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Kidney Cancer

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The 4th Bench-to-Bedside Uro-Oncology: GU Cancers Triad Meeting, organized in conjunction with the 42nd Annual Congress of the Société Internationale d'Urologie, was held on November 11th, 2022, at the Palais des congrès de Montréal in Canada, and transmitted live on the *SIU@U* virtual platform. The session on renal cell carcinoma (RCC) took place in the afternoon and was chaired by Dr. Simon Tanguay (Canada). This session kicked off with a debate on whether adjuvant therapy should be offered to all high-risk patients post nephrectomy. Next were presentations on best options for the treatment of metastatic non–clear cell RCC (nccRCC), preoperative identification and optimal treatment of sarcomatoid RCC, and limits of partial nephrectomy in localized RCC. The session ended with a second debate, this one on the best regimen for first-line therapy in the setting of metastatic RCC.

Dr. Tian Zhang (United States) presented the pro side and Dr. Lori Wood (Canada) presented the con side in the debate on whether adjuvant therapy should be offered to all high-risk RCC patients post nephrectomy. Dr. Zhang started the debate by pointing out that the only positive trial of tyrosine kinase inhibitors (TKIs) targeting vascular endothelial growth factor (VEGF) in the adjuvant setting for RCC was the S-TRAC trial, in which an improvement in disease-free survival (DFS) but not overall survival (OS) was demonstrated with sunitinib[1]. Nevertheless, uptake of this therapy has not been high because toxicity generally outweighs potential benefit of treatment. More recently, there are now four completed phase 3 trials of immune checkpoint inhibitors (ICIs) in this setting: KEYNOTE-564 (pembrolizumab vs. placebo)[2], IMmotion010 (atezolizumab vs. placebo)[3], PROSPER-RCC (nivolumab vs. observation)[4], and CheckMate 914 (nivolumab plus ipilimumab vs. placebo)[5].

Of these, only KEYNOTE-564 was positive[2]. In a 30-month follow-up, DFS was improved with pembrolizumab over placebo, with a hazard ratio (HR) = 0.63 (95% confidence interval [CI] 0.50 to 0.80). The OS data are not yet mature. The more high-risk the patients, the greater the potential absolute benefit of treatment with pembrolizumab, and DFS benefit was specifically shown in the subset of cancers with sarcomatoid features[2]. IMmotion010[3], PROSPER-RCC[4], and CheckMate 914[5] all failed to reach their prespecified DFS primary endpoints. Results of the RAMPART trial, which is exploring durvalumab with or without tremelimumab vs. observation are not yet available[6].

There were some key differences in the inclusion criteria of these trials. Notably, IMmotion010, PROSPER-RCC, and KEYNOTE-564 all allowed M1 no evidence of disease (NED) patients, who had metastasectomy within a year of nephrectomy[2,4]. CheckMate 914 included patients with T2/grade 3 disease[5] and RAMPART included patients with T1 disease[6].

When choosing to offer adjuvant pembrolizumab therapy, it is important to balance the benefits of increasing DFS vs. the potential risks of treatment, including both immune-mediated and financial toxicity. These are decisions that must be made on an individual basis, in collaboration with patients. The

science of inference and decision-making in medicine considers patient factors that may not be captured in clinical trials, such as personal preferences and values[7]. Treatment decisions may be guided by the ASSURE prognostic nomogram, which can provide a helpful framework for discussing risks with patients with RCC[8]. At the very least, patients should be given the information available from clinical trials.

During her presentation, Dr. Wood emphasized that the primary goal of adjuvant therapy is not just to delay recurrence but to prevent recurrence and improve survival. Nevertheless, trials to date have focused primarily on DFS, with OS data largely unavailable. This compromises decision-making in clinical practice.

To date, 6 trials have failed to demonstrate that use of VEGF-TKI therapy and mammalian target of rapamycin (mTOR) inhibitor increases OS: ASSURE[9], S-TRAC[1], PROTECT[10], ATLAS[11], SORCE[12], and EVEREST[13]. Results with pembrolizumab in KEYNOTE-564 are more promising, but OS data remain immature. When OS is reported, it will be important to ensure that patients who recurred on the placebo arm did in fact receive appropriate first-line therapy with ICIs. Notably, at the 30-month follow-up report, 160 patients in the placebo arm had recurrences; 140 patients had distant recurrences, and 59 received immunotherapy[2]. Thus, only 42% of patients at relapse received any immunotherapy, the standard of care. This may result in a decrease of OS in the placebo arm, as highlighted by Dr. Wood.

