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International Kidney Cancer Symposium 2021

Special Issue

IKCS 2021 Conference Coverage

IKCS2021 Top Abstracts

An Educational Service for Medical Oncologists, Hematologist-Oncologists, and Urologists

Bristol Myers Squibb™

Exploring beyond observation Checkmate 914 is exploring adjuvant IO regimen for RCC patients

Bristol Myers Squibb is currently conducting a clinical trial exploring immuno-oncology (IO) agents for early-stage, high-risk renal cell carcinoma (RCC): CheckMate 914.

CheckMate 914 is a randomized, Phase 3 clinical trial evaluating adjuvant nivolumab alone or in combination with ipilimumab in patients who underwent radical or partial nephrectomy and who are at high risk of relapse.

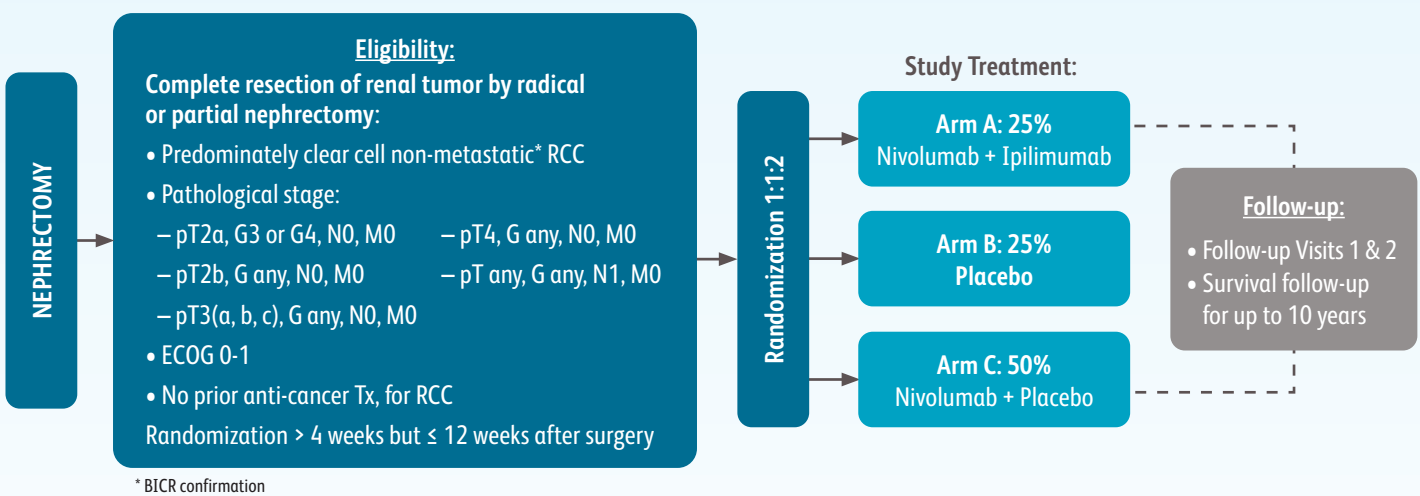
Timing is critical

Research post-surgery plans **before** surgery happens. For this clinical trial, randomization must occur between 4 and 12 weeks from the date of nephrectomy

Exploring beyond observation

This study seeks to investigate the role of an IO agent compared to the current standard of care (observation)

CHECKMATE 914 Study Design



* BICR confirmation

To find out if your patients are eligible for this trial, learn more at **BMSStudyConnect.com/KCJ**.

Reference: Data on file. Clinical protocol CA209-914. Princeton, NJ: Bristol-Myers Squibb Company, 2020.

RCC
CheckMate 914
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

STUDY CONNECT
BMSStudyConnect.com

IKCS 2021: Moving Kidney Cancer Care Forward

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https://doi.org/10.52733/KCJ19n4-ikcs

Austin, Texas served as the site for the Kidney Cancer Association's International Kidney Cancer Symposium (IKCS 2021), with the option for virtual attendance and presentation due to the ongoing pandemic. Live attendants were thrilled to be back in-person for this important annual meeting that sets the standard for disease-specific conferences world-wide.

International Kidney Cancer Symposium

DAY ONE

Sessions began with presentations and discussions around Multimodality Perspectives on Clinical Trial Development and included a discussion in health equity in clinical trials by Dr. Lola Fashoyin-Aje. She explored modernizing clinical trial eligibility criteria to allow for more diverse enrollment with the goal of achieving better understanding of drug effects and efficacy across heterogeneous populations. She also discussed the importance of decentralizing trials to make trials available to a diverse population as well as the importance for leveraging technology to allow for more efficient trials with improved access for patients. These might include utilizing remote assessments and electronic consenting for example.

Dr. Biren Saraiya gave a very provocative talk entitled Enhancing Patient-centered Care in Systemic Therapy and Clinical Trials. He began by reminding the audience of the importance of recognizing that each provider brings to each patient encounter a different personal experience, cultural background, knowledgebase and personal bias, and that patients and caregivers similarly bring these characteristics to each encounter as well. Understanding and recognizing these is a first step towards shared decision making. He suggested physician might consider asking patients, "What have you learned from Google about you condition?" He explained that patients need time to process information that they are given and to deal with the emotions that are attached, and this one of the many reasons that integration of early palliative care into the care of cancer patients can be greatly beneficial. He also noted the importance of providers recognizing their own emotions and approach, particularly in how they communicate the inherent uncertainty which exists in oncology practice.

An excellent panel discussion around neoadjuvant trials in locally advanced RCC prompted much discussion about this novel approach. The goal of such therapy would be to downstage tumors, hopefully leading to smaller surgeries to achieve full resection, and the eradication of micro-metastatic disease, while providing a window into the biology of individual patients' cancer and the mechanism of action of drugs used in this setting. Discussion around the optimal endpoints for neoadjuvant trials suggested that these would need to be individualized based on the mechanism of action of the drugs studied in a particular trial. The question of placebo in the neoadjuvant trials was also addressed, although given the wide variety of active agents in kidney cancer it was felt that placebo-controlled trials in the neoadjuvant setting would largely be unnecessary. Finally, a discussion around the important of considering combination therapy in the neoadjuvant setting was had.

Dr. Ivan Pedrosa gave a compelling lecture entitled "Phenotypic Characterization of Renal Masses – The Virtual Biopsy," in which he delineated the characterization of kidney tumors using MRI. He explained the limitations of attempting tissue diagnosis of every renal mass and introduced the Clear Cell Likelihood Score, a Likert scale for

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interpretation of multiparametric MRI that allows for a non-invasive detection of clear cell RCC and helps predict likelihood of metastases.

