Normally, this pathway serves to promote acute or chronic adaptation to hypoxia[84]. However, if the VHL protein is defective, there is constitutive activation of HIF2α, a subunit of HIFα, that mimics hypoxic conditions even under normal oxygen levels. This leads to upregulation of angiogenesis and tumourigenesis, as seen in VHL-defective ccRCC[85]. Importantly, around 95% of patients with sporadic ccRCC have a defective VHL protein.

The ability to target the HIF complex for therapeutic purposes evolved thanks to the elucidation of its crystal structure and, in particular, the identification of the HIF2α PAS-B domain. This domain is essential for HIF2α dimerization with ARNT[86]. Over time, several small molecules were developed to target the HIF2α PAS-B domain and prevent dimerization, which culminated with the development of the HIF2α inhibitor belzutifan[85].

The first-in-human study of belzutifan included a dose-expansion cohort of 52 patients. Most were IMDC intermediate or poor risk (76%) and had received ≥ 3 prior lines of systemic therapy. Treatment with belzutifan resulted in an ORR of 25% (all partial responses) and a median PFS of 14.5 months[87], suggesting encouraging early response as monotherapy in patients with ccRCC.

In patients with VHL syndrome, belzutifan was investigated in the phase 2 LITESPARK-004 trial. The trial enrolled 61 patients diagnosed with VHL syndrome based on germline mutation who had at least 1 measurable RCC tumour. Daily belzutifan treatment resulted in 49% of patients achieving partial response and another 49% achieving stable disease. Importantly, all patients experienced a reduction of surgical procedures for VHL-associated tumours after being treated with belzutifan[88]. All patients in the trial had a VHL-associated tumour outside the kidney and also experienced an improvement in those tumours from baseline with belzutifan treatment[89].

Another phase 2 trial examined belzutifan in combination with cabozantinib in advanced or metastatic ccRCC in 2 cohorts: cohort 1 included patients who had not received prior IO in this setting, and cohort 2 included patients previously exposed to IO treatment. Results of cohort 2 were recently published[90]. Most patients in this cohort had previously received an IO-IO or IO-TKI combination. Treatment with belzutifan in combination with cabozantinib resulted in DCR of 90% and ORR of 22% (all partial responses). Treatment-related adverse events were on target, resulting more commonly in anemia, fatigue, and hand-foot syndrome.

There are several ongoing studies of belzutifan in refractory ccRCC. The phase 3 LITESPARK-005 trial recently reported positive results for belzutifan vs. everolimus, with significant improvements in ORR and PFS but not OS[91]. In the phase 2 LITESPARK-013 trial, similar efficacy and safety were seen with 120 mg vs. 200 mg of belzutifan daily[92]. In addition, the phase 3 LITESPARK-011 trial (NCT04586231) is investigating the combination of belzutifan with lenvatinib vs. cabozantinib.

B2B: Kidney Cancer Summary

Phase 3 trials are also ongoing in earlier ccRCC settings. In the first-line metastatic setting, the LITESPARK-012 trial (NCT04736706) is randomizing patients to 3 treatment arms: belzutifan + lenvatinib + pembrolizumab, quavonlimab + lenvatinib + pembrolizumab, or lenvatinib + pembrolizumab. In the adjuvant setting after nephrectomy, LITESPARK-022 (NCT05239728) is investigating the combination of pembrolizumab + belzutifan vs. pembrolizumab + placebo.

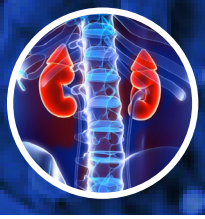
Other small molecule HIF2α inhibitors (NKT2152, DFF332, AB521) as well as silencing small interfering RNA (siRNA) are also under investigation in early-phase trials.

While the results observed with belzutifan are encouraging, prolonged inhibition of a pathway often results in acquired resistance. In a study using tumour xenograft models, researchers identified acquired mutations in the *HIF1β* gene (F446) and *HIF2α* gene (G323) that confer resistance to PT2399, a small molecule HIF2α inhibitor[93]. The HIF2α G233 mutation has been identified in a patient after prolonged treatment with PT2385, a predecessor of belzutifan, resulting in acquisition of resistance[94]. This is an important consideration for patient management.

In summary, HIF2α is now targetable, with belzutifan having a positive impact as standard of care treatment for patients with VHL syndrome. As further trials read out, the role of belzutifan may be expanded for sporadic ccRCC in the refractory setting. Combinations of belzutifan with other effective therapies in ccRCC may also start to impact the landscape of treatment options in earlier settings of first-line metastatic and adjuvant ccRCC. However, it is important to acknowledge that treatment resistance will start to impact HIF inhibition in patients who have prolonged exposure to treatment, posing an additional challenge to patient management.

During a Q&A, Dr. Zhang discussed the toxicity of belzutifan and how to manage it in the clinic. Compared with toxicities from other systemic therapies in this space, those from belzutifan appear more tolerable. Over time, patients may develop anemia and fatigue. She noted that dose titration is an adequate option in those patients, and she also prescribes erythropoietin for patients presenting with severe anemia. For the combination of belzutifan with cabozantinib, patients may experience diarrhea, hypertension, and hand-foot syndrome. Hypoxia and shortness of breath, while not frequent adverse events with belzutifan monotherapy, may be of concern for an older patient population. When they occur, pausing or titrating to a lower dose may be recommended. Usually, these side effects are resolved with a lower dose. Dr. Zhang also noted that, given the prevalence of somatic VHL inactivation and HIF-driven tumourigenesis in ccRCC, trials have so far enrolled all comers. As belzutifan may start to move into earlier settings, markers of treatment resistance may become important for decision-making. Dr. Zhang also discussed the current multidisciplinary management of patients with VHL syndrome who have localized ccRCC. In her practice, the choice of management by a urologist or a medical oncologist will be time dependent. She typically sees patients who have had a radical unilateral nephrectomy and have developed a tumour on the contralateral kidney. To spare renal function, these patients typically start on systemic therapy, such as belzutifan. Dr. Zhang emphasized the need for collaboration between urologists and medical oncologists to optimize outcomes for patients with VHL syndrome.