As for the negative trials of other ICIs, DFS or recurrence-free survival (RFS) curves in the study arms were virtually overlapping for IMmotion010[3], PROSPER-RCC[4], and CheckMate 914[5], suggesting longer-term follow-up is unlikely to yield positive results. Note that further results from the third arm of the CheckMate 914 trial looking at single agent nivolumab are still pending. Since pembrolizumab and nivolumab are both programmed cell death 1 (PD-1) inhibitors, one would expect that, if the positive findings from KEYNOTE-564 represent a true effect, the nivolumab arm of CheckMate 914 should also be positive. The nivolumab arm of CheckMate 914[5] is only 6 months, however, compared with 12 months with pembrolizumab in KEYNOTE-564[2].

Dr. Wood concluded that there is no level 1 evidence to support adjuvant therapy in all intermediate- and high-risk RCC patients post nephrectomy and that DFS, the only endpoint that has been positive to date, reflects an improvement in recurrence rates but not mortality. In KEYNOTE-564, only 35% of patients in the placebo arm had a recurrence, which means that 65% were cured with surgery alone and would thus be overtreated if they received pembrolizumab, a drug that can have significant, life-altering toxicity and is associated with high costs. Also, at the 30-month follow-up, 25% of pembrolizumab-treated patients progressed, which may suggest that some of these patients were undertreated with monotherapy[2]. In the future, patients who received adjuvant pembrolizumab may not be eligible for standard therapy with an immuno-oncology (IO) combination or an IO plus VEGF-targeted therapy, particularly in publicly funded healthcare systems. This could be particularly problematic for M1 NED patients.

Ongoing unanswered questions are: Who will recur? Who will benefit most from adjuvant pembrolizumab? Who will experience the worst toxicity? What will the effect be in nccRCC?

During a Q&A, Dr. Wood confirmed that she does discuss adjuvant pembrolizumab with patients who fit the eligibility criteria for KEYNOTE-564; however, she also discusses the 3 negative ICI trials as well. There are no biomarkers to help drive decision-making that are likely to be clinically available in the next couple of years. There are also ongoing trials for combination therapy in the adjuvant setting, including the ongoing LITESPARK-022 study that is exploring the combination of pembrolizumab plus belzutifan[14].

Next, Dr. Zhang presented the best options for the treatment of metastatic nccRCC. She explained that there have been considerable advances in understanding molecular drivers of this disease. For instance, type 1 papillary tumours are heavily driven by *MET* mutations, whereas type 2 papillary tumours are driven by *FH* mutations. Chromophobe histology is linked to *BHD* mutations, while translocation is driven by *TFE3/TFEB* fusion and medullary cancers by *SMARCB1* and *TP53* mutations[15–17]. Sarcomatoid differentiation can occur with any of these histologies, but is more

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common in clear cell disease and is associated with aggressive disease and poor prognosis[18].

The ASPEN trial revealed superior efficacy with sunitinib vs. everolimus in metastatic nccRCC, but this benefit was not observed in the chromophobe population[19]. Early trials that focused on papillary RCC demonstrated improved objective response rates (ORRs) with erlotinib[20], sunitinib[21], foretinib[22], and bevacizumab/erlotinib[23].

More recently, papillary nccRCC has been better characterized, including identification of increased *MET* gene expression in type 1 and type 2 disease, as well as identification of novel mutations on the *MET* oncogene on chromosome 7[24]. This finding led to the SAVOIR trial, in which patients with locally advanced or metastatic *MET*-driven papillary RCC were randomized to savolitinib or sunitinib. The ORR was 27% with savolitinib vs. 7% with sunitinib, and the median progression-free survival (PFS) was 7 months vs. 5.6 months, respectively (HR = 0.71, $P = 0.313$)[25].

Next, the SWOG 1500/PAPMET trial compared sunitinib, cabozantinib, crizotinib, and savolitinib in patients with histologically confirmed metastatic papillary RCC. The 2 cohorts that received therapies that specifically target MET, crizotinib and savolitinib, were closed early. Median PFS was improved with cabozantinib at 9.0 months vs. 5.6 months with sunitinib[26].