The surgical management of non-clear cell RCC was explored in a presentation by Dr. Ronald Boris of Indiana University. The focus of this talk was on the importance of understanding histological subtypes of RCC and their differences in metastatic potential and surgical outcomes. Dr. Boris explained that the nature of the peritumoral pseudocapsule differs significantly and predictably based on histologic subtypes of disease and can be used to personalize surgical approach and planning.

Dr. Hassanpour discussed the use of artificial intelligence (AI) deep learning in histologic classification of kidney cancer. He and his colleagues have built a AI model to help pathologists accurate classify tissue specimens. Such as system can potentially aid in automatically pre-screening slides to reduce false-negative cases, highlight regions of importance on digitized slides, and provide second opinions.

The role of NF2 in tumorigenesis in RCC was explored by Dr. Kun-Liang Guan. NF2 is a tumor suppressor acting upstream of the Hippo pathway which when mutated increases risk of developing cancerous and benign tumors, and Dr. Guan explained that the novel compound VT103 is in clinical trials in NF2 mutated cancers

Dr. McGregor gave an excellent overview of systemic therapy for non-clear cell RCC and discussed current and future approaches. He discussed PARP inhibitor trials in FH/SDH-deficient RCC, as well, as chemotherapy and immunotherapy combinations for non-clear cell RCCs.

The conference's keynote lecturer was delivered by Noble Laureate Dr. Jim Allison from MD Anderson Cancer Center, one of the world's most respected and well-known scientists and a father of immunotherapy. Allison reviewed the history of immune checkpoint blockage and noting that his early work in this area was not specific to cancer, but instead sought to better understand the function and control of T-cells. Of course, this work led to the approval of immune checkpoint inhibitors that have revolutionized system therapy for most solid tumors over the several years. He reviewed work being done around learning why some cancers respond so well to immunotherapy, while others do not and search for biomarkers that might aid in therapy selection.

Following Allison's keynote lecture, Dr. Hakimi discussed immunological consequences of obesity in clear cell RCC.

* The role of the microbiome in cancer was addressed by Dr. Dizman.
* Dr. Vitaly Margulis discussed the role of metabolomics in RCC.
* Novel Immunotherapy Targets – Dr. Ornstein
* Dr. Divya Bezwada delivered a talk entitled, "*Assessing Human Kidney Cancer Metabolism with Intraoperative Isotope Tracing*."

A session focused on mentoring including a presentation by Dr. Brian Rini on the Academy of Kidney Cancer Investigators, a formalized organization providing research direction and career guidance to early-career investigators. This was followed by presentations by three mentees regarding ongoing research projects. Dr. Rini's presentation as followed by a mentorship roundtable consisting of medical oncologists, urologists, and translational researchers. The panelists gave brief descriptions of their own career journeys and answered a multitude of questions regarding the importance of mentorship, institutional diversity, and other topics. The roundtable was followed by a panel on networking hot topics presented by Drs. Nizar Tannir, Jeff Yorio, W. Kimryn Rathmell, and Brian Shuch. The panel addressed topics such as community oncology and community-based research, grantsmanship, networking, and other topics. An excellent poster walk was hosted by Drs. Eric Kauffman, Ritesh Kotecha, Nizar Tannir, and Stephen Culp.

DAY 2

Day two of the conference, brought lectures on adjuvant therapies and advocacy, an award lecture, and abstracts. Dr. Toni Choueiri spoke on the Future of Adjuvant Therapy in RCC. He reviewed data on adjuvant sunitinib, which while approved in this setting in the US, has had largely disappointing outcomes especially with regards to overall survival. He then described results of the KEYNOTE-564 study which randomizes patients at high-risk of recurrence to pembrolizumab vs placebo after complete resection of RCC (including 5.8 precent of patient with completely resected metastatic disease). The study achieved a disease-free survival (DFS) of 68.1% in placebo arm vs 77.3% in the pembrolizumab arm at 24 months, and while overall survival is still not mature, it trended towards favoring the pembrolizumab arm. He also reviewed data using circulating tumor DNA to predict who might have residual disease and benefit most from an adjuvant therapy approach. This has been challenging as RCC does not shed ctDNA at high rates. Choueiri described cfMeDIP-sequencing that may help improve this approach. He finally mentioned the lack of data on adjuvant strategies of non-clear cell histologies and the need to explore whether strategies giving longer or short durations of adjuvant immunotherapy are appropriate. Dr. Choueiri talk was followed by a panel exploring adjuvant approaches in RCC via an interactive case-based discussion.

The next session of IKCS 2021 focused on advocacy, funding, and the patient experience, starting with a talk by Gretchen E. Vaughan, President and CEO of the Kidney Cancer Association. She reviewed programmatic initiatives including the organization's progress, projects, and goals. Theresa Miller spoke on Congressionally Directed Medical Research Programs (a program of the Department of Defense) and specifically the Kidney Cancer Research Program (KCRP). The KCRP received $50 million in funding in 2021 and funding has increased each year since 2017. She also described the funding opportunities that include concept awards, idea development awards (for early career investigators and established investigators), translational research partnership awards, clinical trial awards, clinical research nurse development award, early career develop awards for the Academy of Kidney Cancer Investigators, and postdoctoral and clinical fellowship awards. A legislative advocacy roundtable followed that included Bruce Hill and Ryan Natzke, both patient advocates, who encouraged physicians and researchers to meet with their elected representatives and their legislative/congressional staffers.

The Andrew C. Novick Award

Lecture was given by Dr. Brian Lane on the topic of the management of T1 renal masses. He reviewed the history and data behind robotic partial nephrectomies that have become the goal standard for most T1 renal masses. He reviewed concepts around loss of renal function following partial nephrectomy, noting that loss of renal function is rare following surgery with those who has underlying chronic kidney disease are at greater risk. He also shared data that showed renal functional outcomes after partial nephrectomy are better than open nephrectomy even with partial nephrectomy is associated with prolonged ischemia. He also discussed the concept of surgical chronic kidney disease, as a distinct entity from other forms of kidney disease and its impact on overall survival. He noted that open nephrectomies may not be as bad as once thought and described a randomized trial. He also introduced MUSIC, the Michigan Urological Surgery Improvement Collaborative, an umbrella that include many quality improvement projects. He finally noted that with greater and appropriate use of high-quality imaging, renal mass biopsy, and surveillance we can better identify patients who can safely avoid intervention. He concluded his presentation by sharing his own personal story of being a patient with two simultaneous types of cancer including kidney cancer.