The final talk was an update on emerging clinical trial data in RCC presented by Dr. Axel Bex (the Netherlands). First, Dr. Bex provided an update on IO-IO and IO-TKI combinations in first-line metastatic ccRCC. As discussed earlier in the Kidney Cancer session, four phase 3 trials have demonstrated improvement in OS HR for IO-IO combination with nivolumab + ipilimumab (CheckMate 214) and IO-TKI combinations with pembrolizumab + axitinib (KEYNOTE-426), nivolumab + cabozantinib (CheckMate 9ER), and pembrolizumab + lenvatinib (CLEAR). However, while OS HR were similar at initial report[43,45–47], extended follow-up revealed an increase in OS HR for IO-TKI combinations over time[61–63]. It is important to note that the proportion of IMDC risk groups included in all 4 trials was different. The IO-TKI trials also included favourable-risk patients in the extended OS analysis,



which may have contributed to the OS HR increase. This differs from the statistical analysis from CheckMate 214[60]. Alternatively, these results may support different strategies discussed earlier in the meeting, where IO-TKI combinations may be used if a rapid response is needed, whereas IO-IO combination may provide a more durable response. Key clinical trials on the horizon examining IO in combination with other agents in the metastatic ccRCC setting include triplet combinations in LITESPARK-012 (NCT04736706) and nivolumab + ipilimumab followed by a risk-adapted approach in PDIGREE (NCT03793166).

Dr. Bex then provided an update on non-ccRCC trials. To date, the majority of trials have been conducted in patients with papillary mRCC. In a phase 2 trial comparing sunitinib, cabozantinib, crizotinib, and savolitinib, PFS was significantly longer with cabozantinib compared to sunitinib[95]. This trial introduced cabozantinib as standard of care for papillary mRCC. Crizotinib and savolitinib arms closed early due to futility. Interestingly, savolitinib appears to have more pronounced activity in patients with *MET* alterations. This hypothesis is currently under investigation in the phase 3 SAMETA trial (NCT05043090), which is randomizing patients to savolitinib + durvalumab vs. durvalumab vs. sunitinib. Confirmed *MET*-driven papillary mRCC by next-generation sequencing is an inclusion criterion for the trial.

Other basket trials have investigated new treatment approaches in non-ccRCC subtypes. Of note is the phase 2 KEYNOTE-B61, which examined the efficacy of pembrolizumab + lenvatinib as first-line treatment for metastatic non-ccRCC. The trial demonstrated an ORR of 49% in the overall population, 54% in papillary RCC, and 28% in chromophobe RCC (all partial responses)[96]. Other trials in IO monotherapy had not demonstrated activity in chromophobe RCC. In KEYNOTE-B61, the estimated 12-month PFS was 63%, and the 12-month OS was 82%[96]. In the phase 2 CaNi Triplet trial, triple therapy with cabozantinib + nivolumab + ipilimumab followed by cabozantinib + ipilimumab was investigated in variant RCC histology. The observed ORR was 18% (25% in papillary and 9% in chromophobe RCC), and the estimated 12-month PFS and OS were 51% and 79%, respectively[97]. However, higher toxicity was also observed with the triplet combination.

Key trials have recently been reported in the second and later lines of therapy for mRCC. The phase 3 CONTACT-03 trial did not meet its co-primary endpoints of PFS and OS with the combination of atezolizumab + cabozantinib vs. cabozantinib alone[98]. The phase 3 LITESPARK-005 trial reported positive results for belzutifan vs. everolimus with significant improvements in ORR and PFS but not OS[91]. Dr. Bex pointed out that a different comparator, such as cabozantinib, might have made the results of LITESPARK-005 more impactful. Also of note in this setting is the phase 3 LITESPARK-011 trial (NCT04586231) investigating the combination of belzutifan + lenvatinib vs. cabozantinib. This trial completed accrual in August 2023.

In the adjuvant setting, IMmotion010[77], PROSPER[99], CheckMate 914 part A[100], and EVEREST[101] all failed to meet their primary endpoints. CheckMate 914 part B (NCT03138512) randomized patients to nivolumab, nivolumab + ipilimumab, or placebo. Results of this cohort are highly anticipated. To date, pembrolizumab is the only agent with positive DFS results in the adjuvant RCC setting based on KEYNOTE-564[73]. On the horizon, adjuvant pembrolizumab in combination with belzutifan is being investigated in LITESPARK-022 (NCT05239728).

Several trials are ongoing in the neoadjuvant setting. Notably, the phase 2 NESCIO trial (NCT05148546) is one of the few in this space randomizing patients to different treatment arms: nivolumab, nivolumab + ipilimumab, or nivolumab + relatlimab, all followed by nephrectomy. The primary endpoint is pathologic response rate according to the international melanoma classification.

There are also some ongoing trials in the metastatic setting investigating deferred treatment of the primary tumour by cytoreductive nephrectomy (NORDIC-SUN, NCT03977571; PROBE, NCT04510597) or stereotactic body radiation therapy (CYTOSHRINK, NCT04090710). There are signals that patients eligible for those trials are living much longer with immune

B2B: Kidney Cancer Summary

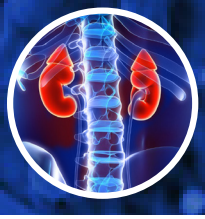
checkpoint inhibitor combination therapy than previously expected based on vascular endothelial growth factor receptor (VEGFR)-TKI data, which indicate that the TKI event rate on which those trials are modelled may be much lower.

Dr. Bex concluded his presentation by emphasizing that the first-line landscape for metastatic ccRCC appears consolidated with the current long-term data available; however, the use of triplet therapies in this setting requires further investigation. IO-TKI combination therapies have demonstrated efficacy in non-ccRCC, including chromophobe RCC. Additional options are under investigation in the second and later lines of therapy and will likely improve the current understanding in this setting. In the perioperative landscape, trials completed thus far have demonstrated contradictory results, and further trials are ongoing to help elucidate the role of systemic therapies in this setting.