Regarding ICI therapy in papillary, chromophobe, or unclassified nccRCC, KEYNOTE-427 cohort B demonstrated an ORR of 26.7% with pembrolizumab[27], whereas HCRN GU16-260 cohort B demonstrated an ORR of 4.3% with nivolumab[28]. Treatment with nivolumab-ipilimumab resulted in an ORR of 27.7% in CheckMate 920[29]. In KEYNOTE-B61, lenvatinib-pembrolizumab was investigated for the treatment of nccRCC across histologies. In the overall population, 6-month PFS rate was 72.3%, and 6-month OS rate was 87.8%. Among those with papillary RCC, ORR was 52.9%[30].

The phase 2 COSMIC-021 trial examined use of cabozantinib-atezolizumab in papillary or chromophobe nccRCC. Among the 32 patients in the trial, 4 had a sarcomatoid component to their cancer. Some patients had good objective and durable responses with this combination[31]. This trial forms the basis of evaluating cabozantinib with immunotherapy for papillary RCC.

The currently enrolling SWOG 2200/PAPMET2 trial (NCT05411081) is randomizing patients with metastatic papillary nccRCC to treatment with cabozantinib with or without atezolizumab. Patients will be treated until progression and will be followed for 5 years after randomization. Also ongoing is the SAMETA trial (NCT05043090), in which patients with MET-driven papillary nccRCC are being randomized to savolitinib, durvalumab, or sunitinib. For now, Dr. Zhang suggested focusing on cabozantinib-based therapies for this patient population. Time will tell if IO offers additional benefits.

Dr. Zhang then focused on metastatic chromophobe RCC, which is a fairly rare form of kidney cancer, with a paucity of dedicated clinical trials and therefore insufficient data on which treatments are effective. Mutations in *mTOR*, *NRAS*, *TSC1/2*, *PTEN*, and *TP53* may be present in these tumours[32,33]. Recent preclinical data revealed that chromophobe RCC is highly susceptible to the ferroptosis pathway through cysteine transport, suggesting the cysteine transporter as a potential therapeutic target[33].

The ASPEN trial suggested that patients with chromophobe histology may have benefited more from everolimus than sunitinib, unlike the rest of the study population. However, the numbers of patients with this histology in ASPEN were too small to make any firm conclusions[19]. In KEYNOTE-B61, ORR with lenvatinib-pembrolizumab was only 13.3% among those with chromophobe histology[30].

Several ongoing clinical trials include patients with chromophobe nccRCC, including the Alliance ICONIC trial (NCT03866382) and Dana Farber CAN-I trial (NCT04413123), both of which are exploring use of cabozantinib-ipilimumab-nivolumab, as well as a Memorial Sloan Kettering Cancer Center (MSKCC) trial (NCT03635892) investigating treatment with nivolumab-cabozantinib. Until results of these trials are available, Dr. Zhang recommended everolimus-based therapy for chromophobe nccRCC.

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Finally, Dr. Zhang discussed medullary nccRCC. This is a particularly aggressive disease and difficult to treat, so continued exploration into its molecular characteristics remains imperative. It is associated with sickle cell trait and sickle cell disease[34]. Known molecular characteristics include upregulated hypoxia pathways and c-MYC-mediated replication stress pathways[17].

In the pediatric setting, there is some evidence that medullary nccRCC may respond to paclitaxel and carboplatin-based chemotherapy[35,36]. One group also had some success with gemcitabine-doxorubicin[37]. Unfortunately, PFS and OS outcomes remain quite limited. Another study demonstrated that a complete response (CR) is possible in these patients with use of nivolumab[38], but the role of ICIs in this setting remains uncertain.

Ongoing trials in metastatic medullary nccRCC include the Alliance ICONIC trial (NCT03866382) looking at cabozantinib-ipilimumab-nivolumab, an MD Anderson trial (NCT03587662) exploring ixazomib-gemcitabine-doxorubicin, another trial from the same centre (NCT05347212) exploring nivolumab-relatlimab, as well as a National Cancer Institute trial (NCT05286801) examining atezolizumab-tiragolumab. Until more data are available, Dr. Zhang recommended use of chemotherapy, such as upfront carboplatin-paclitaxel or gemcitabine-doxorubicin, with the possible addition of radiotherapy as consolidation for this disease. Patients should be considered for clinical trials.