The award lecture was followed by presentations of the conference's top abstracts. Dr. Pedro Barata of Tulane University spoke on his abstract "Gene Expression Profiling (GEP) of non-clear cell renal cell carcinoma (nccRCC) identifies a unique spectrum of transcriptional signature with potential clinical relevance." Dr. Barata explained that 657 patient samples were sequenced including papillary (9.6%), chromophobe (4.6%), medullary (1.2%), collecting duct (0.9%), and mixed (6.2%) nccRCC subtypes. While most ccRCC samples were classified as 'Angiogenic' or 'Angio/stromal' (50%), these molecular subgroups comprised < 10% of nccRCC samples, which were predominately classified as 'Proliferative' (49%). Defective MMR/MSI-H and TMB-High (≥ 10 mutations/Mb) rates were highest (33.3%) in collecting duct carcinoma and rarely observed (< 3.5%) in all other histological subgroups. These observations provide a new understanding for personalized treatment of nccRCC, warranting further evaluation in prospective trials.

Dr. Sari Khaleel presented "Outcomes of cytoreductive nephrectomy followed by active surveillance in metastatic renal cell carcinoma." He presented data on 97 systemic-therapy-naïve mRCC patients who underwent cytoreductive nephrectomy followed by active surveillance between 1989 – 2020. Median follow-up was 31.8 months with an intervention-free survival of 11.6 months. Overall survival was 52.3 months in these patients. Of note, IMDC risk categories did not correlate with outcomes on multivariate analysis.

Dr. Charlotte Spencer spoke on her abstract entitled, "Machine learning predicts BAP1/PBRM1 in clear cell renal cell carcinoma: TRACERx Renal," which described a proof of principle study which showed that mutational status of two ccRCC driver genes, PBRM1 and BAP1 can be accurately predicted with a high degree of accuracy from digital histological images alone.

Dr. Nizar Tannir from MD Anderson spoke on "Frist-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in patients with long-term survival of ≥5 years in the CheckMate 214 trial." Of 550 patients randomized to the immunotherapy arm, long-term survival of greater than 5 years was reported in 236 (43%) patients compared to 171 of 546 (31%) patients in the sunitinib arm. Baseline demographic and clinical characteristics generally did not distinguish which patients would achieve long-term survival, except for lower target lesion burden, IMDC poor risk disease, and bone metastases at baseline.

Dr. Akash Kaushik presented "Glutamine metabolism in clear cell Renal Cell Carcinoma," in which he described metabolic reprogramming in ccRCC, and suggested that mechanisms beyond glutaminase-dependent metabolism may fuel the TCA cycle in ccRCC, such as nitrogen-dependent glutamine and aspartate, suggesting that inhibiting glutaminase and aspartate simultaneously may be a useful therapeutic approach.

The final session of the conference focused on the role of perioperative therapy in RCC, with Dr. Christopher Wright speaking on the use of artificial intelligence for RCC diagnosis with CT scans. Dr. Wright introduced the concept of "segmentation" or having a computer cluster parts of an image together that belong to the same object class. Such segmentation could be used to increase diagnostic certainty, predict best treatment approaches and outcomes, and better estimate post-operative renal function. He asked in artificial intelligence could be used to independently generate an unambiguous nephrometry score. Through crowd sourcing, hundreds of teams were able to generate programs that were able to complete these tasks in ways that were comparable to humans and were able to predict clinical outcomes. Dr. Wright concluded by suggesting broader future uses of this type of technology.

Dr. Hannan explored of stereotactic radiation (SBRT) for RCC inferior vena cava (IVC) thrombosis. He discussed a phase II trial of neoadjuvant SBRT for RCC IVC thrombus to evaluated whether this technique may reduce the risk of RCC recurrence. Results of the safety lead-in were encouraging, with 2 of 3 patients with metastatic disease at diagnosis having a response (1 complete response and 1 partial abscopal response). The study continues to enroll.

Dr. Mohamad Allaf spoke of surgical consideration with perioperative therapy. He reviewed small previous studies of neoadjuvant axitinib and pazopanib which suggested some role to help downstage patients prior to surgery but will increase risk of surgical complications. He reviewed pre-clinical data and data in other cancer types for neoadjuvant immunotherapy. Finally, he reviewed results of a small study (n=17) of non-metastatic, high-risk RCC patients who 3 cycles of nivolumab prior to partial or radical nephrectomy. Although some patients achieved tumor shrinkage all except one had statistically stable disease after treatment. He also described EA8143:PROSPER RCC trial, a large randomized study of perioperative nivolumab which has completed enrollment, but whose results are forthcoming.

The 2021 Kidney Cancer Association IKCS Meeting not only provided researchers and providers a terrific venue for networking and collaboration but also disseminated a great deal of knowledge as progress in the fight again kidney cancer marches on.

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https://doi.org/10.52733/KCJ19n4-abs

TIP01 - SWOG S1931 (PROBE): Phase III randomized trial of immune checkpoint inhibitor (ICI) combination regimen with or without cytoreductive nephrectomy (CN) in advanced renal cancer [NCT04510597]

Vaishampayan U, Tangen C, Tripathi A, Shuch B, Pal S, Barata P, Tan A, Zuckerman P, Mayerson E, Lara P, Agarwal N, Vogelzang N, Thompson I, Kim H

Patient and Methods: Eligible patients with primary tumor and metastases are treated with one of the FDA approved ICI based combinations: ipililumab and nivolumab, axitinib and pembrolizumab, or axitinib and avelumab. Cabozantinib + nivolumab and lenvatinib + pembrolizumab combinations are being added into the next amendment. Urology evaluation and response assessment is required. Randomization occurs between 10-14 weeks of therapy; 1:1 to receive CN followed by systemic therapy or to continue on systemic therapy.
Statistical Design & Endpoints: The primary endpoint is overall survival. We estimate the median survival from time of randomization for the non-surgical arm will be 25 months. The study hypothesis is that CN will result in improvement in OS outcomes in advanced synchronous RCC post-initial systemic immune checkpoint-based combination therapy. With a sample size of 302 eligible, randomized participants (151 per arm) and a one-sided alpha=0.025, the study has 85% power to detect a 47% improvement in median survival (HR=0.68; 1/0.68 = 1.47)
Funding: NIH/NCI/NCTN grants U10CA180888, U10CA180819, U10CA180820

TIP09- 89Zr-TLX250 for PET/CT imaging of clear cell kidney cancer

Shuch B, Hayward C, Pantuck A

Trial Design: Zircon is an open label, phase 3 study evaluating the performance of Zirconium-89-labeled girentuximab (89Zr-TLX250) for detecting ccRCC. The trial is open at 34 international sites (NCT03849118). The primary endpoint is the sensitivity/specificity of PET/CT imaging with 89Zr-TLX250 to non-invasively predict resection histology. Secondary endpoints include safety/tolerability, performance in cT1a, positive/negative predictive value, and inter/intra-observer variability. Key inclusion criterion includes a solitary, localized, cT1 lesion scheduled for resection. Exclusion criterion include planned biopsy and concurrent malignancy requiring treatment <4 weeks prior to 89Zr-TLX250 administration. Eligible subjects undergo 89Zr-TLX250 administration followed by PET/CT 3-7 days later. Resection is performed <90 days with local/central pathologic review required and CA9 immunohistochemical staining planned. Monitoring of stage/histology allows for modification of sample size (n=252) which currently has 90% power to detect a sensitivity of 83% in the cT1a group. The U.S. FDA granted Breakthrough Therapy designation for 89Zr-TLX250 which aims to improve the diagnosis and staging of ccRCC.