In the Q&A, Dr. Bex noted that the majority of contemporary clinical trials have not sufficiently explored opportunities to improve risk stratification and the development of biomarkers in RCC. He emphasized that trials designed and led by academic centres may help to drive future developments in this particular field.

Abbreviations Used in the Text

^{89}Zr	zirconium-89
^{99m}Tc	technetium-99m
^{124}I	iodine-124
AI	artificial intelligence
ARNT	aryl hydrocarbon receptor nuclear translocator
AUC	area under the curve
CAIX	carbonic anhydrase IX
ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CR	complete response
CT	computed tomography
DCR	disease control rate
DFS	disease-free survival
DoR	duration of response
EAU	European Association of Urology
HIF	hypoxia-inducible factor
HR	hazard ratio
IMDC	International mRCC Database Consortium
IO	immunotherapy
mRCC	metastatic renal cell carcinoma
MRI	magnetic resonance imaging
NPV	negative predictive value
ORR	objective response rate
OS	overall survival
PD-L1	programmed cell death ligand-1
PET	positron-emission tomography
PFS	progression-free survival
PPV	positive predictive value
QoL	quality of life
RCC	renal cell carcinoma
SPECT	single-photon emission computed tomography
TKI	tyrosine kinase inhibitor
VHL	von Hippel-Lindau



References

1. Capitanio U, Bensalah K, Bex A, Boorjian SA, Bray F, Coleman J, et al. Epidemiology of renal cell carcinoma. *Eur Urol.*2019;75(1):74–84. doi:10.1016/j.eururo.2018.08.036
2. Johnson DC, Vukina J, Smith AB, Meyer AM, Wheeler SB, Kuo TM, et al. Preoperatively misclassified, surgically removed benign renal masses: a systematic review of surgical series and United States population level burden estimate. *J Urol.* 2015;193(1):30–35. doi:10.1016/j.juro.2014.07.102
3. Kim JH, Li S, Khandwala Y, Chung KJ, Park HK, Chung BI. Association of prevalence of benign pathologic findings after partial nephrectomy with preoperative imaging patterns in the United States from 2007 to 2014. *JAMA Surg.*2019;154(3):225. doi:10.1001/jamasurg.2018.4602
4. Ljungberg B, Albiges L, Bedke J, Bex A, Capitanio U, Giles R, et al. EAU guidelines on renal cell carcinoma. European Association of Urology (EAU). Published 2023. Accessed March 21, 2023. https://uroweb.org/guideline/renal-cell-carcinoma/
5. Roussel E, Capitanio U, Kutikov A, Oosterwijk E, Pedrosa I, Rowe SP, et al. Novel imaging methods for renal mass characterization: a collaborative review. *Eur Urol.* 2022;81(5):476–488. doi:10.1016/j.eururo.2022.01.040
6. Pierorazio PM, Cheaib JG, Tema G, Patel HD, Gupta M, Sharma R, et al. Performance characteristics of clinical staging modalities for early stage testicular germ cell tumors: a systematic review. *J Urol.* 2020;203(5):894–901. doi:10.1097/ju.0000000000000594
7. Furrer MA, Spycher SCJ, Büttiker SM, Gross T, Bosshard P, Thalmann GN, et al. Comparison of the diagnostic performance of contrast-enhanced ultrasound with that of contrast-enhanced computed tomography and contrast-enhanced magnetic resonance imaging in the evaluation of renal masses: a systematic review and meta-analysis. *Eur Urol Oncol.*2020;3(4):464–473. doi:10.1016/j.euo.2019.08.013
8. Kay FU, Canvasser NE, Xi Y, Pinho DF, Costa DN, Diaz de Leon A, et al. Diagnostic performance and interreader agreement of a standardized MR imaging approach in the prediction of small renal mass histology. *Radiology.* 2018;287(2):543–553. doi:10.1148/radiol.2018171557
9. Rowe SP, Gorin MA, Solnes LB, Ball MW, Choudhary A, Pierorazio PM, et al. Correlation of 99mTc-sestamibi uptake in renal masses with mitochondrial content and multi-drug resistance pump expression. *EJNMMI Res.* 2017;7(1):80. doi:10.1186/s13550-017-0329-5
10. Gorin MA, Rowe SP, Baras AS, Solnes LB, Ball MW, Pierorazio PM, et al. Prospective evaluation of 99mTc-sestamibi SPECT/CT for the diagnosis of renal oncocytomas and hybrid oncocytic/chromophobe tumors. *Eur Urol.*2016;69(3):413–416. doi:10.1016/j.eururo.2015.08.056
11. Wilson MP, Katlariwala P, Murad MH, Abele J, McInnes MDF, Low G. Diagnostic accuracy of 99mTc-sestamibi SPECT/CT for detecting renal oncocytomas and other benign renal lesions: a systematic review and meta-analysis. *Abdom Radiol (NY).* 2020;45(8):2532–2541. doi:10.1007/s00261-020-02469-8
12. Su ZT, Patel HD, Huang MM, Meyer AR, Pavlovich CP, Pierorazio PM, et al. Cost-effectiveness analysis of 99mTc-sestamibi SPECT/CT to guide management of small renal masses. *Eur Urol Focus.*2021;7(4):827–834. doi:10.1016/j.euf.2020.02.010
13. Stillebroer AB, Mulders PFA, Boerman OC, Oyen WJG, Oosterwijk E. Carbonic anhydrase IX in renal cell carcinoma: implications for prognosis, diagnosis, and therapy. *Eur Urol.*2010;58(1):75–83. doi:10.1016/j.eururo.2010.03.015
14. Divgi CR, Pandit-Taskar N, Jungbluth AA, Reuter VE, Gönen M, Ruan S, et al. Preoperative characterisation of clear-cell renal carcinoma using iodine-124-labelled antibody chimeric G250 (124I-cG250) and PET in patients with renal masses: a phase I trial. *Lancet Oncol.* 2007;8(4):304–310. doi:10.1016/S1470-2045(07)70044-X
15. Divgi CR, Uzzo RG, Gatsonis C, Bartz R, Treutner S, Yu JQ, et al. Positron emission tomography/computed tomography identification of clear cell renal cell carcinoma: results from the REDECT trial. *J Clin Oncol.* 2013;31(2):187–194. doi:10.1200/JCO.2011.41.2445
16. Shuch BM, Pantuck AJ, Bernhard JC, Morris MA, Master VA, Scott AM, et al. Results from phase 3 study of 89Zr-DFO-girentuximab for PET/CT imaging of clear cell renal cell carcinoma (ZIRCON). *J Clin Oncol.*2023;41(6_suppl):LBA602–LBA602. doi:10.1200/JCO.2023.41.6_suppl.LBA602
17. Wang HY, Ding HJ, Chen JH, Chao CH, Lu YY, Lin WY, et al. Meta-analysis of the diagnostic performance of [18F]FDG-PET and PET/CT in renal cell carcinoma. *Cancer Imaging.*2012;12(3):464–474. doi:10.1102/1470-7330.2012.0042