For sarcomatoid differentiation in nccRCC, several clinical trials (CheckMate 214, KEYNOTE-426, Javelin Renal 101, and IMmotion 151) have shown benefits of different IO combinations[39–41], with high ORRs and CRs, particularly with nivolumab-ipilimumab. Thus, IO combination may provide a good treatment approach in this patient population.

During a Q&A, Dr. Zhang explained that, for chromophobe tumours with localized oligometastases, her team typically adopts stereotactic body radiation therapy and surgical resection as a primary treatment approach, given the limited efficacy of pharmacotherapeutic options.

Next, Dr. Philippe Spiess (United States) discussed preoperative assessment and optimal treatment of sarcomatoid RCC. He highlighted the fact that much remains unknown about the biology of these tumours. A Surveillance, Epidemiology, and End Results (SEER) study revealed that sarcomatoid tumours represent the largest component of variant histology tumours and are associated with a higher cancer-specific mortality than clear cell RCC (ccRCC)[42].

Given the poor prognosis associated with sarcomatoid RCC, it is important to understand how imaging and radiomics may help to identify these tumours and guide treatment decisions. A single-centre, retrospective study examining the role of magnetic resonance imaging (MRI) in differentiation between sarcomatoid and non-sarcomatoid RCC revealed a predictive ability to detect sarcomatoid histology of only ~76%[43]. Another study looking at machine learning and multiparametric MRI as a differentiation tool only had an accuracy rate of about 70% for identification of sarcomatoid tumours[44]. A third study, this time exploring tumour characteristics via computed tomography, revealed that larger tumours are more likely to be sarcomatoid, but this characteristic is not highly sensitive for tumour differentiation[45]. While Dr. Spiess believes that machine learning combined with tumour radiographic and clinical characteristics could ultimately be used to accurately identify sarcomatoid tumours, the technology has not evolved sufficiently yet.

An infiltrative tumour, compared with a discrete mass, is often indicative that the lesion may have a sarcomatoid component and could indicate the merit of performing a pretreatment biopsy. A retrospective study evaluating the accuracy of percutaneous primary tumour biopsy for metastatic RCC, comparing biopsy findings to final pathology, among patients undergoing cytoreductive nephrectomy revealed that sarcomatoid features were present in 20.5% of the biopsies, but only 11.8% were identified preoperatively on percutaneous biopsy[46]. Dr. Spiess noted that a core biopsy often provides more information than a fine needle aspiration, although a core biopsy is more invasive. Abel et al. demonstrated that a multi-quadrant biopsy technique improves the sensitivity for identifying sarcomatoid features compared with the standard biopsy technique (86.7% vs. 25.0%), without an increase in complications [47].

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With respect to clinical management of sarcomatoid tumours, a population-based study of 879 patients with sarcomatoid RCC revealed that only 39.1% of patients presented with localized/locally advanced disease (cT1-3) at time of diagnosis. On multivariable analysis, older age (HR = 1.01), higher tumour stage (HR = 3.81), and performance of nephrectomy (HR = 0.53) were associated with disease-specific survival. The authors concluded that nephrectomy should be considered in all patients with sarcomatoid tumours, provided they have acceptable surgical risk, including in carefully selected metastatic patients[48].

Dr. Spiess noted there should be some nuance involved in this decision, based on patient and disease characteristics. In a retrospective study of 167 patients undergoing cytoreductive nephrectomy for metastatic RCC (127 ccRCC and 40 nccRCC) conducted by Dr. Spiess and his team, 11.0% of patients with ccRCC and 32.5% with nccRCC had sarcomatoid features. In both ccRCC and nccRCC, patients with sarcomatoid features had poorer outcomes, with limited to no benefit with cytoreductive nephrectomy. Interestingly, the amount of sarcomatoid component identified was not a driver of outcomes[49].

Importantly, sarcomatoid histology is associated with a greater likelihood of nodal disease[50], and lymph node metastasis is one of the strongest predictors of survival in patients with locally advanced RCC. In one study, competing regression risk modelling revealed that lymph node positivity increased the risk of cancer-specific mortality 1.8-fold for sarcomatoid RCC[51]. Thus, presurgical evidence of the presence of sarcomatoid histology is an indicator that patients may require lymph node dissection.