TIP10 A randomized trial of radium-223 (Ra-223) dichloride and cabozantinib in patients (pts) with advanced renal cell carcinoma (RCC) with bone metastases (RADICAL / Alliance A031801)

McKay RR, JacenHe, Atherton P, Perez-Burbano G, Ajmera A, Baghaie S, Koball J, Zemla T, Chen R, Choudhury A, Lang JM, Cole S, Al Baghdadi T, Kwok Y, Beltran H, George D, Morris M, Choueiri TK

Background: Bone metastases are prevalent in approximately 30% of patients with advanced RCC. Patients with bone metastases have a worse prognosis compared to patients without bone metastases and are at risk of symptomatic skeletal events (SSEs). Cabozantinib, a multitargeted inhibitor of multiple kinases, including vascular endothelial growth factor (VEGF) receptor and MET, has improved survival in pts with metastatic RCC and has enhanced activity in bone. Ra-223, an alpha-emitting radioisotope with natural bone-seeking proclivity, has prolonged survival in men with castration-resistant prostate cancer. We previously conducted a pilot study of Ra-223 with VEGF inhibition and demonstrated safety and declines in bone turnover markers (McKay et al, CCR 2018). We designed a randomized phase 2 study through the National Clinical Trials Network investigating cabozantinib with or without Ra-223 in patients with RCC with bone metastases.
Methods: This is an open-label multicenter study. Eligible patients have metastatic RCC of any histology with ≥1 untreated metastatic bone lesion(s). Patients with non-clear cell RCC are eligible. Patients must have a Karnofsky performance status of ≥60% and be on osteoclast-targeted therapy. Patients are randomized 1:1 to cabozantinib with (Arm A) or without (Arm B) Ra-223.
Endpoints: The primary endpoint is SSE-free survival. Secondary endpoints include safety, progression-free survival, overall survival, quality of life measures, and correlative analyses including liquid biopsy studies and tumor tissue analysis. Target accrual is 210 patients.

CTR11- First-line nivolumab plus ipilimumab (NIVO+IPI) versus sunitinib (SUN) in patients with long-term survival of ≥5 years in the CheckMate 214 trial

Tannir NM, Motzer RJ, McDermott DF, Plimack ER, George S, Amin A, Tykodi SS, Srinivas S, Carthon B, Hutson TE, Lee CW, Desilva H, Jiang R, Hammers HJ

Background: First-line NIVO+IPI provided long-term survival benefits versus SUN in patients with advanced renal cell carcinoma (aRCC) after 5 years follow-up in CheckMate 214.
Methods: Patients with clear cell aRCC were randomized to NIVO 3 mg/kg plus IPI 1 mg/kg Q3W×4 then NIVO 3 mg/kg Q2W versus SUN 50 mg QD (4 weeks of 6-week cycles). In this post hoc exploratory analysis, outcomes in patients with overall survival ≥5 years (long-term survivors; LTS) were assessed by IMDC risk (intermediate/poor [I/P-risk] and favorable [FAV-risk]).
Results: Overall, 163/425 I/P-risk and 73/125 FAV-risk patients in the NIVO+IPI arm versus 112/422 I/P-risk and 59/124 FAV-risk patients in the SUN arm were LTS. Baseline characteristics generally did not distinguish LTS from intent-to-treat patients

with NIVO+IPI, except target lesions were smaller and fewer patients had bone metastases. Regardless of risk group in LTS, there were more durable and complete responses with NIVO+IPI versus SUN. Fewer LTS required subsequent systemic therapy with NIVO+IPI versus SUN, and most patients in the SUN arm with subsequent therapy received NIVO monotherapy regardless of risk. More LTS who responded experienced a treatment-free interval with NIVO+IPI versus SUN. Treatment-related adverse events leading to discontinuation did not preclude surviving ≥5 years.
Conclusions: These results highlight the long-term clinical benefits and continued durability of response observed with NIVO+IPI in patients across a spectrum of baseline characteristics and regardless of IMDC risk.

CTR12- Outcomes with first-line nivolumab plus cabozantinib (NIVO+CABO) versus sunitinib (SUN) in patients with advanced renal cell carcinoma (aRCC) and treatment-related adverse event (TRAE) timing/management in CheckMate 9ER
Kessler ER, Burotto M, Shah AY, Ryan CW, Shaheen M, Drakaki A, Tomita Y, George S, Motzer RJ, Choueiri TK, Simsek B, Zhang J, Scheffold C, Apolo AB, Bedke J.

Background: First-line NIVO+CABO demonstrated superiority versus SUN in aRCC patients in the phase 3 CheckMate 9ER trial.
Methods: Patients with any IMDC risk and clear cell aRCC were randomized to NIVO 240 mg every 2 weeks + CABO 40 mg once daily versus SUN 50 mg once daily (4/6-week cycles). In this post hoc exploratory analysis, timing/management of grade ≥3 TRAEs and outcomes in patients with these events were assessed to better understand the impact of safety kinetics with NIVO+CABO in first-line aRCC.
Results: Of all treated patients, 310/320 (NIVO+CABO) versus 298/320 (SUN) had any-grade TRAEs and 199 versus 168 had grade ≥3 TRAEs, respectively. Most baseline characteristics in patients with grade ≥3 TRAEs were similar to intent-to-treat patients and generally balanced between arms. Grade ≥3 TRAE time to onset/resolution patterns and management are summarized (Table). Of patients with ≥1 subsequent dose delay/reduction due to any adverse event (72% [NIVO+CABO] vs 70% [SUN]), most continued on therapy. Additionally, progression-free survival (PFS) was improved with NIVO+CABO versus SUN (HR, 0.62 [95% CI, 0.47-0.82]) in patients with grade ≥3 TRAEs (Table).
Conclusions: The safety profile of NIVO+CABO was manageable, most common grade ≥3 TRAEs resolved, and almost all patients assessed here with ≥1 dose delay/reduction continued on therapy. PFS was notably improved with NIVO+CABO in patients with grade ≥3 TRAEs regardless of dose delay/reduction patterns.