B2B: Kidney Cancer Summary

18. Golan S, Aviv T, Groshar D, Yakimov M, Zohar Y, Prokocimer Y, et al. Dynamic 68Ga-PSMA-11 PET/CT for the primary evaluation of localized renal mass: a prospective study. *J Nucl Med.*2021;62(6):773–778. doi:10.2967/jnumed.120.251272

19. Mühlbauer J, Egen L, Kowalewski KF, Grilli M, Walach MT, Westhoff N, et al. Radiomics in renal cell carcinoma—a systematic review and meta-analysis. *Cancers (Basel).* 2021;13(6):1348. doi:10.3390/cancers13061348

20. Ma Y, Cao F, Xu X, Ma W. Can whole-tumor radiomics-based CT analysis better differentiate fat-poor angiomyolipoma from clear cell renal cell carcinoma: compared with conventional CT analysis? *Abdom Radiol (NY).* 2020;45(8):2500–2507. doi:10.1007/s00261-020-02414-9

21. Cui EM, Lin F, Li Q, Li RG, Chen XM, Liu ZS, et al. Differentiation of renal angiomyolipoma without visible fat from renal cell carcinoma by machine learning based on whole-tumor computed tomography texture features. *Acta Radiol.*2019;60(11):1543–1552. doi:10.1177/0284185119830282

22. Li H, Li A, Zhu H, Hu Y, Li J, Xia L, et al. Whole-tumor quantitative apparent diffusion coefficient histogram and texture analysis to differentiation of minimal fat angiomyolipoma from clear cell renal cell carcinoma. *Acad Radiol.*2019;26(5):632–639. doi:10.1016/j.acra.2018.06.015

23. Klontzas ME, Koltsakis E, Kalarakis G, Trpkov K, Papathomas T, Karantanas AH, et al. Machine learning integrating 99mTc sestamibi SPECT/CT and radiomics data achieves optimal characterization of renal oncocytic tumors. *Cancers (Basel).*2023;15(14):3553. doi:10.3390/cancers15143553

24. Welch HG, Skinner JS, Schroeck FR, Zhou W, Black WC. Regional variation of computed tomographic imaging in the United States and the risk of nephrectomy. *JAMA Intern Med.*2018;178(2):221. doi:10.1001/jamainternmed.2017.7508

25. DI Trapani E, Dell'oglio P, Larcher A, Nini A, Muttin F, Cianflone F, et al. Pathological high-risk renal cell carcinoma: trends in clinical characteristics over 25 years. *Anticancer Res.* 2018;38(7):4123–4130. doi:10.21873/anticanres.12703

26. Frank I, Blute ML, Cheville JC, Lohse CM, Weaver AL, Zincke H. Solid renal tumors: an analysis of pathological features related to tumor size. *J Urol.* 2003;170(6):2217–2220. doi:10.1097/01.ju.0000095475.12515.5e

27. Bhindi B, Thompson RH, Lohse CM, Mason RJ, Frank I, Costello BA, et al. The probability of aggressive versus indolent histology based on renal tumor size: implications for surveillance and treatment. *Eur Urol.* 2018;74(4):489–497. doi:10.1016/j.eururo.2018.06.003

28. Richard PO, Jewett MAS, Bhatt JR, Kachura JR, Evans AJ, Zlotta AR, et al. Renal tumor biopsy for small renal masses: a single-center 13-year experience. *Eur Urol.* 2015;68(6):1007–1013. doi:10.1016/j.eururo.2015.04.004

29. Richard PO, Violette PD, Bhindi B, Breau RH, Gratton M, Jewett MAS, et al. 2023 Update - Canadian Urological Association guideline: management of cystic renal lesions. *Can Urol Assoc J.* 2023;17(6):162–174. doi:10.5489/cuaj.8389

30. Winters BR, Gore JL, Holt SK, Harper JD, Lin DW, Wright JL. Cystic renal cell carcinoma carries an excellent prognosis regardless of tumor size. *Urol Oncol.* 2015;33(12):505.e9–13. doi:10.1016/j.urolonc.2015.07.017

31. Psutka SP, Gulati R, Jewett MAS, Fadaak K, Finelli A, Legere L, et al. A clinical decision aid to support personalized treatment selection for patients with clinical T1 renal masses: results from a multi-institutional competing-risks analysis. *Eur Urol.* 2022;81(6):576–585. doi:10.1016/j.eururo.2021.11.002

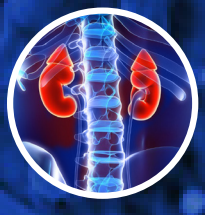
32. Schoots IG, Zaccai K, Hunink MG, Verhagen PCMS. Bosniak classification for complex renal cysts reevaluated: a systematic review. *J Urol.* 2017;198(1):12–21. doi:10.1016/j.juro.2016.09.160