The presence of sarcomatoid histology is also a strong indicator that the patients should receive adjuvant therapy. A post-hoc analysis of ECOG-ACRIN E2805, which compared adjuvant sunitinib, sorafenib, or placebo, revealed no benefit for either adjuvant sunitinib or sorafenib in patients with sarcomatoid tumours[52]. On the other hand, in the 30.1-month follow-up of KEYNOTE-564, adjuvant pembrolizumab improved DFS in patients with sarcomatoid ccRCC (HR = 0.63)[2].

In the metastatic setting, outcomes of the combination of chemotherapy with targeted therapy for sarcomatoid RCC have not been encouraging, but outcomes with IOs and TKIs have been far more promising[18]. In a post-hoc analysis of the phase 3 CheckMate 214 trial, which analyzed the efficacy of nivolumab-ipilimumab vs. sunitinib in metastatic RCC, 139 of the 1096 patients in the trial had sarcomatoid RCC tumours. In these patients, there was a significant benefit in terms of OS, PFS, and ORR among those treated with the nivolumab-ipilimumab combination[41].

With respect to locally recurrent disease, an analysis of the MD Anderson Cancer Center RCC database between 1990–2007 identified 2945 radical nephrectomies with curative intent, with 54 isolated local recurrences. Estimated median RFS was 11 months, and median cancer-specific survival was 61 months among those with sarcomatoid tumours. These patients received perioperative systemic therapy as an adjunct to surgical resection in 69% of cases; however, compared to those without sarcomatoid tumours, patients presenting sarcomatoid features experience worse outcomes[53].

Dr. Spiess concluded that definitive treatment of sarcomatoid tumours should be tailored to the burden of disease, with aggressive surgery, possibly with lymph node dissection, recommended more in localized tumours than in the metastatic or recurrent setting, where benefit is less clear. Systemic therapies, including adjuvant therapy for primary tumours or IO combination in the advanced setting, are encouraging and should be considered in most, if not all, patients.

During a Q&A session, Dr. Spiess confirmed that patients with locally advanced sarcomatoid disease who are identified preoperatively may benefit from neoadjuvant therapy, especially if they have bulky tumours and positive lymph nodes. He also explained that, with regard to a second resection following cancer recurrence, he is less aggressive than he once was and is more likely to try systemic therapy first. Nevertheless, he will conduct a re-resection in patients for whom he suspects the original resection may have been incomplete or inadequate.

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The next talk, by Dr. Simon Tanguay (Canada), covered the limits of partial nephrectomy in localized RCC. Partial nephrectomy is a standard approach for small renal masses, with different surgical techniques available. What remains in question, he said, are the limitations to this approach and whether there are limits to pushing treatment boundaries. Clear indications for extensive resection include solitary kidney tumours, bilateral tumours, or chronic renal failure. Relative indications include comorbidities that may lead to loss of renal function and stone disease.

For T1b/2 disease, there has been a shift over time away from radical nephrectomy toward partial nephrectomy[54]. One study demonstrated a small OS benefit with partial nephrectomy (HR = 0.73; 95% CI 0.70 to 0.75 for T1a and HR = 0.88; 95% CI 0.83 to 0.94 for T1b/2)[54], but it is unclear if this difference is clinically meaningful in T1b/2 patients. This OS benefit disappears with older patients, particularly those with larger masses[54].

In the case of partial nephrectomy for complex renal tumours (PADUA score ≥ 10), partial nephrectomy has been shown to be safe and feasible according to results of the RECORD2 Project[55]. Interestingly, the surgical approach depends significantly on technique used, with robotic surgeons performing far more enucleation than surgeons who used an open approach. Nevertheless, these differences did not affect the rate of positive margins or RFS[55].

Tumour size is associated with tumour stage. In an evaluation of 1306 patients who underwent partial nephrectomy for cT1/2 tumours, 153 (11.7%) were upstaged to pT3a. Predictors of sinus fat invasion included ccRCC (88.2% vs. 50%), higher RENAL score (9 vs. 7), and hilar location (23% vs. 4%). Tumour size was not predictive of upstaging[56].

In a study of 298 patients with large (median 7.6 cm), complex (median RENAL score = 9) T2 renal tumours treated with robotic surgery, median ischemia time was 25 minutes, and 5% of patients required intraoperative blood transfusion. While the complication rate was high at 21%, only 5% of patients had Clavien–Dindo grade ≥ 3 complications. In addition, 34% of patients had postoperative acute kidney injury. Most concerning was an 8% positive margin rate. Notably, 37% of T2 tumours were upstaged to T3, and outcomes were worse in these patients[57].