CTR15- First results of 68Ga-EMP-100 PET for imaging c-MET expression in metastatic renal cell carcinoma
Mittlmeier L, Todica A, Gildehaus FJ, Unterrainer M, Beyer L, *Brendel M, Albert NL, Ledderose ST, Vettermann FJ, Schott M, Rodler S, Marcon J , Ilhan H, Cyran CC, Stief CG, Bartenstein P and Staehler M*

Background: c-MET as receptor tyrosin kinase is upregulated in renal cell carcinoma and has been shown to be correlated with patients' survival in metastatic renal cell carcinoma (mRCC). Prediction of treatment response to tyrosin kinase receptor inhibitors targeting c-MET such as cabozantinib is important to improve disease management in mRCC. 68Ga-EMP-100 is a novel PET ligand that directly targets c-MET expression. Here we present first-in human data of 68Ga-EMP-100 in mRCC comparing uptake characteristics on an intra- and interindividual level.
Methods: 12 patients with mRCC prior or at assessment of further therapy options underwent 68Ga-EMP-100 PET/CT imaging. Uptake of mRCC lesions were compared by SUVmean and SUVmax measurements.
Results: Overall, 87 tumor lesions were delineated: Of these, 79.3% were visually rated c-MET positive (median SUVmax of 4.4 / SUVmean 2.5). Comparing tumor sites, the highest uptake was at the primary tumor followed by bone, lymph node and visceral metastases. The highest number of PET-negative metastatic sites were in lung and liver.
Conclusions:68Ga-EMP-100 which targets c-MET expression shows increased uptake in mRCC patients with high inter- and intraindividual differences. Our pilot study shows that 68Ga-EMP-100 could be a promising molecular imaging tool for mRCC patients undergoing tyrosin kinase inhibitor therapies.

N16- Anti-CAIX BBζ CAR4/8 T cells exhibit superior efficacy in a clear cell renal cell carcinoma (ccRCC) mouse model
Wang Y, Buck A, Grimaud M, Culhane AC, Kodangattil S, Razimbaud C, Bonal D, Nguyen QD, Zhu Z, Wei K, O'Donnell ML, Huang Y, Signoretti S, Choueiri TK, Freeman GJ, Zhu Q, Marasco WA

Improving CAR-T cell therapy for solid tumors requires a better understanding of CAR design and cellular composition. Here, we compared second-generation (BBζ, 28ζ) with third-generation (28BBζ) carbonic anhydrase IX (CAIX) targeted CAR constructs and investigated the anti-tumor effect of CAR-T cells with different CD4/CD8 proportions in vitro and in vivo. The results demonstrated that BBζ exhibited superior efficacy compared to 28ζ and 28BBζ CAR-T cells in a ccRCC skrc-59 cell bearing NSG-SGM3 mouse model. The mice treated with a single dose of BBζ CAR4/8 showed complete tumor remission and remained tumor-free 72 days after CAR-T cells infusion. Profiling tumor infiltrating T cells via scRNAseq, we found that BB CAR8 upregulated expression of HLA II and cytotoxicity associated genes, while downregulating inhibitory immune checkpoint receptor genes and diminishing differentiation of Tregs, leading to excellent therapeutic efficacy in vivo. Increased memory phenotype, elevated tumor infiltration, and decreased exhaustion genes were observed in the CD4/8 UNT cells compared to CD8 alone, suggesting that CD4/8 is the preferred cellular composition for CAR-T cell therapy with long-term persistence. In summary, these findings support that BBζ CAR4/8 T cells are a highly potent, clinically translatable cell therapy for ccRCC.

N19 - COVID-19 vaccination in patients with renal cell carcinoma receiving immune checkpoint inhibitors
Dzimitrowicz H, Hwang J, Shah R, Ashcraft K, George DJ, Salama A, Zhang T

Background: Patients on cancer treatment were excluded from COVID-19 vaccine trials; thus safety of COVID-19 vaccination in patients with RCC receiving ICIs is not well described.

follow up at Duke Cancer Center. We retrospectively reviewed encounters over 3 months post-vaccination. Primary outcome was adverse events attributed to vaccination; other outcomes included subsequent immune related adverse events (IRAE) and COVID-19 infection. Results: 36 study patients (vax+ with ICI) and 36 control patients (vax+) were identified. Baseline characteristics are in Table 1. 22.2% of study patients (N=8/36) reported vaccination-related symptoms: chills (8.3%; N=3), headache (5.6%; N=2), fatigue (5.6%; N=2), and one with fever, nausea, vomiting, diarrhea, myalgias, injection site pain, and rash. One control patient developed PVCs. Two study patients (5.6%) developed new/worsening IRAE requiring systemic steroids and/or treatment hold (colitis and adrenal insufficiency). One study patient (2.8%) and 0 patients developed COVID-19 infection after one and two vaccine doses, respectively. Conclusions: In a population of patients with RCC receiving ICI, COVID-19 vaccination appears to be well tolerated and safe. The higher rate of post-vaccination symptoms reported in ICI+ patients may be related to more frequent visits vs controls. In solid tumor populations at higher risk for severe COVID19 infections, vaccination is important to mitigate this risk.

N22- Nivolumab plus cabozantinib (N+C) versus sunitinib (S) in patients with advanced renal cell carcinoma (aRCC) and bone metastasis: subgroup analysis of the Phase 3 CheckMate 9ER trial

Apolo A, Powles T, Bourlon MT, Suarez C4, Porta C, George S, Choueiri TK, Motzer R, Scheffold C, Zhang J, Mangeshkar M, Shah AY, Escudier B,

Background: In the phase 3 CheckMate 9ER trial (NCT03141177), N+C significantly improved progression-free survival (PFS), overall survival (OS), and objective response rate (ORR) vs S in first-line aRCC. This exploratory analysis evaluated outcomes by baseline bone metastasis status per investigator.
Methods: 651 patients with clear cell aRCC were randomized 1:1 to N (240 mg Q2W) plus C (40 mg QD) or S (50 mg QD for 4 weeks of 6-week cycles). Data cut-off was Sep 10, 2020. PFS and ORR were per blinded independent central review per RECIST v1.1.
Results: 151 patients had bone metastasis at baseline. PFS was longer with N+C vs S in patients with or without bone metastasis and the HR favored N+C vs S (Table). The OS HR also favored N+C vs S. ORR was higher, and duration of objective response (OR) was longer in N+C vs S in both groups. Both subgroups had longer duration of treatment for N+C vs S. All-causality Grade 3-4 adverse events for N+C vs S were 78% vs 67% and 71% vs 68%, in patients with and without bone metastasis, respectively; treatment-related Grade 3-4 adverse events were 71% vs 42% and 59% vs 55%.
Conclusions: Treatment with N+C vs S improved PFS, OS, and ORR in patients with first-line aRCC irrespective of bone metastasis at baseline, consistent with outcomes in all randomized patients.