33. Fatemeh Z, Nicola S, Satheesh K, Eranga U. Ensemble U-net-based method for fully automated detection and segmentation of renal masses on computed tomography images. *Med Phys.* 2020;47(9):4032–4044. doi:10.1002/mp.14193

34. Lin Z, Cui Y, Liu J, Sun Z, Ma S, Zhang X, et al. Automated segmentation of kidney and renal mass and automated detection of renal mass in CT urography using 3D U-Net-based deep convolutional neural network. *Eur Radiol.* 2021;31(7):5021–5031. doi:10.1007/s00330-020-07608-9

35. Zabihollahy F, Schieda N, Krishna S, Ukwatta E. Automated classification of solid renal masses on contrast-enhanced computed tomography images using convolutional neural network with decision fusion. *Eur Radiol.*2020;30(9):5183–5190. doi:10.1007/s00330-020-06787-9

36. Anush A, Rohini G, Nicola S, WalaaEldin EM, Eranga U. Deep-learning-based ensemble method for fully automated detection of renal masses on magnetic resonance images. *J Med Imaging (Bellingham).*2023;10(02):024501. doi:10.1117/1.JMI.10.2.024501



37. Yap FY, Varghese BA, Cen SY, Hwang DH, Lei X, Desai B, et al. Shape and texture-based radiomics signature on CT effectively discriminates benign from malignant renal masses. *Eur Radiol.* 2021;31(2):1011–1021. doi:10.1007/s00330-020-07158-0

38. Nassiri N, Maas M, Cacciamani G, Varghese B, Hwang D, Lei X, et al. A radiomic-based machine learning algorithm to reliably differentiate benign renal masses from renal cell carcinoma. *Eur Urol Focus.* 2022;8(4):988–994. doi:10.1016/j.euf.2021.09.004

39. Ferro M, Musi G, Marchioni M, Maggi M, Veccia A, Del Giudice F, et al. Radiogenomics in renal cancer management—current evidence and future prospects. *Int J Mol Sci.*2023;24(5):4615. doi:10.3390/ijms24054615

40. Wang T, Yang H, Hao D, Nie P, Liu Y, Huang C, et al. A CT-based radiomics nomogram for distinguishing between malignant and benign Bosniak IIF masses: a two-centre study. *Clin Radiol.* 2023;78(8):590–600. doi:10.1016/j.crad.2023.04.011

41. Dana J, Lefebvre TL, Savadjiev P, Bodard S, Gauvin S, Bhatnagar SR, et al. Malignancy risk stratification of cystic renal lesions based on a contrast-enhanced CT-based machine learning model and a clinical decision algorithm. *Eur Radiol.* 2022;32(6):4116–4127. doi:10.1007/s00330-021-08449-w

42. He QH, Feng JJ, Lv FJ, Jiang Q, Xiao MZ. Deep learning and radiomic feature-based blending ensemble classifier for malignancy risk prediction in cystic renal lesions. *Insights Imaging.* 2023;14(1):6. doi:10.1186/s13244-022-01349-7

43. Motzer RJ, Tannir NM, McDermott DF, Arén Frontera O, Melichar B, Choueiri TK, et al. Nivolumab plus ipilimumab versus sunitinib in advanced renal-cell carcinoma. *N Engl J Med.* 2018;378(14):1277–1290. doi:10.1056/NEJMOA1712126

44. Motzer RJ, Tannir NM, McDermott DF, Burotto M, Choueiri TK, Hammers HJ, et al. 661P conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *Ann Oncol.* 2021;32:S685–S687. doi:10.1016/j.annonc.2021.08.057

45. Rini BI, Plimack ER, Stus V, Gafanov R, Hawkins R, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* 2019;380(12):1116-1127. doi:10.1056/NEJMoa1816714

46. Choueiri TK, Powles T, Burotto M, Escudier B, Bourlon MT, Zurawski B, et al. Nivolumab plus cabozantinib versus sunitinib for advanced renal-cell carcinoma. *N Engl J Med.* 2021;384(9):829–841. doi:10.1056/nejmoa2026982

47. Motzer R, Alekseev B, Rha SY, Porta C, Eto M, Powles T, et al. Lenvatinib plus pembrolizumab or everolimus for advanced renal cell carcinoma. *N Engl J Med.* 2021;384(14):1289–1300. doi:10.1056/NEJMOA2035716

48. Haanen JBAG, Larkin J, Choueiri TK, Albiges L, Rini BI, Atkins MB, et al. Extended follow-up from JAVELIN Renal 101: subgroup analysis of avelumab plus axitinib versus sunitinib by the International Metastatic Renal Cell Carcinoma Database Consortium risk group in patients with advanced renal cell carcinoma. *ESMO Open.* 2023;8(3):101210. doi:10.1016/j.esmoop.2023.101210

49. Choueiri TK, Powles T, Albiges L, Burotto M, Szczylik C, Zurawski B, et al. Cabozantinib plus nivolumab and ipilimumab in renal-cell carcinoma. *N Engl J Med.* 2023;388(19):1767–1778. doi:10.1056/NEJMoa2212851

50. Powles T, Motzer RJ, Albiges L, Suárez C, Schutz FAB, Heng DYC, et al. Outcomes by IMDC risk in the COSMIC-313 phase 3 trial evaluating cabozantinib (C) plus nivolumab (N) and ipilimumab (I) in first-line advanced RCC (aRCC) of IMDC intermediate or poor risk. *J Clin Oncol.* 2023;41(6_suppl):605–605. doi:10.1200/JCO.2023.41.6_suppl.605

