

Conference Report

B2B: Kidney Cancer Summary

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The 7th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 45th Annual Congress of the Société Internationale d'Urologie, was held on 31 October 2025, in Edinburgh, Scotland, and transmitted live on the *SIU@U* Congress app. The second session, on kidney cancer (KCa), took place in the afternoon and was moderated by Dr. Simon Tanguay (Canada). This session began with a presentation on immunotherapy (IO) rechallenge after adjuvant IO, followed by a presentation on cytoreductive nephrectomy (CN) in the era of IO. The session continued with a debate when it is best to use surgery vs. stereotactic body radiation therapy (SBRT) to treat oligometastatic renal cell carcinoma (RCC) and a panel discussion on systemic therapy combinations in metastatic RCC (mRCC). The session concluded with a presentation on belzutifan in metastatic clear cell RCC (ccRCC).

Dr. Viktor Grünwald (Germany) started the session with a presentation on IO-rechallenge after adjuvant IO. He explained that response to an immune checkpoint inhibitor (ICI) is dependent on the pre-existing T-cell repertoire [1], the disease stage, and the tumour microenvironment [2]. In localized disease, there are typically more proficient immune cells than in later stages. As the cancer progresses, the immune microenvironment becomes more complex, with more immunosuppressive cells present [2].

There is good evidence that patients with intermediate-high- or high-risk local or locoregional RCC should be offered 1 year of adjuvant pembrolizumab [3], which has become the standard of care. In this setting, the KEYNOTE-564 study revealed an improved disease-free survival (DFS) (hazard ratio [HR] 0.72, 95% confidence interval [CI] 0.59–0.87) and overall survival (OS) (HR 0.62, 95% CI 0.44–0.87) with adjuvant pembrolizumab [4]. The problem in the clinical setting is the lack of biomarkers to determine which patients are likely to respond to this therapy.

What to do when the tumour recurs is less clear. Importantly, every recurrence is unique, with each meriting an individualized approach to care. In most countries, tyrosine kinase inhibitor (TKI)-IO combinations are the standard of care [3,5]. In KEYNOTE-564, the majority of patients received vascular endothelial growth factor (VEGF)/VEGF receptor (VEGFR) inhibitors upon disease progression [4].



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The role of re-exposure to an immune agent remains controversial, particularly with respect to timing of recurrence. Grünwald et al. performed a Delphi consensus among European experts, asking what duration after completion of adjuvant therapy renders a patient's disease ICI-refractory. Most responded that this occurs within the first 6 months [6]. The researchers also asked at which timepoint after completion of adjuvant therapy an ICI combination should be considered. Almost all experts agreed that an ICI combination would be appropriate 12 months after completion of adjuvant therapy with pembrolizumab, with about half of respondents reporting that 6 months or more would be sufficient [6]. This is also in line with recommendations from the Society for Immunotherapy of Cancer (SITC) [7].

Because there is no high level of evidence to drive such decisions, they remain opinion based. Generally, progression on therapy or soon after (<6 months after last dose) triggers treatment with a TKI. In intermediate or late progressors (>6 months or >12 months after last dose), combination ICI therapy is a more likely option, with the exact cutoffs for the timing of progression remaining open for debate [5,6]. Clinical trials in this setting are sorely needed to help clarify the best treatment approach.

Regarding the use of IOs after TKI therapy, Grünwald et al. demonstrated that IO maintenance with nivolumab, given after 3 months of TKI induction in patients with mRCC without disease progression, was not beneficial [8]. These findings suggest that TKI-sensitive patients should remain on a TKI instead of switching to an IO.

In mRCC, switching from ICI monotherapy to an escalated ICI combination has limited efficacy, according to several clinical trials [9–14]. Thus, the SITC recommends that disease progression within 6 months of adjuvant IO could be considered a contraindication for doublet IO therapy, although they acknowledge the activity of IO doublets in this setting remains unknown [7]. In the Delphi consensus, experts largely disagreed on which immune combination to offer [6].

A retrospective analysis of real-world data examined response to first-line therapy among patients who failed IO in the adjuvant setting, comparing VEGF-targeted therapy vs. IO-IO vs. IO plus VEGF-targeted therapy. Outcomes for all 3 options were quite similar [15]; however, Dr. Grünwald warned that these findings are strongly biased by the fact that different types of patients are offered different kinds of treatment.

The only randomized controlled trial (RCT) data available to guide therapy in this setting explored TKI-IO combinations in the second- or third-line setting after patients had already failed a TKI and an immune component. In this setting, TKI-IO did not offer additional benefits beyond the TKI activity [16,17]. Very few patients in these studies received adjuvant therapy, so outcomes may not be the same for these patients.

