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Caris Life Sciences’ Multiplatform Tumor Profiling Helps to Identify Potential Predictive Biomarkers in Renal Cell Carcinoma

Research Presented at 2015 Genitourinary Cancers Symposium Provides Potential Implications for Choice of Therapy and Clinical Trial Participation

Irving, Texas, Feb. 26, 2015 – Caris Life Sciences® today announced the presentation of two posters at the 2015 Genitourinary Cancers Symposium in Orlando, Fla., one of which was selected for the Audio Poster Tour. Both studies utilized Caris Molecular Intelligence™, the company’s panomic, comprehensive tumor profiling service. These studies showed that panomic testing can help identify potential predictive biomarkers in renal cell carcinomas (RCC), providing insights that may drive selection of therapy and clinical trial participation.

In one of the RCC presentations, researchers reported that Caris Molecular Intelligence facilitated identification of 30 different clinically relevant biomarker results in a clear-cell renal cell carcinoma (ccRCC) cohort, in which 12 were gene alterations. All but one of the 166 cases had identified a clinically actionable target as a means to predict responses to currently available targeted therapies. In a separate presentation, use of Caris Molecular Intelligence led researchers to conclude that chromophobe renal cell carcinoma (chRCC), a rare subtype that accounts for 5% of RCC cases, may be amenable to certain types of chemotherapy, based on the expression (or lack thereof) of various predictive biomarkers. In the 12 chRCC cases studied, researchers identified 15 different clinically relevant biomarker results, none of which were gene alterations (NGS). In this study, 100% of chRCC cases had identified a clinically actionable target.

Both studies, to be presented on Saturday, February 28, 2015, utilized Caris Molecular Intelligence’s multi-platform approach, which included gene sequencing (Sanger and next-generation sequencing [NGS]), protein expression analysis (immunohistochemistry [IHC]), and gene copy number analysis (chromogenic or fluorescence in situ hybridization [CISH or FISH]). Investigators in each study examined tumor samples for underlying molecular alterations that may yield potentially different therapeutic options for patients with RCC.

“The advent of targeted therapy has greatly expanded the range of treatment options for renal cell carcinoma, but practicing oncologists need to be able to identify which patients are likely to respond to these therapies,” noted Sandeep K. Reddy, M.D., Chief Medical Officer at Caris Life Sciences, and a co-investigator in each of the two studies. “The data presented at the Genitourinary Cancers Symposium demonstrate how multiplatform molecular profiling, beyond just DNA sequencing, with Caris Molecular Intelligence can provide therapeutic guidance by identifying biomarkers predictive of response to specific agents, and may also inform clinical trial design.”
Caris now offers custom multiplatform testing for key markers that define recently identified subtypes of RCC, such as \textit{SETD2}, \textit{PBRM1}, as well as immuno-modulatory proteins.

**RCC Study Highlights**
Researchers used Caris Molecular Intelligence to identify potentially actionable recurrent molecular abnormalities in 166 RCC samples. The samples were subtyped into clear cell (ccRCC, n=91), papillary (PRCC, n=20), sarcomatoid (n=21), translocation (n=6), or medullary RCC (n=4). Nearly two-thirds (63%) of the tumor samples were metastatic.

Researchers observed that VHL mutations were identified in 50% of ccRCC tumors. Loss of PTEN, a tumor suppressor protein, was observed in 52% of ccRCC samples and in only 21% of PRCC samples ($P=0.02$). All four of the ccRCC samples with sarcomatoid features showed aberrant expression of the programmed cell death protein ligand 1 (PD-L1) and were infiltrated with PD-1-positive tumor-infiltrating lymphocytes; all tested non-ccRCC sarcomatoid samples also had aberrant expression of PD-L1. Sixty percent of the ccRCC samples exhibited loss of expression of PBRM1, a tumor suppressor gene. Loss of histone 3 lysine 36 trimethylation (H3K36me3), which is associated with \textit{SETD2} mutations (which also play a role in tumor suppression), was observed in 30% of ccRCC samples.

Half (50%) of the studied samples exhibited overexpression, amplification, or mutation of cMET, a receptor tyrosine kinase implicated in cancer development and progression. Investigators observed lower rates of mutation of the \textit{TP53} oncogene (14%), the oncogenic protein ATM (6%), and the \textit{PIK3CA} oncogene (4% ccRCC, 7% PRCC) than are typically seen in other cancers.

“Our findings have potential implications for therapeutic decision-making in patients with RCC, in that \textit{PIK3CA}, cMET pathway alterations may be a therapeutic target, and preliminary evidence suggests that RCC with sarcomatoid features may respond to immunotherapies targeting PD-1 or PD-L1,” noted lead investigator Thai Ho, M.D., assistant professor of medicine in the Division of Hematology/Oncology at the Mayo Clinic Cancer Center in Scottsdale, Ariz. “Molecular profiling thus appears to be particularly useful in evaluating clear cell RCC, and may inform future clinical trials by identifying kidney cancer epigenetic subtypes.”

**Chromophobe RCC Study Highlights**
Investigators used Caris Molecular Intelligence to evaluate tumor samples from 12 patients with chRCC, including five with metastatic disease, which is notable because chRCC infrequently metastasizes or recurs after definitive local therapy. None of the tumors expressed thymidylate synthase (TS), a protein involved in making and repairing DNA, and which may influence tumor formation and response to treatment when expressed at high levels. Similarly, absence of the ribonucleotide reductase M1 (RRM1) and O-6-methylguanine-DNA methyltransferase (MGMT) proteins, indicative of increased carcinogenic risk, was reported in 11 of 12 tumors. PTEN was absent in seven tumors.

Expression of cKIT was observed in six of nine tumors assayed for this oncogenic protein. By contrast, the platelet-derived growth factor receptor (PDGFR), which regulates cancer cell growth, development, and proliferation, was absent in all four tumors assayed for this marker. Additionally, point mutations in the APC and \textit{TP53} oncogenes were detected in one of seven and in three of seven tumors, respectively. The investigators did not identify any mutations in the other 45 genes tested; nor did they detect any changes in copy number.
“Based on biomarker analysis, we speculate that 5-fluorouracil, gemcitabine, or temozolomide might be active in advanced chromophobe RCC because of the lack of expression of TS, RRM1, and MGMT, respectively,” observed Philip Abbosh, M.D., Urologic Oncology Fellow at Fox Chase Cancer Center in Philadelphia, Pa. “Such an approach has been used successfully in targeted treatment of other cancers. Our findings also suggest that sunitinib or imatinib, but not sorafenib, may be preferable to tyrosine kinase inhibitors in this patient population, as we detected expression of cKIT but not of PDGFR.”

About Caris Life Sciences® and Caris Molecular Intelligence™
Caris Life Sciences® is a leading biosciences company focused on fulfilling the promise of precision medicine through quality and innovation. Caris Molecular Intelligence™, the industry’s leading tumor profiling service with more than 68,000 patients profiled, provides oncologists with the most potentially clinically actionable treatment options available to personalize cancer care today. Using a variety of advanced profiling technologies to assess relevant biological changes in each patient’s tumor, Caris Molecular Intelligence correlates biomarker data generated from a tumor with biomarker-drug associations supported by evidence in the relevant clinical literature. The company is also developing a series of tests based on its proprietary Carisome® TOP™ platform, a revolutionary blood-based testing technology for diagnosis, prognosis, and theranosis of cancer and other complex diseases. Headquartered in Irving, Texas, Caris Life Sciences offers services throughout Europe, the U.S., Australia and other international markets. To learn more, please visit www.CarisLifeSciences.com.

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