In a Canadian prospective registry study that included 1347 patients with nonmetastatic cT2 renal tumours, 42 received partial nephrectomy. About half of these patients who received partial nephrectomy had high-grade disease, and complication rate was 17%. The positive margin rate was 10%, and local recurrence occurred in 17%. These findings indicate that partial nephrectomy in larger tumours may be associated not only with a high rate of positive margins, but also higher risk of recurrence[58].

Dr. Tanguay discussed the conflicting data regarding positive margins in patients with kidney cancer. A multicentre study of 1103 patients revealed that, among the 6.4% with positive margins, there was a trend toward higher recurrence in patients with positive margins, although this did not reach statistical significance. Predictors of positive margins in this study were ≥ pT3 stage and grade 4 disease[59]. Dr. Tanguay pointed out that the cohort is too small and the follow-up too short to determine this definitively, but an American multicentre experience among 1240 patients with a 7.8% positive margin rate revealed similar findings. Positive margins were associated with an increased risk of recurrence among patients with higher stage and grade disease, as well as those with clear cell histology[60]. Dr. Tanguay emphasized, however, that not all positive margins have an equal impact on the risk of recurrence depending on pathologic stage, histologic subtype, and grade.

In a Mayo Clinic database study of 109 patients who underwent unplanned conversion from partial to radical nephrectomy and who were matched with controls, predictors of unplanned conversion were higher RENAL score and hilar location. The primary reasons for the conversion were oncologic concerns of positive margins or upstaging or technical difficulties suggesting the kidney cannot be safely spared because of bleeding encountered or more extensive resection than anticipated[61]. Over time, there was a decrease in the percentage of aborted partial nephrectomies, both through open and laparoscopic approaches, as

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surgeons became more comfortable with the procedure and patient selection.

In a meta-analysis evaluating outcomes of partial vs. radical nephrectomy for cT1b/2 tumours, postoperative complications were higher among patients who underwent partial nephrectomy (odds ratio [OR] = 1.74; 95% CI 1.34 to 2.24), but renal function was far better preserved. Interestingly, recurrence rates were lower with partial nephrectomy (OR = 0.60; 95% CI 0.46 to 0.79), as was cancer-specific mortality (OR = 0.58; 95% CI 0.41 to 0.81)[62]. Notably, when looking only at pT2 tumours, complication rate was actually higher with partial nephrectomy (risk ratio = 2.00; 95% CI 1.50 to 2.68). In patients with pT2 tumours, there were also trends favouring partial nephrectomy for recurrence and cancer-specific mortality, but Dr. Tanguay cautioned that the number of patients was too small for these findings to be definitive[62].

European Association of Urology guidelines reflect study findings, strongly recommending partial nephrectomy for small renal masses, and recommend against laparoscopic radical nephrectomy when nephron-sparing surgery is technically feasible. Patients with T2 tumours should be offered partial nephrectomy in the context of imperative indications, such as solitary kidney or chronic kidney disease when technically feasible[63]. For larger renal masses, Derweesh et al. offer a useful algorithm for when to choose partial vs. radical nephrectomy[64]. Dr. Tanguay emphasized that partial nephrectomy is not likely to be beneficial to older patients (≥ 75) with complex renal masses who do not have a contraindication for radical nephrectomy. Also, patients with more aggressive, high-grade (4) or with a sarcomatoid component, and infiltrative tumours would likely best benefit from a radical approach.

During a Q&A, Dr. Tanguay clarified that he does not routinely conducts a biopsy prior to performing a partial nephrectomy. However, if there is evidence that the tumour might be infiltrative or otherwise high risk for local recurrence, it is worth considering biopsy prior to surgery.

The final presentation was a debate on the best first-line therapy for metastatic RCC, with Dr. Christian Kollmannsberger (Canada) arguing in favour of IO-IO therapy and Dr. Wood in favour of IO-TKI therapy. Available IO-IO therapy in this setting is ipilimumab-nivolumab (CheckMate 214)[65,66]. Available IO-TKI options are pembrolizumab-axitinib (KEYNOTE-426)[67], nivolumab-cabozantinib (CheckMate 9ER)[68,69], and pembrolizumab-lenvatinib (KEYNOTE-581)[70].