The general recommendations that Grünwald et al. were able to derive from the Delphi study [6] were

- Patients who relapse during or within 6 months of completing adjuvant ICI therapy are considered to have ICI-refractory disease.
- Focal therapies with curative intent for patients previously treated with adjuvant ICI therapy who have an oligometastatic recurrence should always be considered.
- Patients with ICI-refractory disease should receive targeted therapy without an ICI component or be considered for clinical trial inclusion.
- Patients who experience recurrence more than 12 months after completing adjuvant ICI treatment and are not candidates for focal therapy should receive standard-of-care first-line therapy.
- Ipilimumab-nivolumab in patients with sarcomatoid RCC or asymptomatic ccRCC may be considered after recurrence following adjuvant pembrolizumab.

- Patients with uncertain radiologic findings suggesting recurrence should not receive immediate systemic treatment.
- In asymptomatic patients with oligometastatic disease, active surveillance may be offered.

To clarify if there is a better way to use TKIs in this setting, the PEDIGREE trial (NCT03793166) is recruiting patients with mRCC who have received no prior systemic therapy. All patients will receive nivolumab-ipilimumab. Those with a complete response will continue on nivolumab, while the remainder will additionally receive cabozantinib.

Dr. Grünwald concluded that post-adjuvant treatment remains poorly defined. Only a small proportion of patients benefit from IO-rechallenge, and VEGFR TKIs are the preferred choice in early progressors (<6 months after adjuvant therapy).

During a Q&A session, Dr. Tanguay asked whether the positive results of the LITESPARK-022 trial, demonstrating benefits of combining pembrolizumab with belzutifan [18,19], will make it more appealing to treat high-risk patients with combination therapy. Dr. Grünwald replied that adding belzutifan could be a way forward in the adjuvant setting, given that hypoxia-inducible factor (HIF) inhibition likely has a more prominent role in earlier stages of disease, but so far only DFS results are available for this trial, and OS findings are needed.

An audience member expressed skepticism about adjuvant combination IO therapy because most studies on it to date have been negative, and the benefits are limited even in the positive trials. He suggested that sequencing of IO is not effective at all, and it is imperative to conduct trials to determine what IO combinations to offer patients who relapse after adjuvant treatment. Single-agent PD-1 inhibitor treatment may represent undertreatment in high-risk patients, given the success of IO combinations in the metastatic setting. Dr. Grünwald replied that identifying patients as moderate- or high-risk for clinical trials remains a challenge, with different trials using different criteria, and these risk categories do not predict response to IO.

Next, Dr. Arnaud Méjean (France) spoke about CN in the era of IO, noting at the outset of his talk that there are actually 2 types of CN. The first is the neoadjuvant strategy, in which patients with high-risk non-metastatic, locally advanced RCC receive IO systemic therapy prior to surgery in order to shrink the tumour. In this case, a “closing” nephrectomy might be performed, which may be followed by pembrolizumab monotherapy. Patients with intermediate-risk mRCC, on the other hand, may either undergo systemic therapy followed by nephrectomy or undergo upfront nephrectomy, followed by additional treatment. Notably, the 2-year OS for these patients is about 70% in both cases [20,21]. There is a paucity of evidence for treatment in the neoadjuvant setting. The International Neoadjuvant Kidney Cancer Consortium grand stewardship initiative is aiming to fill this gap [22].

Dr. Méjean then focused on treatment of mRCC, using a case study to illustrate key take-home messages. The first case was of a 69-year-old male with a left deltoid tumefaction. Computed tomography (CT) scan revealed a 94 mm right renal tumour with synchronous metastasis to the left deltoid muscle, lymph nodes, and right adrenal gland, with small chest lesions. Deltoid muscle biopsy revealed ccRCC. He was otherwise in good health. Based on the International Metastatic RCC Database Consortium (IMDC) risk calculator, his median survival was estimated to be 22.5 months. In 2007, CN would have been selected as the first-line treatment for this patient. However, since 2018, new evidence from the CARMENA [23] and SURTIME [24] trials has suggested a role for systemic therapy with sunitinib prior to surgery. Today, in the era of combination IO therapy, there are no RCTs evaluating the role of CN in the metastatic setting. Patients with high-risk, non-metastatic, locally advanced RCC can be started on systemic therapy first, with the decision to move onto CN dependent on response. The only evidence to guide therapy is in the

form of studies with a high level of bias due to small size, retrospective design, and/or inconsistency in the types of combinations used.