N25 - Cost per survivor (CPS) and cost per life-month (CPLM) of nivolumab plus ipilimumab (NIVO+IPI) versus pembrolizumab plus axitinib (PEMBRO+AXI) for previously untreated advanced renal cell carcinoma (aRCC)

Huo S, Del Tejo V, Du EX, Wu A, Chin A, Betts KA

Background: NIVO+IPI and PEMBRO+AXI demonstrated survival benefits versus sunitinib (SUN) for previously untreated aRCC in the CheckMate 214 and KEYNOTE-426 trials, respectively. In the absence of head-to-head trial, their comparative costs have not been assessed. This study compared the CPS and CPLM of the two treatments.
Methods: Overall survival (OS) rates were derived from a matching-adjusted indirect comparison of NIVO+IPI (CheckMate 214, median follow-up: 55 months) versus PEMBRO+AXI (KEYNOTE-426, median follow-up: 43 months). Treatment costs (2020 USD) included costs of drug acquisition, administration, and grade 3/4 adverse events. The monthly incremental CPS for NIVO+IPI or PEMBRO+AXI relative to SUN was calculated as the difference in monthly costs divided by the difference in OS rates at 12, 24, 36, and 48 months. The incremental CPLM was estimated similarly using restricted mean survival time.
Results: The monthly incremental CPS relative to SUN for NIVO+IPI decreased over time and were consistently lower than that for PEMBRO+AXI (at 48 months: $18,881 vs. $136,342) (Figure 1). Similarly, NIVO+IPI had consistently lower incremental CPLM (relative to SUN) compared with PEMBRO+AXI throughout follow-up with a difference in incremental CPLM of $63,611 over 48 months.
Conclusions: NIVO+IPI had consistently lower incremental CPS and CPLM (relative to SUN) compared with PEMBRO+AXI over time, indicating greater cost efficiency for NIVO+IPI as first-line aRCC treatment.

N33- Outcomes of cytoreductive nephrectomy followed by active surveillance in metastatic renal cell carcinoma

Khaleel S, Silagy A, Duzgol C, Kotecha R, Rappold P, Weiss K, Dinatale R, Patil S, Coleman J, Russo P, Voss M, Hakimi A.

Background: Cytoreductive nephrectomy (CRN) for management of metastatic renal cell carcinoma (mRCC) has been recently debated. We retrospectively evaluated systemic therapy (ST)-naïve mRCC patients undergoing CRN followed by active surveillance (CRN+AS), subclassified into favorable- and unfavorable-risk based on prognostic criteria proposed by Rini et al for length of AS after CRN (2016). We assessed intervention-free survival (IFS), overall survival (OS), progression-free survival (PFS), and cancer-specific survival (CSS).
Methods: We searched our institutional mRCC database for ST-naïve patients undergoing CRN+AS between 1989-2020. Categorical and continuous outcomes were assessed using Chi-squared and Welch T-test, respectively. Cox regression and Kaplan-Meier method were used to assess survival outcomes.
Results: Of 517 ST-naïve patients who underwent CRN, 414; (80%) had residual disease, followed by AS vs ST in 97 (23.4%) vs 295 (76.6%) patients. Median IFS was 22.2 months in the CRN+AS cohort, with 58 patients undergoing further ST/surgery. Median PFS, OS and CSS were 7.7, 52.3, and 56.5 months, respectively. Favorable Rini-risk was significantly associated with longer IFS (HR 0.60; 95% CI: 0.38–0.95, p=0.026) and CSS (HR 0.51; 95% CI: 0.27–0.99, p=0.041), but not OS or PFS, in CN+AS patients (Figure 1).

Conclusions: In this retrospective study, mRCC patients selected for primary CRN+AS had median IFS of 22.2 months, supporting CRN+AS in well-selected patients, avoiding the morbidity of primary or adjuvant ST. Prognostic criteria proposed by Rini et al for CRN+AS patients may aid in patient selection and management.

Methods: We identified patients with RCC who received at least 1 dose of an FDA-authorized COVID-19 vaccine (vax+), on or off ICI, between 12/1/2020 and 4/1/2021, with at least 3 months

E42- Characterizing the immune response in patients with renal cell carcinoma (RCC) following COVID-19 vaccination

Malhotra J, Salgia S, Zengin Z, Meza L, Ely J, Hsu J, Kelley E, Mead H, Chehrazi-Raffle A, Govindarajan A, Muddasani R, Dizman N, Chawla N, Dorff T, Lyou Y, Karczewska E, Trent J, Salgia R, Altin J, Pal SK

Background: There are limited data evaluating COVID-19 vaccine efficacy and response among RCC patients.
Methods: Patients with genitourinary cancer (prostate, kidney, and bladder) who had not received any COVID-19 vaccine were included. Blood was collected prior to vaccination, as well as at 2, 6, and 12 months following administration of one vaccine dose. Patients receiving systemic treatments provided additional blood at three consecutive therapy cycles. An ELISA assay was used to assess the blood specimens for antibody titers and the result was reported as an immune status ratio (ISR).
Results: Of the 80 patients that submitted both baseline and 2-month specimen, 33 had RCC. A majority of these patients were receiving systemic therapy (n=31, 93.9%), with immune checkpoint inhibitors as the most common (n=19, 61.2%) followed by targeted agents (n=11, 35.5%). The median age was 64 (interquartile range [IQR], 57.5-72.0), with a majority of male (n=22, 66.7%) and white (n=28, 84.8%) patients. BNT162b2 (Pfizer) was the most commonly administered vaccine (n=20, 60.6%). In the 33 patients included in this analysis, the median baseline ISR was 0.14 (IQR, 0.12-0.24) compared to 7.33 (IQR, 7.08-7.34) at 2 months (P<0.001). Results demonstrated a seroconversion rate of 90.9% by the 2-month timepoint, and no significant difference in ISR change between baseline and month 2 based on systemic treatment rendered.
Conclusions: Our data demonstrates sufficient immune response in RCC patients who have received a commercially available COVID-19 vaccine and encourages continued vaccination in these patients.

E43- Nivolumab plus cabozantinib in patients with non-clear cell renal cell carcinoma: results of a phase 2 trial.