Dr. Kollmannsberger pointed out that all currently approved IO-TKI and IO-IO combinations improve OS in this setting, with similar HRs across trials[65–70]. Thus, selecting a particular regimen can be facilitated by looking at different endpoints. Which endpoints are most important can vary from patient to patient depending on personal preferences and clinical presentation. Most patients favour late and durable endpoints. That is, they want to live as long as possible with a good quality of life.

Available IO-TKI regimens improve PFS and response rate (RR), but duration of response (DoR) may be limited. The CheckMate 214 study revealed notable separation in PFS curves favouring nivolumab-ipilimumab vs. sunitinib starting at about 24 months, with a consistent plateau also occurring around this time[66]. In KEYNOTE-426, by contrast, separation of the PFS curves for pembrolizumab-axitinib vs. sunitinib occurred much sooner, at about 4 months, but the curves in both groups continued to drop rather than plateau[67]. Similarly, no plateau formed in the recent CheckMate 025 ≥ 7-year follow-up update for nivolumab vs. everolimus[71]. Long-term survival with a PD-1 inhibitor monotherapy or TKI monotherapy is low and median DoR has been reached in all IO-TKI trials Dr. Kollmannsberger considered it unlikely that the IO-TKI combination will produce a similar plateau in PFS as compared to nivolumab-ipilimumab.

In all the IO-TKI regimens, the DoR has been reached and generally ranges between 23–26 months[67]. On the other hand, median DoR has not been reached yet in CheckMate 214 with nivolumab-ipilimumab, even after median follow-up of 5 years[66]. These findings are reminiscent of results of high-dose interleukin-2, which demonstrated that patients in

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remission at 24 months have a very good chance of long-term DoR[72].

A common problem with IO-IO therapy is immune-mediated toxicity, which can require use of high-dose steroids. When looking at the chronological distribution of toxicity, however, it is evident that while nivolumab-ipilimumab can induce early toxicity in about 30% of patients, there is very little toxicity after the first 6 months. In contrast, TKI toxicity is ongoing throughout treatment[73]. In addition, most IO-IO–related immune-mediated toxicity is reversible and controllable with steroid treatment[74], and the health-related quality-of-life analysis in CheckMate 214 actually favoured nivolumab-ipilimumab[73]. Patients who had to stop this therapy due to toxicity had similar outcomes to those who did not, with 78% of CRs still ongoing despite 46% of patients being off treatment without subsequent therapy. There were significantly more patients off treatment without toxicity in the nivolumab-ipilimumab arm than in the sunitinib arm[75,76].

A potential solution to the conundrum of first-line treatment in metastatic RCC may be to offer triplet IO-IO-TKI therapy. However, Dr. Kollmannsberger is cautious about this option because the benefits of nivolumab-ipilimumab-cabozantinib in the COSMIC-313 trial are thus far modest (ORR 43% vs. 36%, compared with nivolumab-ipilimumab; PFS HR = 0.73; 95% CI 0.57 to 0.94), despite significant toxicity and discontinuations in the triplet arm[77]. He does not expect the OS to be different between these 2 arms.

Next, Dr. Wood started her presentation by listing the important considerations when selecting therapy: efficacy (PFS/OS), CR, primary progression rate, DoR, time to response, toxicity, drug discontinuation rates, second-line options, impact of long-term therapy, and patient preferences. She also noted the key differences among the currently available IO-IO and IO-TKI clinical trials. Notably, follow-up to date is longest for nivolumab-ipilimumab[66], pembrolizumab-lenvatinib had the largest proportion of favourable-risk patients[70], and nivolumab-ipilimumab-cabozantinib[77] and nivolumab-cabozantinib[68,69] had the greatest proportion of poor-risk patients. She agreed with Dr. Kollmannsberger that the OS among all these trials is fairly similar[65–70,77].

Looking at RRs, the highest reported to date is with the IO-TKI combination pembrolizumab-lenvatinib, at 71%[70]. The highest CR is 17.2%, with the same combination[70]. The lowest primary progression rates are with IO-TKI combinations, with up to 20% of patients experiencing primary progression on nivolumab-ipilimumab[66]. Nevertheless, Dr. Wood also agreed with her debate opponent that DoR rates do appear to be best with nivolumab-ipilimumab[66]. She questioned, however, whether the other combinations will demonstrate similar DoR with longer follow-up. Time to response appears to be about the same for all combinations[65–70,77].