One meta-analysis carried out in Singapore explored the role of deferred CN in patients with mRCC. The trial comprised 12 studies, and the primary endpoint was OS, comparing deferred CN with no deferred CN, the latter of which could include upfront CN, systemic therapy alone, or CN alone. Deferred CN was found to be superior to no deferred CN (HR 0.61, 95% CI 0.51–0.74.) as well as to upfront CN (HR 0.71, 95% CI 0.61–0.82). Importantly, deferred CN outperformed no deferred CN even when looking only at patients treated with IO therapy (HR 0.59, 95% CI 0.37–0.95) [25]. Thus, it appears that, in selected patients who have mRCC with a resectable tumour, adequate performance status (PS) for surgery, and response to IO, delayed CN may improve OS. A systematic review and individual patient data meta-analysis supported these findings [26].

An open question is whether the paradigm established by CARMENA and SURTIME can be continued in the mRCC setting with combination IO therapy. In patients with intermediate-poor IMDC risk, mRCC, combination IO has been shown to have an objective response rate (ORR) of 42–71% [27–30]. In this patient population, said Dr. Méjean, combination IO may decrease the size of the primary tumour by up to 30% and tumour at metastatic sites by up to 70% with IO-TKI therapy.

The feasibility of CN following systemic therapy appears to be good, according to 2 studies. The first included 75 patients treated with upfront ICIs. The rate of open nephrectomy was 72%, and only 4% experienced intraoperative complications. The 90-day postoperative complication rate was 25%, with no deaths recorded [31]. The second was a series of 113 patients who also received upfront ICI therapy. Overall, 53% had open nephrectomy, with an intraoperative complication rate of 2% and 90-day postoperative complication rate of 24% [32].

Returning to the case, Dr. Méjean reported that the patient was treated with nivolumab-ipilimumab, then nivolumab alone, with good results. He was stable after 2 cycles, with a partial response at 7 months. Toxicity included symptomatic thyroiditis, with transition to atrial fibrillation, pruritic skin rash, and adrenal insufficiency. Following nivolumab-ipilimumab treatment, the patient underwent a right enlarged nephrectomy, with pathology revealing ccRCC 7.5 cm nuclear grade 4 focal and stage ypT3a N0 M1 disease with a healthy renal vein border. The medical team decided to stop IO, and a recent CT showed no evidence of disease.

Ongoing studies that are exploring deferred CN will shed additional light on how to manage patients in this setting, including the NORDIC-SUN RCT (NTC03977571) [33] and PROBE phase 3 trial (NTC04510597) [34]. Dr. Méjean noted that the decision to use deferred CN in these trials is an indication that this is already becoming the preferred timing for surgery.

He added that the results of CARMENA could probably be extrapolated to patients with low IMDC risk oligometastatic disease and a good PS, suggesting these patients should be treated with upfront CN, with or without local treatment of metastases and delayed systemic therapy. This approach might also be suitable for patients without oligometastatic disease who are intermediate IMDC risk, with one risk factor and one metastatic site. For those with more than one risk factor or metastatic site or with poor IMDC risk status, systemic therapy with an ICI, TKI, or a combination, followed by deferred CN if there is a partial or complete response could be a good option. For those with stable disease or progression on systemic therapy, a second-line systemic therapy should be considered.

During a Q&A, an audience member pointed out that in the NORDIC-SUN and PROBE trials, patients who progress on combination IO therapy are not being included in the randomization, meaning these trials will not answer questions on how best to

treat these patients. Next, Dr. Tanguay asked at what point we should move to CN in patients receiving systemic therapy. Dr. Méjean replied that it depends on the response to systemic therapy as well as how well it is tolerated, but it is usually performed after about 9–12 months. A medical oncologist in the audience said that CN should take place at the time of maximum response, based on CT serial scanning.

Next in the session was a debate on how best to treat oligometastatic RCC. Making the case for surgery was Dr. Axel Bex (United Kingdom). He started by noting that there has been a massive surge in publications about oligometastatic disease, likely because improvements in the efficacy of systemic therapy mean that patients are living longer, necessitating greater focus on the use of successive treatments [35]. Some expert groups define oligometastatic disease as up to 3 metastases at a single site, while others go up to 5. There is a plethora of other definitions associated with oligometastatic disease, such as a de novo synchronous, metachronous, or induced oligoprogression after treatment [36].

Patients with single metastasis or recurrence and those with oligometastasis may both be good candidates for metastasis-directed therapy (MDT). Options in this setting include surveillance, surgery (metastasectomy), external beam radiation therapy, SBRT, and thermal ablation. Among patients who have achieved a complete or near complete response of metastatic sites with systemic therapy, the primary tumour can be treated with CN, partial nephrectomy, or SBRT.

The most recent systematic review of local treatment for mRCC comparing incomplete or no metastasectomy with complete metastasectomy was published in 2014 [37], but no new RCTs have been conducted to examine this topic since then. Most of the studies included in that meta-analysis had a high risk of bias [37].