51. Choueiri T, Powles T, Albiges L, Burotto M, Szczylik C, Zurawski B, et al. LBA8 - Phase III study of cabozantinib (C) in combination with nivolumab (N) and ipilimumab (I) in previously untreated advanced renal cell carcinoma (aRCC) of IMDC intermediate or poor risk (COSMIC-313). *Ann Oncol.* 2022;33(suppl_7):S808-S869. doi:10.1016/annonc/annonc1089

52. Grünwald V, McKay RR, Krajewski KM, Kalanovic D, Lin X, Perkins JJ, et al. Depth of remission is a prognostic factor for survival in patients with metastatic renal cell carcinoma. *Eur Urol.* 2015;67(5):952–958. doi:10.1016/j.eururo.2014.12.036

53. Grünwald V, Choueiri TK, Rini BI, Powles T, George S, Grimm MO, et al. Association between depth of response and overall survival: exploratory analysis in patients with previously untreated advanced renal cell carcinoma (aRCC) in CheckMate 214. *Ann Oncol.* 2019;30:v382–v383. doi:10.1093/annonc/mdz249.046

54. Grünwald V, Powles T, Kopyltsov E, Kozlov V, Alonso-Gordoa T, Eto M, et al. Survival by depth of response and efficacy by International Metastatic Renal Cell Carcinoma Database Consortium subgroup with lenvatinib plus pembrolizumab versus sunitinib in advanced renal cell carcinoma: analysis of the phase 3 randomized CLEAR study. *Eur Urol Oncol.* 2023;6(4):437–446. doi:10.1016/j.euo.2023.01.010

B2B: Kidney Cancer Summary

55. Parmar A, Bjarnason GA. Individualization of dose and schedule based on toxicity for oral VEGF drugs in kidney cancer. *Kidney Cancer.* 2019;3(4):213–225. doi:10.3233/KCA-190077

56. Houk BE, Bello CL, Michaelson MD, Bukowski RM, Redman BG, Hudes GR, et al. Exposure-response of sunitinib in metastatic renal cell carcinoma (mRCC): a population pharmacokinetic/pharmacodynamic (PKPD) approach. *J Clin Oncol.* 2007;25(18_suppl):5027–5027. doi:10.1200/jco.2007.25.18_suppl.5027

57. Huang AC, Orlowski RJ, Xu X, Mick R, George SM, Yan PK, et al. A single dose of neoadjuvant PD-1 blockade predicts clinical outcomes in resectable melanoma. *Nat Med.* 2019;25(3):454–461. doi:10.1038/s41591-019-0357-y

58. Huang AC, Postow MA, Orlowski RJ, Mick R, Bengsch B, Manne S, et al. T-cell invigoration to tumour burden ratio associated with anti-PD-1 response. *Nature.* 2017;545(7652):60–65. doi:10.1038/nature22079

59. Augustin RC, Luke JJ. Induction exposure dose of ipilimumab and failure of adjuvant nivolumab plus ipilimumab in melanoma. *J Clin Oncol.* 2023;41(3):443–446. doi:10.1200/JCO.22.01770

60. Motzer RJ, Tannir NM, McDermott DF, Burotto M, Choueiri TK, Hammers HJ, et al. Conditional survival and 5-year follow-up in CheckMate 214: first-line nivolumab + ipilimumab (N+I) versus sunitinib (S) in advanced renal cell carcinoma (aRCC). *Ann Oncol.* 2021;32:S685–S687. doi:10.1016/J.ANNONC.2021.08.057

61. Burotto M, Powles T, Escudier B, Apolo AB, Bourlon MT, Shah AY, et al. Nivolumab plus cabozantinib vs sunitinib for first-line treatment of advanced renal cell carcinoma (aRCC): 3-year follow-up from the phase 3 CheckMate 9ER trial. *J Clin Oncol.* 2023;41(6_suppl):603–603. doi:10.1200/JCO.2023.41.6_suppl.603

62. Motzer RJ, Porta C, Eto M, Powles T, Grünwald V, Hutson TE, et al. Final prespecified overall survival (OS) analysis of CLEAR: 4-year follow-up of lenvatinib plus pembrolizumab (L+P) vs sunitinib (S) in patients (pts) with advanced renal cell carcinoma (aRCC). *J Clin Oncol.* 2023;41(16_suppl):4502–4502. doi:10.1200/JCO.2023.41.16_suppl.4502

63. Rini BI, Plimack ER, Stus V, Gafanov R, Waddell T, Nosov D, et al. Pembrolizumab plus axitinib versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma: 5-year analysis of KEYNOTE-426. *J Clin Oncol.* 2023;41(17_suppl):LBA4501–LBA4501. doi:10.1200/JCO.2023.41.17_suppl.LBA4501

64. Choueiri TK, Powles T, Eto M, Grünwald V, Hutson TE, Alekseev B, et al. A phase 3 trial of lenvatinib plus pembrolizumab versus sunitinib as a first-line treatment for patients with advanced renal cell carcinoma: overall survival follow-up analysis (CLEAR Study). In: *International Kidney Cancer Symposium 2021*; 2021.

65. Rini BI, Plimack ER, Stus V, Waddell T, Gafanov R, Pouliot F, et al. Pembrolizumab (pembro) plus axitinib (axi) versus sunitinib as first-line therapy for advanced clear cell renal cell carcinoma (ccRCC): results from 42-month follow-up of KEYNOTE-426. *J Clin Oncol.* 2021;39(15_suppl):4500–4500. doi:10.1200/JCO.2021.39.15_suppl.4500

66. Powles T, Choueiri TK, Burotto M, Escudier B, Bourlon MT, Shah AY, et al. Final overall survival analysis and organ-specific target lesion assessments with two-year follow-up in CheckMate 9ER: nivolumab plus cabozantinib versus sunitinib for patients with advanced renal cell carcinoma. *J Clin Oncol.* 2022;40(6_suppl):350–350. doi:10.1200/JCO.2022.40.6_suppl.350