Lee CH, Voss MH, Carlo MI, Chen YB, Zucker M, Knezevic A, Lefkowitz RA, Shapnik N, Dadoun C, Reznik E, Shah NJ, Owens CN, McHugh DJ, Aggen DH, Laccetti AL, Kotecha R, Feldman DR, Motzer RJ

Background: Cabozantinib plus nivolumab (CaboNivo) improved objective response rate (ORR), progression-free survival (PFS), and overall survival (OS) over sunitinib in a phase 3 trial for metastatic clear cell renal cell carcinoma (RCC). (Choueiri, abstract 6960, ESMO 2020) We report the results of a phase 2 trial of CaboNivo in patients (pts) with non-clear cell RCC.
Methods: Pts had advanced non-clear cell RCC, 0 or 1 prior systemic therapies excluding prior immune checkpoint inhibitors, and measurable disease by RECIST. Cabo 40 mg/day plus Nivo 240 mg every 2 weeks or 480 mg every 4 weeks was given across two cohorts. Cohort 1: papillary, unclassified, or translocation associated RCC; Cohort 2: chromophobe RCC. The primary endpoint was ORR by RECIST; secondary endpoints included PFS, OS, and safety. Cohort 1 was a single stage design that met its primary endpoint and was expanded to produce more precise estimates of ORR. Cohort 2 was a Simon two-stage design that closed early for lack of efficacy. Correlative analyses by next generation sequencing were performed and to be presented.
Results: A total of 40 pts were treated in Cohort 1, and 7 pts were treated in Cohort 2 (data cutoff: Jan 20, 2021). Median follow up time was 13.1 months (range 2.2 – 28.6). In Cohort 1, 26 (65%) pts were previously untreated, and 14 (35%) pts had 1 prior line: 10 (25%) received prior VEGF-targeted therapy and 8 (20%) received prior mTOR-targeted therapy. ORR for Cohort 1 was 48% (95% CI 31.5–63.9; Table). Median PFS was 12.5 months (95% CI 6.3–16.4) and median OS was 28 months (95% CI 16.3–NE). No responses were seen among 7 patients in Cohort 2 with chromophobe histology (Table). Grade 3/4 treatment emergent adverse events were consistent with that reported in the phase 3 trial; Grade 3/4 AST and ALT were 11% and 13%, respectively. Cabozantinib and nivolumab were discontinued due to toxicity in 13% and 17% of pts, respectively.
Conclusions: CaboNivo had an acceptable safety profile and showed promising efficacy in metastatic non-clear cell RCC pts with papillary, unclassified, or translocation associated histologies whereas activity in patients with chromophobe RCC was limited.

LB47 Molecular dissection of clear cell renal cell carcinoma reveals prognostic significance of epithelial-mesenchymal transition gene expression signature

Nallandhighal S, Vince R, Karim R, Groves S, Stangl-Kremser J, Russell C, Hu K, Pham T, Cani AK, CJ, Zaslavsky A, Mehra R, Cieslik M, Morgan TM, Palapattu GS, Udager AM, Salami S

Background: There is an ongoing need to develop prognostic biomarkers to improve the management of clear cell carcinoma (ccRCC).
Methods: We retrospectively identified two complementary discovery cohorts of patients with ccRCC who underwent: 1) radical nephrectomy (RNx) with inferior vena cava (IVC) tumor thrombectomy (Patients=5, Samples=24); and 2) RNx for localized disease and developed recurrence vs. no recurrence (n=36). Using TCGA ccRCC cohort for validation (n=386), Kaplan-Meier (KM) survival analysis and multivariable cox-proportional hazard testing were utilized to investigate the prognostic impact of cell cycle proliferation (CCP) and a novel 22-gene epithelial mesenchymal transition (EMT) score on progression free survival (PFS) and disease specific survival (DSS).
Results: In the discovery cohorts, we observed over-expression of WT1 and CCP genes in the tumor thrombus vs. the primary tumor, as well as in patients with recurrence vs. those without recurrence. Hallmark pathway analysis demonstrated enrichment of EMT and CCP related pathways in patients with high WT1 expression in the TCGA (validation) ccRCC cohort. CCP and EMT scores were derived in the validation cohort which was stratified into four risk groups using Youden-Index cut points: CCPlow/EMTlow; CCPlow/EMThigh; CCPhigh/EMTlow; and CCPhigh/EMThigh. CCPhigh/EMThigh risk group was associated with the worst PFS and DSS (both p<0.001). In a multivariable analysis, CCPhigh/EMThigh was independently associated with poor PFS and DSS (HR=4.6 and 10.3, respectively; p<0.001).
Conclusions: We demonstrate the synergistic prognostic impact of EMT in tumors with high CCP score. Our novel EMT score has the potential to improve risk stratification and provide potential novel therapeutic targets.

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Q&A with Sallie McAdoo, MS, CGC

Medical Director, *Kidney Cancer Association*

https://doi.org/10.52733/KCJ19n4-q

KCJ: You have a background in clinical genetics and medical affairs, what kind of perspective are you bringing to the role of medical director at KCA and what does this role mean to you?

Sallie McAdoo (SM): It is unusual to have a medical director that is not an MD. But we think for an advocacy group for sure my background was melding together the need for patient education, as well as sort of helping the physician transverse the landscape for genetics, that really made me a good fit to balance the patient and physician sides that we have at KCA and that's how I came on board. I think some of the pushes that I want to do within KCA are really trying to find a way to have those elements complement each other, you need the physician education, as well as the patient education in order to work together to get a really good shared decision making and help empower the patients. And my background in genetics gives me a special interest in the rare kidney cancer forms. So the ones that don't tend to get as much clinical research done, don't tend to get as much education, I am trying to bring awareness to those better classification, that is something I am used to in genetics with genetics being rare a lot of times.

> "The empowerment is really making people understand it's not just information but the knowledge of where resources are available and knowing who and where to go to for the information. We are not only empowering the patients but also their caregivers, who are often the biggest source of support for the patient."

KCJ: You took up this role when the whole world was hit by a pandemic. There is a tremendous hit in cancer research funding and trials as well. How are you managing this on the KCA side at such an unprecedented time?

SM: Well, obviously, clinical trials meant for patients have had a little bit of a slowdown, if not a big slowdown in terms of enrollments and getting patients to visits. So one of the things we decided to do is to go outside of our normal grant program, where we give money for grants that some people have made an exception on due to COVID-19. We're creating more of a large data federation that can be mined while maintaining patient privacy. We reattacked the way we're going to handle research while still doing grants. But we want more data that's available so that the patients don't need to worry about necessarily getting multiple visits, or worry about institutions putting tons of paper together and having people in the office. It's a really cool project that will be launching soon has really allowed us to expand research regardless of getting into the clinic. And I think the second thing for us is even though some of the other things slowed down, we were able to start our Patient Navigator Program in the middle of last year at a really great time. So there's a person answering the phone for the patients that can help direct them to resources that they need especially when they're not really getting as much input and need to step back from their physicians who are focused on other things. And we're able to create more patient programs because our conferences turned to virtual, we have manpower needed to be on site to launch more programs and educational initiatives for the patients as a means of support.