Notably, use of local therapy vs. surveillance alone for oligometastatic disease has never been evaluated in an RCT. One study did show, however, that surveillance is an option, as it can take 16 months for progression to occur [38]. Among patients who underwent metastasectomy following the results of the KEYNOTE-564 trial, adjuvant pembrolizumab could also be considered [39]. This trial provided some insight into how patients were treated for recurrent disease following adjuvant therapy, with 51.5% in the pembrolizumab arm and 48.5% in the placebo arm receiving local therapy (metastasectomy or radiotherapy). Dr. Bex noted, however, that decisions about treatment may have been influenced by what was available at a particular centre that was part of the trial.

Importantly, metastasectomy comes at a price. A large multinational series revealed that patients who underwent this procedure had a 25% 30-day postoperative Clavien-Dindo grade III–IV complication rate [40]. There is little to guide surgeons on when to conduct metastasectomy and what treatment options to offer afterwards. At the very least, said Dr. Bex, patients should receive a follow-up CT scan to determine how their disease is progressing.

Dr. Bex presented the case of a 70-year-old male who underwent radiofrequency ablation for a left cT1a biopsy-proven ccRCC. Three years later, a local recurrence was treated with cryotherapy and the patient was kept under observation at increasing intervals. After another 8 years, the patient developed a 6 cm biopsy-proven para-aortal lymph node recurrence. In this patient, SBRT was an option, given the proximity of the tumour to the bowel, but the patient declined.

Dr. Bex also presented the imaging findings of 2 patients who underwent primary tumour resection following complete response at the metastatic tumour site with systemic combination IO therapy. One patient had severe desmoplastic changes while receiving nivolumab-cabozantinib. The other had bowel perforation into the tumour following response to ipilimumab-nivolumab. Dr. Bex acknowledged that these cases can be difficult, but said that should not deter clinicians from offering deferred cytoreductive nephrectomy

because this can slow tumour progression. A recent study in a group of 287 patients whose primary tumour was treated with ipilimumab-nivolumab demonstrated that about 20% were able to undergo deferred CN, usually because they had an exceptional response to therapy at metastatic sites. Those who had good control of disease, but nevertheless experienced progression of their primary tumour, appeared to still have about as good a response to deferred CN as patients who had a complete or near complete response [41].

Until additional evidence is collected to help guide therapy, Dr. Bex recommended that patients with synchronous oligometastatic RCC who have had a good response to systemic therapy at metastatic sites should be considered for surgery to address the primary tumour. While the only high-level evidence available is for surgical metastasectomy plus adjuvant therapy, based on KEYNOTE-564 [42], in practice it might be attractive to use SBRT to limit potentially morbid surgery in situations of uncertain disease dynamics. Dr. Bex recommended that urologists consider surgery when the disease is durably controlled elsewhere, and the lesion is either too large for alternative focal therapies or in close proximity to the bowel.

Arguing in favour of SBRT for oligometastatic RCC was Dr. Amy Clifford (United Kingdom). She started by dispelling the myth that RCC is resistant to radiotherapy, as seen on historical in vitro studies [43] and older studies showing that patients with RCC treated with adjuvant radiotherapy had worse outcomes [44]. Newer evidence indicates that radiotherapy using larger fraction sizes can be beneficial in the primary and metastatic settings [45,46].

Oligometastatic and oligoprogressive RCC are distinct disease states, but in both cases, MDT can be beneficial, with the goal of reducing tumour-related symptoms, delaying the need to change or commence systemic therapy, and/or improving survival. There is evidence that all 3 of these aims can be achieved with SBRT across different tumour sites.

In the context of MDT for RCC, there is a lack of comparative data for surgery vs. SBRT. There is evidence, however, of an OS benefit with complete surgical metastasectomy in a series from the Mayo Clinic demonstrating a 36% improvement in cancer-specific survival [47]. But these benefits come at the risk of complications, notably an 8% risk of major complications, with a 1% risk of perioperative death in one series [48]. As a result, surgery is preferred for younger patients with few comorbidities. In older, frailer patients or those who do not want surgery, SBRT can be a good option, with local control rates between 82% and 98% [49,50].

Dr. Clifford described SBRT as a highly precise and advanced form of radiotherapy, delivering ablative doses to extracranial tumours, while minimizing the dose to surrounding healthy tissue. It is a non-invasive outpatient treatment that is delivered over 1–5 sessions via gamma knife, Cyberknife, linac, or proton beam. The SABR OCRA meta-analysis of 28 studies comprising 1602 patients (679 with extracranial disease) demonstrated a 1-year local control rate of 89.1%, and a 1-year OS of 86.1%. In patients with extracranial tumours, the rate of grade 3–4 toxicity was only 0.7% [51].