Regarding toxicity, it is important to consider patient comorbidities. Patients with autoimmune disorders such as ulcerative colitis or systemic lupus erythematosus are likely to have worse toxicity from IO-IO combinations. Pembrolizumab-axitinib may not be a good choice for patients with cirrhosis, as this combination may have synergistic nephrotoxicity. Considering discontinuation of therapy, the high discontinuation rates in CheckMate 214 with ipilimumab-nivolumab are a concern[73]. However, the trial mandated stopping both drugs in the event of toxicity, while in the real world, patients may often continue on with single agent nivolumab. In addition, 35% of patients in CheckMate 214 required high-dose steroid treatment for toxicity[73], which can trigger multiple issues, including obesity, type 2 diabetes, infections, and muscle mass wasting. Similarly, 58% of patients required steroids with the IO-IO-TKI triplet[77], but this only occurred in 19.1% of patients receiving nivolumab-cabozantinib in CheckMate 9ER[68,69]. Regardless of what regimen is used, education of patients, primary care physicians, and emergency departments on the recognition and management of immune-related toxicities is important.

Duration of therapy is a consideration with respect to toxicity, with nivolumab being the easiest drug to tolerate long term from a patient perspective compared to long term VEGF-TKI[73]. It also important to take logistics into account. Patients who must travel

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long distances to receive treatment may be better served with shorter-term protocols or with IO-TKI combinations that are orally administered, requiring fewer site visits. There have been no formal studies on patient preferences with regard to the available IO-IO and IO-TKI regimens. Thus, it is important to have detailed discussions with patients about the risks and benefits of each.

Dr. Wood emphasized that, while first-line therapy should not be driven by what is likely to be available as second-line therapy, it is important to be mindful that first-line nivolumab-ipilimumab leaves more second- and third-line options open than using a TKI upfront. In Canada, for instance, patients who receive pembrolizumab-axitinib would only be eligible for cabozantinib second line. These restrictions will vary regionally.

According to Dr. Wood, patients in Canada who she feels are the best candidates for IO-TKI upfront therapy are those with a favourable-risk profile, since nivolumab-ipilimumab is not yet approved for these patients, as well as those who cannot afford to have primary progression. This includes, for example, those with vertebral metastases with soft tissue involvement or significant cancer-related symptoms. Finally, patients who are likely to be unable to tolerate the additional immune-mediated toxicity from IO-IO therapy, such as those with symptomatic or active autoimmune disorders and those who cannot tolerate high-dose steroids, may have better outcomes with IO-TKI regimens.

Greater clarity on patients who are the best candidates for IO-TKI treatment will arise with longer-term follow-up of IO-TKI studies, as well as greater real-world experience with all regimens. Biomarkers may become available to help treatment selection, but this is not likely to happen in the next couple of years. It is still unclear whether a subset of RCC patients can be cured and what the role of newer drugs such as belzutifan will be in the coming years.

During a Q&A session, Dr. Wood emphasized that duration of immunotherapy remains a major unknown factor. Until more data are available, decisions must be made on an individual basis, as some patients may have disease control for years off treatment. Dr. Kollmannsberger added that consolidative surgery or radiotherapy is likely to gain a significant role in management. This question is being examined with ongoing research. Dr. Tanguay also noted that patients without symptoms may be reluctant to undergo radical nephrectomy, which may have an important impact on future management.

Abbreviations Used in the Text

ccRCC	clear cell renal cell carcinoma
CI	confidence interval
CR	complete response
DFS	disease-free survival
DoR	duration of response
HR	hazard ratio
ICI	immune checkpoint inhibitor
IO	immuno-oncology
MRI	magnetic resonance imaging
MSKCC	Memorial Sloan Kettering Cancer Center
mTOR	mammalian target of rapamycin
nccRCC	non–clear cell renal cell carcinoma
NED	no evidence of disease
OR	odds ratio
ORR	objective response rate
OS	overall survival
PD-1	programmed cell death 1
PFS	progression-free survival
RCC	renal cell carcinoma
RFS	recurrence-free survival
RR	response rate
SEER	Surveillance, Epidemiology, and End Results
TKI	tyrosine kinase inhibitor
VEGF	vascular endothelial growth factor

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