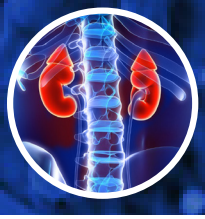
67. Albiges L, Tannir N, Burotto M, McDermott DF, Plimack ER, Barthélémy P, et al. Nivolumab + ipilimumab (N+I) vs sunitinib (S) for first-line treatment of advanced renal cell carcinoma (aRCC) in CheckMate 214: 4-year follow-up and subgroup analysis of patients (pts) without nephrectomy. *Ann Oncol.* 2020;31:S559–S560. doi:10.1016/j.annonc.2020.08.783

68. Powles T, Plimack ER, Soulières D, Waddell T, Stus V, Gafanov R, et al. Pembrolizumab plus axitinib versus sunitinib monotherapy as first-line treatment of advanced renal cell carcinoma (KEYNOTE-426): extended follow-up from a randomised, open-label, phase 3 trial. *Lancet Oncol.* 2020;21(12):1563–1573. doi:10.1016/S1470-2045(20)30436-8

69. Battle D, Vaishampayan UN, Msaouel P, Pal SK, Zhang T, Staehler MD. Patient priorities and expectations of systemic therapy in metastatic renal cell carcinoma. *J Clin Oncol.*2023;41(16_suppl):4560–4560. doi:10.1200/JCO.2023.41.16_suppl.4560

70. Russo P, Jang TL, Pettus JA, Huang WC, Eggener SE, O'Brien MF, et al. Survival rates after resection for localized kidney cancer: 1989 to 2004. *Cancer.*2008;113(1):84–96. doi:10.1002/cncr.23520

71. Janjigian YY, Wolchok JD, Ariyan CE. Eradicating micrometastases with immune checkpoint blockade: strike while the iron is hot. *Cancer Cell.*2021;39(6):738–742. doi:10.1016/j.ccell.2021.05.013



72. Motzer RJ, Ravaud A, Patard JJ, Pandha HS, George DJ, Patel A, et al. Adjuvant sunitinib for high-risk renal cell carcinoma after nephrectomy: subgroup analyses and updated overall survival results. *Eur Urol.* 2018;73(1):62–68. doi:10.1016/j.eururo.2017.09.008

73. Powles T, Tomczak P, Park SH, Venugopal B, Ferguson T, Symeonides SN, et al. Pembrolizumab versus placebo as post-nephrectomy adjuvant therapy for clear cell renal cell carcinoma (KEYNOTE-564): 30-month follow-up analysis of a multicentre, randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet Oncol.* 2022;23(9):1133–1144. doi:10.1016/S1470-2045(22)00487-9

74. Rosiello G, Larcher A, Fallara G, Giancristofaro C, Martini A, Re C, et al. Head-to-head comparison of all the prognostic models recommended by the European Association of Urology guidelines to predict oncologic outcomes in patients with renal cell carcinoma. *Urol Oncol.* 2022;40(6):271.e19–271.e27. doi:10.1016/j.urolonc.2021.12.010

75. Campbell SC, Uzzo RG, Karam JA, Chang SS, Clark PE, Souter L. Renal mass and localized renal cancer: evaluation, management, and follow-up: AUA guideline: part II. *J Urol.* 2021;206(2):209–218. doi:10.1097/JU.0000000000001912

76. Harshman LC, Xie W, Moreira RB, Bossé D, Ruiz Ares GJ, Sweeney CJ, et al. Evaluation of disease-free survival as an intermediate metric of overall survival in patients with localized renal cell carcinoma: a trial-level meta-analysis. *Cancer.* 2018;124(5):925–933. doi:10.1002/cncr.31154

77. Pal SK, Uzzo R, Karam JA, Master VA, Donskov F, Suarez C, et al. Adjuvant atezolizumab versus placebo for patients with renal cell carcinoma at increased risk of recurrence following resection (IMmotion010): a multicentre, randomised, double-blind, phase 3 trial. *Lancet.* 2022;400(10358):1103–1116. doi:10.1016/S0140-6736(22)01658-0

78. Brooks SA, Brannon AR, Parker JS, Fisher JC, Sen O, Kattan MW, et al. ClearCode34: a prognostic risk predictor for localized clear cell renal cell carcinoma. *Eur Urol.* 2014;66(1):77–84. doi:10.1016/j.eururo.2014.02.035

79. Rini B, Goddard A, Knezevic D, Maddala T, Zhou M, Aydin H, et al. A 16-gene assay to predict recurrence after surgery in localised renal cell carcinoma: development and validation studies. *Lancet Oncol.* 2015;16(6):676–685. doi:10.1016/S1470-2045(15)70167-1

80. Kubiliute R, Jarmalaite S. Epigenetic biomarkers of renal cell carcinoma for liquid biopsy tests. *Int J Mol Sci.* 2021;22(16):8846. doi:10.3390/ijms22168846

81. Millan B, Breau RH, Mallick R, Wood L, Rendon R, Finelli A, et al. Comparison of patients with renal cell carcinoma in adjuvant therapy trials to a real-world population. *Urol Oncol.* 2023;41(7):328.e15–328.e23. doi:10.1016/j.urolonc.2023.04.015

82. Choueiri TK, Tomczak P, Park SH, Venugopal B, Symeonides S, Hajek J, et al. Patient-reported outcomes in KEYNOTE-564: adjuvant pembrolizumab versus placebo for renal cell carcinoma. *Oncologist.* 2023; Epub ahead of print. doi:10.1093/oncolo/oyad231

83. Maher ER, Neumann HP, Richard S. von Hippel–Lindau disease: a clinical and scientific review. *Eur J Hum Genet.* 2011;19(6):617–623. doi:10.1038/ejhg.2010.175

84. Kaelin WG, Ratcliffe PJ. Oxygen sensing by metazoans: the central role of the HIF hydroxylase pathway. *Mol Cell.* 2008;30(4):393–402. doi:10.1016/j.molcel.2008.04.009

85. Choueiri TK, Kaelin WG. Targeting the HIF2–VEGF axis in renal cell carcinoma. *Nat Med.* 2020;26(10):1519–1530. doi:10.1038/s41591-020-1093-z