There are few prospective trials examining SBRT in oligometastatic disease. One was a phase 2 trial involving 23 treatment-naïve patients with oligometastatic RCC who had ≤ 3 metastases. Patients received SBRT to all sites. At 1 year, the rate of freedom from systemic treatment (FFST) was 87%, and local control rate was 100%. Patients experienced no significant decline in quality of life (QOL), and only 3 patients experienced treatment grade 1 toxicity [52]. The second trial was also phase 2, involving 121 patients with ccRCC and ≤ 5 metastases. These patients were not on systemic anti-cancer therapy, but about one-third had received prior treatment. The IMDC risk was favourable in 47% and intermediate in 50%. Patients underwent MDT to all sites and could potentially receive further SBRT, if

they developed new metastases. Median progression-free survival (PFS) was 17.7 months, median FFST was 34 months, and only 7% of patients experienced grade 3–4 toxicity [53].

In the setting of oligoprogressive disease, where patients can have any number of metastases, with only a small number starting to progress, a phase 2 study explored outcomes among 20 patients treated with SBRT to 36 sites. The use of SBRT extended PFS in 14 patients off systemic treatment > 6 months (70%). Again, toxicity rates were low, with only 4 patients experiencing grade 1–2 toxicity [49].

Dr. Clifford presented the case of an 80-year-old female with mRCC treated with ipilimumab and nivolumab. Three years later, she developed oligoprogressive disease in a para-aortic node. Based on her age and comorbidities, a course of SBRT was selected, which she tolerated well, aside from a mild pleural reaction with small effusion, which resolved shortly after treatment. She continued systemic treatment and just over a year later developed oligoprogression in the form of a right para-renal mass. She received SBRT a second time, with a slight dose reduction. Again, she tolerated it well, experiencing only grade 1 fatigue. The patient continued on nivolumab for about a year but then stopped it after developing IO-related hepatitis. Six months later, there was no measurable disease, and patient has not received any additional treatment.

In a Delphi consensus from the European Association of Urology and European Society for Radiation Oncology on use of SBRT for oligometastatic and oligoprogressive RCC, 71% recommended SBRT to delay change of systemic treatment, and 67% favoured SBRT as optimal local therapy in slowly progressive disease. SBRT was also identified by most as the preferred treatment modality for adrenal (88%) and bone (80%) metastases, with a divided opinion on potentially resectable sites such as the pancreas (67%) or lung (63%) [54].

Limitations of SBRT include the proximity of the tumour to normal surrounding structures, so called “organs at risk”, and previous high dose radiotherapy to that site, both of which can limit the dose that can be delivered, as well as the presence of connective tissue disease or inflammatory bowel disease (in the case of abdominal or pelvic targets). In some countries, funding re-imburement can also be a challenge.

Benefits largely outweigh these limitations, however, and include the ability to deliver SBRT noninvasively in an outpatient setting, suitability for patients with comorbidities assessed as high risk for surgical/anaesthetic morbidity, good tolerability, minimal interruption to systemic treatment, ability to treat multiple sites at once, multiple courses possible, potential for immunogenic benefit that may augment response to systemic treatment, and lower cost compared with surgery or a prolonged course of systemic anti-cancer treatment.

During an ensuing Q&A, Dr. Tanguay asked if it is the number of metastases or number of sites of metastases that drives the decision to offer MDT vs. systemic treatment. Dr. Clifford replied that this depends on patient characteristics as well as biomarker status. It is important not to select SBRT for good local control at the risk of relapse elsewhere. Dr. Bex agreed. He pointed out that, in trials comparing those who had surgery with those who did not, there was always a good reason why patients did not undergo surgery, which introduces bias. There may also be cases that appear initially to be oligometastatic but then advance to rapidly progressive disease. Dr. Tanguay noted that, in Canadian registries of patients who underwent metastatic resection, the number of sites or organ(s) involved was an important predictor for the risk of failure. Surgical morbidity when multiple organs are involved can also be important. He speculated that in such cases, SBRT may be a better option.

Dr. Bex added that the biology of the tumour is often highly influential on outcomes, and an audience member echoed this, noting that in the trial by Alt et al. [47], the patients who benefited from MDT had metachronous, not synchronous disease. He added that MDT is becoming a standard of care without clear evidence to support it. The audience

member asked whether it would be ethical at this point to conduct RCTs in this setting. Dr. Bex replied that now is the right time to conduct such trials, and some are ongoing, such as the SOAR trial [55]. Of special importance are trials that combine systemic therapy with surgery or SBRT.

Next was a panel discussion on systemic therapy combination in mRCC moderated by Dr. Tanguay with a panel of experts comprising Dr. Viktor Grünwald (Germany), Dr. Christian Kollmannsberger (Canada), and Dr. Karima Oualla (Morocco). Dr. Tanguay first reiterated that there are many treatment options in mRCC [3,56,57]. All have some evidence of efficacy, but it is unclear how they compare with one another. A 2024 systematic review and meta-analysis of first-line IO-based treatments for mRCC with extended follow-up data revealed great variability in the PFS of each regimen, with pembrolizumab-lenvatinib having the longest PFS, compared with other IO/TKI regimens. Nivolumab-ipilimumab had the shortest PFS and lowest ORR, compared with IO/TKI regimens, but a longer duration of response than other IO combinations [58].

