Abstracts Highlight Progress in the Fight Against Kidney Cancer - IKCS 2022

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ABSTRACT

The International Kidney Cancer Symposium (IKCS) took place in Austin, Texas November 4-5, 2022, providing an opportunity for kidney cancer researchers, clinicians, patients, and advocates to join together in-person and virtually to explore the latest science and emerging data in the fight again this dreaded disease. Here, we highlight key kidney cancer research updates presented at the meeting. Slides from the meeting's presentations are available on the KCA-IKCS meeting website.

The International Kidney Cancer Symposium (IKCS) took place in Austin, Texas November 4-5, 2022, providing an opportunity for kidney cancer researchers, clinicians, patients, and advocates to join together in-person and virtually to explore the latest science and emerging data in the fight against this dreaded disease.

Dr. David McDermott served as the conference's keynote speaker in a session moderated by Dr. Tian Zhang. Dr. McDermott's talk, entitled "Making Remissions More Common in Kidney Cancer," began with a focus on the rise of immunotherapies such as IL-2, followed by a decline during the development of targeted therapies, and the recent rise of

Figure 1. Oral presentation at the 2022 Kidney Cancer Symposium.

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immunotherapies again with the develop of PD-1/PD-L1 inhibitors. He discussed the importance of appropriate end-points in clinical trials, suggesting that "percent surviving" may provide a clearer picture of both early and late outcomes and a more robust measure of overall success. He ended his talk with a review of strategies being explored to increase immunotherapy effectiveness and elicit more durable remissions in advanced kidney cancers, including novel combination therapies, early work on TIL therapies, novel targets, and vaccines.

A number of oral abstract presentations illustrated knowledge around the basic biologic mechanisms driving kidney cancer. For example, Dr. Allison May presented an abstract that explored the capacity of spatial molecular imaging (SMI) to dissect the tumor immune microenvironment (TiME) and epithelial to mesenchymal transition EMT, specifically in sarcomatoid RCC. It is thought that sarcomatoid renal cell carcinoma (RCC) arises from other forms of the disease, most commonly clear cell RCC via EMT. May and colleagues spatially capture single cell level transcriptomic data from a RCC sample from a responder to immunotherapy and one from a non-responder. Forty fields of view and over 100,000 single cells were captured. They found significant differences in epithelial staining and the immune microenvironment between clear cell and sarcomatoid regions in the sample and unique differences between the immunotherapy responder and non-responder. Although the sample size of this study is too small to draw definitive conclusions, it does demonstrate the utility of this technique in sarcomatoid RCC.

Gemma Davies presented an interesting study of CD200, which along with its receptor CD200R is an immunosuppressive checkpoint which contributes to cancer cell immune evasion. These investigators found that ccRCC CD200 expression contributes to immune evasion by increasing Treg levels and causing activated NK cell dysfunction, apoptosis, and decreased cytotoxic

FIGURE 2. The Keynote speaker Dr. David McDemott delivering an oral talk at IKCS2022

response. They hypothesize that CD200:CD200R checkpoint inhibition may be a potential novel therapeutic target in ccRCC.

Other oral abstracts focused on advancing clinical science of kidney cancer. Dr. Blum presented a biomarker study of 18 patients with renal medullary carcinoma (RMC), in which he and his colleagues evaluated trends among several common biomarkers. They found that the magnitude of both lactic dehydrogenase (LDH) and CA-125 elevation was directly proportional to the total metastatic burden, and that CA-125 levels in widely metastatic patients were more than 200% higher than upper-limit normal. They concluded that biomarkers such as CA-125 may assist in predicting development of metastatic disease, trending treatment response or efficacy, identifying new therapeutic targets in RMC.

Overly stringent clinical trial eligiblity criteria create slow-accruing, lengthy, and expensive trials whose data are not usually generalizable to larger populations. A recent joint statement by the Friends of Cancer Research (FCR) and the American Society of Clinical Oncology (ASCO) has highlighted the need to broaden eligibility criteria in cancer trials to increase patient accrual and enhance the generalizability of study results. Daniela Castro systemically reviewed eligibility criteria in 423 RCC trials in the clinicaltrials.gov database to assess this issue, finding 112 trials that had enough publicly available data to be evaluable. She found that hepatitis, concurrent malignancies, HIV, and brain metastases were among the most frequently cited exclusionary criteria in these studies, and that a substantial proportion of RCC studies incorporated exclusionary criteria deemed by the FCR-ASCO statement to be potentially excessive.

Dr. Causa Andrieu presented a large database study of 25,200 patients who underwent germline analysis to investigate prevalence and features of rare hereditary RCC, including Hereditary Papillary Renal Carcinoma (HPRC), Birt-Hogg-Dube syndrome (BHDS), BAP1 tumor predisposition syndrome (TPDS), and Hereditary Paraganglioma/ Pheochromocytoma syndrome (PGL/PCC). Prevalence of related gene mutations were: MET: 1 mutation (with associated RCC) out of 25,000 (0.004%); FLCN: 17/25000 (0.067%), 23.5% of which had RCC; BAP1: 22/25000 (0.087%), 18.2% with RCC; and SDH: 39/25000 (0.155%), 23.1% with RCC.