KCJ: How do you want to collaborate with other patient related organizations or associations in the kidney cancer sphere moving forward?

SM: I think historically, KCA has been around the longest, as the others came onboard. We each found our own little niche in terms of what we focus in on in assisting the patients within the research realm. We should start work together to find some projects where we can use our strengths in each of the different organizations to push something forward than doing it separately.

KCJ: Can you give us an overview of how you plan to advance goals and strategic objectives of KCA as the director of KCA?

SM: At KCA, our biggest strengths are education, empowerment, and advocacy. Education is something that can definitely be ongoing. We're continuously trying to keep up with how things have been changing, making sure patients are getting them in a language that they can understand as well as physicians are getting information that is up to date. The empowerment is really making people understand it's not just information but the knowledge of where resources are available and knowing who and where to go to for information. We are not only empowering the patient but also their caregivers, who are often the biggest source of support for the patient. The last thing would be the advocacy side. From the advocacy aspect, we really want to make more of a push for the government to pay attention to kidney cancer as this field does not get as much funding or awareness. For this, we're starting to partner with other organizations. We did have a partnership this year with the Sickle Cell Disease Association of America due to the connection between sickle cell trait and renal medullary carcinoma. We are really trying to start such partnerships to create stronger advocacy to bring more awareness and funding.

KCJ: What is the greatest challenge that KCA is facing now to engage with patients and organizations during the pandemic?

SM: I think the hardest part right now is the burnout that people are experiencing whether it's our pharma partners, the kidney cancer community or the physicians when they're already stretched in terms of their limits on what they can do in this zoom environment that we are on during this pandemic. It's harder to make those connections and get that attention. But I think from a patient perspective, the finances are really hitting them hard as over 40% of our calls are about medical bills, but what is hitting them even harder is help with everyday needs like covering transportation or getting childcare. Everyone is still trying to adjust and get back to whatever may be their new normal, so it is challenging to find resources for patients in a society that's already strapped for resources due to the pandemic. KCA is really making sure we could get those financial resources to the patient.

KCJ: On the KCA front, do you have any research and education initiatives you are looking to expand?

SM: Initially, I've alluded to that data system that we're doing, one side is the patient arm. This is something similar to the breast cancer world, where patients can directly have their records sent to us and we will extract information into a registry of sorts. This registry can be used not only for research, but also to connect patients, mapping them to clinical trials, getting them specific updates for their specific kidney cancer profile, etc. That will serve as a very tailored information source to them, versus patients having to parse through generic information that may not be applicable. It will also allow our pharma partners to find rare kidney cancer patients for specific research initiatives so it can sort of work both ways. And hopefully the registry will help connect patients with rare kidney types together. In the current system, they can't find each other easily. We are calling it the data federation and the patient arm will be launching later this year, which will then be integrated into a multi-center 7 site institution data where the patient information from those institutions will be compiled together for research purposes.

KCJ: Will the KCA launch any new initiatives on the legislative front to increase government funding of kidney cancer research?

SM: That is what we're looking at now to make our legislative push for more robust advocacy in the kidney cancer space. We really want to push for more directed funding and we're just trying to figure out the best way to do that, and who we want to work with in order to get as we mentioned before, make that a little more robust instead of diluting it out. So that's really one of our main focuses as we move into planning for 2022. As far as for the exact strategy, stay tuned on that.

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Exploring beyond observation Checkmate 914 is exploring adjuvant IO regimen for RCC patients

Bristol Myers Squibb is currently conducting a clinical trial exploring immuno-oncology (IO) agents for early-stage, high-risk renal cell carcinoma (RCC): CheckMate 914.

CheckMate 914 is a randomized, Phase 3 clinical trial evaluating adjuvant nivolumab alone or in combination with ipilimumab in patients who underwent radical or partial nephrectomy and who are at high risk of relapse.

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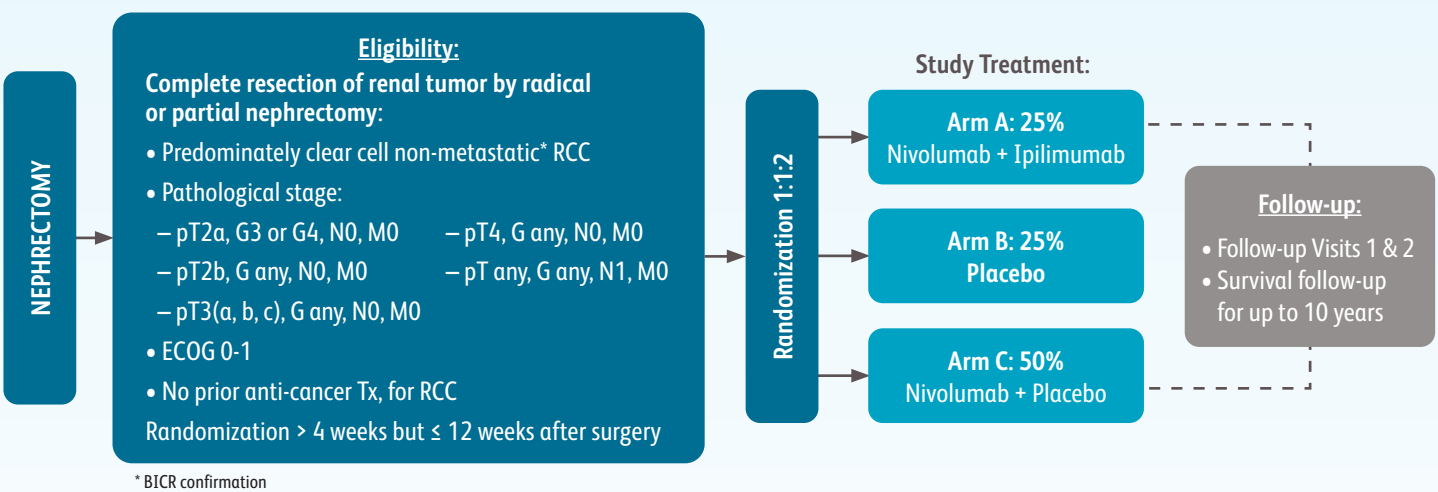
Research post-surgery plans **before** surgery happens. For this clinical trial, randomization must occur between 4 and 12 weeks from the date of nephrectomy

Exploring beyond observation

This study seeks to investigate the role of an IO agent compared to the current standard of care (observation)

CHECKMATE 914 Study Design



* BICR confirmation

To find out if your patients are eligible for this trial, learn more at **BMSStudyConnect.com/KCJ**.

Reference: Data on file. Clinical protocol CA209-914. Princeton, NJ: Bristol-Myers Squibb Company, 2020.

RCC
CheckMate 914
CHECKpoint pathway and nivoluMAb clinical Trial Evaluation

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