The first case was that of a 76-year-old male with hypertension, asthma, type 2 diabetes, and obesity. He presented with a right thigh mass. A positron emission tomography (PET) revealed a significant right renal mass, a large mass in the right thigh, and multiple bilateral lung nodules. Biopsy of the right thigh mass revealed a very necrotic specimen, likely ccRCC, and IMDC intermediate risk.

Dr. Oualla suggested that first-line treatment for this patient should be one of the IO-TKI combinations approved for this indication. Selection of individual agents would depend on specific goals. The greatest overall ORR was observed with pembrolizumab-lenvatinib [58], so that could be a good option when the tumour is large and there is an imminent need to shrink it. Another option could be pembrolizumab-axitinib. Dr. Kollmannsberger agreed, noting that the patient is eligible for either of these combinations. Another option would be an IO-IO combination, given the renal and thigh tumours are likely resectable, leaving only lung metastases to tackle with systemic therapy. An IO-IO may offer a substantially more durable response. Nevertheless, preventing tumour progression could be a priority here, which would favour the IO-TKI combination.

The patient was treated with IO-IO nivolumab-ipilimumab for 4 cycles, followed by nivolumab monotherapy. Two years later, the thigh mass had disappeared, the renal mass remained stable, and lung nodules were almost completely resolved. Treatment with nivolumab was continued, but it remains unclear how long this should be continued. Dr. Kollmannsberger noted that with a positive response like this one, the next question would be whether to resect the renal mass. Should that be successful, it still remains unclear how long to continue nivolumab. He suggested continuing it for another 6–12 months. Often, patients who tolerate the therapy well are reluctant to stop. Dr. Grünwald added that at his centre they operate on these cases within the first year because most responses last about 6–12 months. A complete response on imaging would suggest that the remaining renal tumour likely has few viable tumour cells left. If this can be confirmed by pathology, there is likely no need for additional treatment.

The patient received radical nephrectomy of the right kidney, with successful complete resection of the tumour. Pathology revealed pT3a N0 papillary RCC with rhabdoid features, ISUP grade 4, with sinus fat invasion, and tumour necrosis present. In this patient, Dr. Grünwald would use CA-IX PET to confirm the lack of the presence of disease, which could reassure the patient to stop therapy, and then continue with observation. Dr. Kollmannsberger also agreed that it would be appropriate to stop treatment, as negative imaging means there is nothing to treat. But he noted that the biology of KCa remains unpredictable, and the patient may well relapse. Dr. Oualla would do the same but would also conduct pathological analysis to look for biomarkers, such as MET alterations,

given the papillary histology. This could help guide treatment should the patient relapse. Dr. Tanguay asked whether KIM-1 could, in the future, be an avenue for determining how to manage these patients. Dr. Kollmannsberger replied that it is too early to say, and prospective studies to confirm the predictive value of KIM-1 are ongoing.

If the papillary pathology had been known at the outset, the panelists agreed they would have been more likely to initiate treatment with an IO-TKI combination. Dr. Oualla added she would also have tested sooner for biomarkers. Dr. Grünwald added that the SUNNIFORECAST suggests that IO-IO therapy could be a good option in some of these patients, but subgroup analysis revealed that patients with papillary tumours did not respond as well to this combination [59]. For papillary disease, he uses nivolumab-ipilimumab. Dr. Kollmannsberger added that nivolumab-ipilimumab would be a particularly good choice if an upfront biopsy had demonstrated rhabdoid pathology, but with non-ccRCC, IO-IO therapy remains hit and miss.

The next case was that of a 73-year-old female with hypertension and chronic obstructive pulmonary disease with a left renal mass. A chest CT was normal, and the patient received left laparoscopic nephrectomy. Pathological findings were pT1b ccRCC grade 3, and she was placed on routine postoperative surveillance. Just under 2 years later, routine follow-up imaging revealed new solitary lytic lesions in the left sacrum. She remained asymptomatic, and chest CT was once again negative. IMDC risk was favourable.

For this case, Dr. Oualla would consider PET/CT to confirm oligometastatic disease and then consider local MDT. Given the location of the lesion, SBRT might be the right option. She would not offer systemic treatment, nor would she perform a biopsy prior to treatment, unless she had reason to doubt the diagnosis or suspect another cancer was involved.