86. Scheuermann TH, Tomchick DR, Machius M, Guo Y, Bruick RK, Gardner KH. Artificial ligand binding within the HIF2α PAS-B domain of the HIF2 transcription factor. *Proc Natl Acad Sci USA.* 2009;106(2):450–455. doi:10.1073/pnas.0808092106

87. Choueiri TK, Bauer TM, Papadopoulos KP, Plimack ER, Merchan JR, McDermott DF, et al. Inhibition of hypoxia-inducible factor-2α in renal cell carcinoma with belzutifan: a phase 1 trial and biomarker analysis. *Nat Med.* 2021;27(5):802–805. doi:10.1038/s41591-021-01324-7

88. Jonasch E, Donskov F, Iliopoulos O, Rathmell WK, Narayan VK, Maughan BL, et al. Belzutifan for renal cell carcinoma in von Hippel–Lindau disease. *N Engl J Med.* 2021;385(22):2036–2046. doi:10.1056/NEJMoa2103425

89. Srinivasan R, Iliopoulos O, Rathmell WK, Narayan V, Maughan BL, Oudard S, et al. LBA69 Belzutifan, a HIF-2α inhibitor, for von Hippel-Lindau (VHL) disease-associated neoplasms: 36 months of follow-up of the phase II LITESPARK-004 study. *Ann Oncol.* 2022;33:S1433–S1434. doi:10.1016/j.annonc.2022.08.074

90. Choueiri TK, McDermott DF, Merchan J, Bauer TM, Figlin R, Heath EI, et al. Belzutifan plus cabozantinib for patients with advanced clear cell renal cell carcinoma previously treated with immunotherapy: an open-label, single-arm, phase 2 study. *Lancet Oncol.* 2023;24(5):553-562. doi:10.1016/S1470-2045(23)00097-9

B2B: Kidney Cancer Summary

91. Albiges L, Rini BI, Peltola K, De Velasco Oria GA, Burotto M, Suarez Rodriguez C, et al. LBA88 Belzutifan versus everolimus in participants (pts) with previously treated advanced clear cell renal cell carcinoma (ccRCC): randomized open-label phase III LITESPARK-005 study. *Ann Oncol.* 2023;34:S1329–S1330. doi:10.1016/j.annonc.2023.10.090

92. Agarwal N, Brugarolas J, Ghatalia P, George S, Haanen JBAG, Gurney HP, et al. 1881O Safety and efficacy of two doses of belzutifan in patients (pts) with advanced RCC: results of the randomized phase II LITESPARK-013 study. *Ann Oncol.*2023;34:S1011. doi:10.1016/j.annonc.2023.09.1111

93. Chen W, Hill H, Christie A, Kim MS, Holloman E, Pavia-Jimenez A, et al. Targeting renal cell carcinoma with a HIF-2 antagonist. *Nature.*2016;539(7627):112–117. doi:10.1038/nature19796

94. Courtney KD, Ma Y, Diaz de Leon A, Christie A, Xie Z, Woolford L, et al. HIF-2 complex dissociation, target inhibition, and acquired resistance with PT2385, a first-in-class HIF-2 inhibitor, in patients with clear cell renal cell carcinoma. *Clin Cancer Res.*2020;26(4):793–803. doi:10.1158/1078-0432.CCR-19-1459

95. Pal SK, Tangen C, Thompson IM, Balzer-Haas N, George DJ, Heng DYC, et al. A comparison of sunitinib with cabozantinib, crizotinib, and savolitinib for treatment of advanced papillary renal cell carcinoma: a randomised, open-label, phase 2 trial. *Lancet.*2021;397(10275):695–703. doi:10.1016/S0140-6736(21)00152-5

96. Albiges L, Gurney H, Atduev V, Suarez C, Climent MA, Pook D, et al. Pembrolizumab plus lenvatinib as first-line therapy for advanced non-clear-cell renal cell carcinoma (KEYNOTE-B61): a single-arm, multicentre, phase 2 trial. *Lancet Oncol.*2023;24(8):881–891. doi:10.1016/S1470-2045(23)00276-0

97. McGregor BA, Huang J, Xie W, Xu W, Bilen MA, Braun DA, et al. Phase II study of cabozantinib (Cabo) with nivolumab (Nivo) and ipilimumab (Ipi) in advanced renal cell carcinoma with variant histologies (RCCvh). *J Clin Oncol.*2023;41(16_suppl):4520–4520. doi:10.1200/JCO.2023.41.16_suppl.4520

98. Pal SK, Albiges L, Tomczak P, Suárez C, Voss MH, de Velasco G, 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(10397):185–195. doi:10.1016/S0140-6736(23)00922-4

99. Allaf M, Kim SE, Harshman LC, McDermott DF, Master VA, Signoretti S, et al. LBA67 Phase III randomized study comparing perioperative nivolumab (nivo) versus observation in patients (Pts) with renal cell carcinoma (RCC) undergoing nephrectomy (PROSPER, ECOG-ACRIN EA8143), a National Clinical Trials Network trial. *Ann Oncol.*2022;33(suppl 7):S1432–S1433. doi:10.1016/j.annonc.2022.08.072

100. Motzer RJ, Russo P, Grünwald V, Tomita Y, Zurawski B, Parikh O, et al. Adjuvant nivolumab plus ipilimumab versus placebo for localised renal cell carcinoma after nephrectomy (CheckMate 914): a double-blind, randomised, phase 3 trial. *Lancet.*2023;401(10379):821–832. doi:10.1016/S0140-6736(22)02574-0

101. Ryan CW, Tangen CM, Heath EI, Stein MN, Meng M V, Alva AS, et al. Adjuvant everolimus after surgery for renal cell carcinoma (EVEREST): a double-blind, placebo-controlled, randomised, phase 3 trial. *Lancet.* 2023;402(10407):1043–1051. doi:10.1016/S0140-6736(23)00913-3