Nazli Dizman presented the long-term follow-up results of a randomized phase Ib trial of 29 patients with metastatic RCC treated with nivolumab/ipilimumab (nivo/ipi) with or without CBM588, a bifidogenic live bacterial product. Overall response rate (ORR) was 20% in the control arm and 58% in those receiving CBM588 in addition to immunotherapy. Disease control rate was 79% in the experimental arm, compared to 20% those who did not receive CBM588. . Median progression free survival (PFS) was 36.4 (95% CI 9.4-63.5) months in the CBM588 arm versus 2.5 (95% CI 2.0-2.9) months in those receiving nivolumab and ipilumumab without CMB588. Median duration of response was 36.4 (95% CI 20.6-52.2) months in the experimental arm versus 4.5 (95% CI NA-NA) in the control arm. Median overall survival was not reached in either arm. The study was limited by small sample size, but the impressive results warrant further investigation of gut microbiome modulation in patients receiving immunotherapy for RCC.

Karie Runcie presented results of a trial exploring the ideal timing of holding neoadjuvant cabozantinib and nivolumab prior to nephrectomy, evaluating the safety of 14 days vs 21 days between discontinuation of cabozantinib and surgery. The study concluded that the combination of cabozantinib and nivolumab can be safely administered up to 14 days prior to cytoreductive nephrectomy.

Ritesh Kotecha presented an analysis of genetic ancestry and its molecular correlations within subtypes of RCC. The study analyzed 953 patients and found differences in histology, stage at presentation, rate of poor-risk disease, and genetic alterations among different ethnic groups. These researchers concluded that population-specific variations do exists in patients of different ancestry, however, it is challenging to determine what role genetic and non-genetic (social determinants of health for example) factors might play into creating the disparities seen amongst populations.

In addition to oral abstract sessions, more than 45 abstracts were selected for poster presentations,

amongst these were abstracts that focused on optimizing clinical aspects of kidney cancer management. For example, Dr. Sven Lundstam presented results of a study aimed at exploring the development of end-stage renal disease (ESRD) following treatment for RCC. They identified 215 patients with RCC and subsequent ESRD and compared these to 9,299 patients with RCC without ERSD from the National Swedish Kidney Cancer Register. The incidence of ESRD after diagnosis of RCC was 2.5%, ten times higher than in the control population. Radical nephrectomy compared to partial nephrectomy or tumor ablation was a significant risk factor during the first year following surgery, while male sex, advanced T-stage, diabetes, hypertension, chronic kidney disease were significant risk factors over a 5 year period following surgery.

Similar to exploring risk factors for ERSD in RCC patients, it is equally important to be able to predict which RCC are at higher risk for developing cardiotoxicity. Dr. Hesham Yasin presented a project that used artifacial intelligence (AI) to accurately predict which RCC patients had the highest cardiotoxicity risk. Dr. Yasin and colleagues suggested that integration of such AI models into electronic medical records (EMR) would assist physicians with identifying patients at highest risk and allow for expedited, proactive referrals for cardio-oncology treatment/monitoring.

Several abstracts explored various nuances of cytoreductive nephrectomy (CN), including one by Pranjal Agrawal that non-clear cell RCC histology doesn't negatively impact survival outcomes after CN for metastatic RCC compared to clear cell RCC, and another poster by the same author that showed inferior vena cava (IVC) tumor thrombectomy with concurrent CN is associated with surgical morbidity, but similar survival as compared to who underwent CN without IVC tumor thrombectomy. A poster by Dr. Andrew Hahn explored CN in patients with metastatic sarcomatoid and/or rhabdoid RCC who were treated with immune checkpoint therapy. This study found that CN offered no difference in immunotherapy treatment duration or differences in survival.

A study presented by Dr. Kelly Fitzgerald retrospectively analyzed 173 real-world patients undering first line combination therapy for metastatic clear cell RCC and found a significant difference in depth of response between those receiving combinations of two immunotherapies vs an immunotherapy and a targeted-therapy. More objective responses were seen in those receiving targeted-therapy based combinations (65%) compared to immunotherapy-only combinations (38%).

Several abstracts updated data from large prospective trials, such as the Checkmate 214 study which randomized patients to receive untreated metastatic RCC patients to receive nivolumab and ipilimumab versus sunitinib. At 60-months, treatment free survival (TFS) for favorable-risk patients was 14.4 months in the combination arm 5.5 months in the control arm, while TFS for intermediate/poor-risk patients at 60-months was 10.1 vs. 4.1 months.

An updated analysis from the CLEAR trial showed that metastatic ccRCC patients who completed 2 years of pembrolizumab combined with lenvatinib had an overall survival rate of 94.5%. A long-term analysis of the TIVO-3 study found that PFS was superior with tivozanib compared to sorafenib in second and third line metastatic RCC patients. Mean PFS rates were 12% and 7.6% at 3 and 4-years for those receiving tivozanib compared to 2% and 0% for those on the comparator arms during the same time periods.

Finally, a poster presented by Dr. Stephen Reese described features of NF2-mutated RCC, a lethal unclassified form of kidney cancer, which metastasizes early and is associated with a 18-month survival in this cohort. A number of posters also described trials in progress among other abstracts.

In summary, abstracts from IKCS 2022, continued to show the diverse work being done around the country and around the world in the fight against kidney cancer.