The patient underwent SBRT to the sacrum and then active surveillance. Nine months later, she developed pain, and CT suggested local progression, with no other site of disease. Dr. Clifford said SBRT could be repeated, but there would be a concern the tumour may be radioresistant, and the dose needed to treat it may carry too high a risk of adverse events. Dr. Kollmannsberger said this is a difficult situation because it necessitates considering giving systemic therapy for a disease with only one site, which is usually avoided due to risk of toxicity and reduced patient QOL. Dr. Tanguay asked the panelists if they give these patients bone protective agents. Dr. Grünwald does not because current therapies are highly effective, but he might in this patient if the risk of fracture was high and because the location of the tumour would result in a particularly inconvenient fracture. Dr. Kollmannsberger warned against combining bone protective agents with TKIs because this increases the risk of osteonecrosis.

This patient was treated with radiotherapy a second time, the tumour shrank, and pain improved. Six months later, she had a new lesion in the right sacrum, with no other site of disease. Dr. Kollmannsberger would consider treating this new site with radiotherapy, if the radiation oncologist felt that the likelihood of tumour control was high. Dr. Grünwald pointed out that the interval to progression was short, suggesting further radiotherapy would not be beneficial and medical therapy would be a better option. Dr. Clifford noted that repeat SBRT may improve the PS of patients, making them better candidates for systemic therapy.

The patient underwent repeat SBRT to the new lesion and remained well for 1 year, at which imaging revealed progressive bone disease, with no other site of disease. The patient also had progressive pain. IMDC risk remained favourable. In this patient, Dr. Kollmannsberger would treat with an IO-TKI combination. With no head-to-head comparisons available, it is difficult to choose a specific combination, but he would likely choose lenvatinib-pembrolizumab because he has good personal experience with it, and it

has shown good response in patients with bone metastases [28,60]. Dr. Oualla added that, with IMDC favourable risk, virtually any IO-TKI combination could be used. The concern in such patients is overtreatment. They might do just as well with monotherapy with an agent like cabozantinib.

The patient was treated with cabozantinib-nivolumab. Dr. Kollmannsberger said that cabozantinib as a single agent has established activity in the second-line setting. Thus, it could be reserved for this setting unless there is a compelling reason to use it in first-line treatment.

On this treatment, the patient is improving, with pain diminishing. She did develop toxicity, however, with grade 2 hand-foot syndrome and hypertension and grade 1 diarrhea. Dr. Tanguay asked whether this treatment approach really bought the patient more time or only delayed time to experience toxicity from systemic therapy. Dr. Oualla replied that key goals of MDT are to delay progression as well as exposure to therapies with toxicity.

Dr. Kollmannsberger was involved in the development of the MyRCC app, which can be used to help guide individualized treatment decision for patients with advanced RCC. It is available on desktop and mobile devices. Importantly, it includes a component on patient goals for treatment, so that these can be taken into account when making therapeutic decisions. It provides a visual comparison of the pros and cons of each available option, to support shared decision-making between physician and patient.

In a final session, Dr. Kollmannsberger spoke about belzutifan, a novel treatment option in metastatic ccRCC. He started by quickly reviewing the history of treatment for KCa, highlighting improvements over the past 20 years, notably with the development of targeted agents and IO. With today's therapy, the median OS is about 4.5–5 years [61,62]. Nevertheless, he pointed out that the benefit of current regimens is fully realized, and new agents with novel mechanisms of action are needed.

HIF- α is a key driver of ccRCC and remains the basis for VEGF-targeted therapies. Within that mechanism, HIF-2 α is a key transcription factor [63–65]. Belzutifan is the first clinically available therapeutic agent that inhibits this factor, as it has been shown to stop further progression of mRCC. For the phase 3 LITESPARK-005 trial, patients with unresectable locally advanced or mRCC with progression after 1–3 previous systemic therapies, including at least one PD-(L)1 inhibitor and VEGF-targeted TKI, were randomized to everolimus or belzutifan. The primary endpoints of the trial were PFS and OS. Most patients in the trial had received 2–3 prior lines of therapy, and most had IMDC intermediate- or poor-risk disease. Patients were about evenly divided between those who had received 1 or >1 anti-VEGF therapy [66].

The ORR was 22.7% with belzutifan vs. 3.5% with everolimus, for an estimated difference of 19.2% (95% CI 14.8–24.1). The complete response rate was 3.5% with belzutifan, and there were no complete responses in the everolimus group. Among patients with an ORR, median duration of response was 19.3 months with belzutifan vs. 13.7 months with everolimus. Median PFS was 5.6 months in both groups. Nevertheless, PFS was superior for belzutifan (HR 0.75, 95% CI 0.63–0.88). To date, OS remains similar for both groups [66]. Unfortunately, there is no clinical biomarker available to predict which patients will respond to belzutifan. Subgroup analyses revealed that the drug appeared to be about equally effective regardless of prior treatment or IMDC risk category.

Belzutifan was reasonably well-tolerated, with a tolerability profile that is superior to VEGF-targeting TKIs. The most problematic toxicities were anaemia and dyspnoea. These occur because HIF- α is involved in the production of erythropoietin as well as the body's response to low oxygen levels. These are both relatively easy to manage. Most toxicities occur early and have a manageable duration [66].

A QOL analysis of patients treated with belzutifan further supports its manageable toxicity profile. Patients' QOL was greater with belzutifan than with everolimus, using 2 different measurement scales [66]. This toxicity profile allows for the possibility of using belzutifan as part of combination therapy.

Dr. Kollmannsberger then shifted to discuss one of his cases. This was a 68-year-old male who underwent right radical nephrectomy for early stage, localized RCC. Pathology revealed ccRCC, nuclear grade 2/4, with a maximum tumour diameter of 6.7 cm and stage T1b N0 M0 disease. A year later, the patient developed lung and salivary gland metastases and was started on pembrolizumab-axitinib for IMDC favourable risk disease. Despite a good response, he progressed and was started on cabozantinib a year later. After another 14 months, the patient progressed further, with lung and pleural metastases. He was subsequently enrolled into the LITESPARK-005 trials and randomized to belzutifan. On this treatment, the patient achieves complete response and has been in remission for more than 2.5 years, with minimal toxicity. He remains on belzutifan.

Results of the LITESPARK-005 trial led to the approval of belzutifan for advanced/mRCC in the second-line setting or beyond [3]. With several options available, many questions remain regarding the best sequencing.

Given the lack of OS benefit and early progression rate compared with the "low bar" comparator everolimus, Dr. Kollmannsberger raised the question of whether belzutifan is a relevant and worthwhile option. This question will be answered as it is taken up (or not) in clinical practice as well as through studies that have recently completed or are upcoming. These include the phase 1/2 KEYMAKER-U03 trial that examined belzutifan combinations including pembrolizumab-belzutifan vs. lenvatinib-belzutifan with lenvatinib-pembrolizumab as a standard comparator. The lenvatinib-belzutifan arm had the greatest ORR (46.9%), followed by pembrolizumab-lenvatinib (39.7%), and finally pembrolizumab-belzutifan (19.4%). A similar pattern was observed for median PFS (12.5 vs. 9.4 vs. 5.4 months, respectively) and OS (32.3 vs. 27.4 vs. not reached, respectively) [67].

There are several upcoming trials that include belzutifan in the first-line as well as the second- and third-line settings. The study examining belzutifan combination in the first-line setting has 3 arms: lenvatinib-pembrolizumab-belzutifan vs. lenvatinib-pembrolizumab vs. lenvatinib-MK-1308A (pembrolizumab/quavonlimab) [68]. In further lines of therapy, lenvatinib-belzutifan is being compared with cabozantinib [69] and in the adjuvant setting, pembrolizumab-belzutifan is being compared with pembrolizumab monotherapy [18]. For these latter 2 studies, the manufacturer has announced that the primary endpoints have been met, with the full results soon to be made available [70]. In addition, other HIF- α inhibitors, such as casdatifan, are on the horizon.

During a subsequent Q&A session, Dr. Peter Black (Canada) asked why belzutifan is not being studied in the neoadjuvant setting. Dr. Kollmannsberger agreed that such trials are needed, particularly in the era of IO therapy. In the perioperative setting, personalized tumour mRNA vaccines that contain several antigens taken directly from patients' tumours are under investigation. Another audience member asked in which line of therapy HIF inhibition will likely be most effective. Dr. Kollmannsberger replied that the later-line benefits he presented were quite modest. That can be improved upon either with biomarkers that predict response to HIF inhibitors or with combination therapy. There is good evidence that both HIF-1 α and HIF-2 α inhibition is important, so combining both may be more effective. Dr. Tanguay added that HIF inhibitors need to be studied in earlier settings if the benefits are to be fully understood.

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Abbreviations

ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CN	cytoreductive nephrectomy
CT	computed tomography
DFS	disease-free survival
FFST	freedom from systemic treatment
HIF	hypoxia-inducible factor
HR	hazard ratio
ICI	immune checkpoint inhibitor
IMDC	International Metastatic RCC Database Consortium
IO	immunotherapy
ORR	objective response rate
OS	overall survival
MDT	metastasis-directed therapy
mRCC	metastatic renal cell carcinoma
PET	positron emission tomography
PFS	progression-free survival
QOL	quality of life
RCC	renal cell carcinoma
RCT	randomized controlled trial

SBRT	stereotactic body radiation therapy
SITC	Society for Immunotherapy of Cancer
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor
VEGFR	vascular endothelial growth factor receptor

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