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Multi-Platform Molecular Profiling from Caris Life Sciences Identifies Clinically Actionable Targets for Novel Immunotherapy Drugs

ASCO Presentations Highlight Therapeutic Implications of PD-1/PD-L1 Expression and Interaction with Signaling Pathways in Patients with Colorectal and Pancreatic Cancers

IRVING, Tex., May 29, 2015 – Caris Life Sciences® today announced the presentation of data from two studies in which researchers utilized Caris Molecular Intelligence®, the company’s panomic, comprehensive tumor profiling service, to identify potential therapeutic targets in patients with colorectal and pancreatic cancer subtypes, based on expression of the programmed cell death protein 1 (PD-1) and its ligand, PD-L1. The findings, presented on June 1 at the 2015 American Society of Clinical Oncology Annual Meeting (ASCO) in Chicago, Ill., underscore the importance of PD-1/PD-L1 expression in various oncogenic signaling pathways, providing insights that may inform targeted treatment strategies in certain patient populations.

“As more is learned about the role of PD-1 and its ligands in down-regulating the immune system, and as anti-PD-1 agents, such as pembrolizumab and nivolumab, are further investigated in clinical trials, there is a greater need to identify patients who are likely to respond to these so-called immune checkpoint inhibitors, based on molecular characterization of their tumors,” said Wafik El-Deiry, M.D., Ph.D., Deputy Director and Program Leader at Fox Chase Cancer Center in Philadelphia, Pa. “The latest data presented at ASCO shed light on the apparent relationships between PD-1/PD-L1 expression and key oncogenic drivers in subpopulations of patients with colorectal and pancreatic cancers.”

Dr. El-Deiry and colleagues presented data suggesting that PD-1/PD-L1 protein expression is inversely associated with KRAS mutation status in patients with microsatellite instability high (MSI-H) colorectal cancer (CRC), a tumor sub-type that comprises roughly 15% of CRC cases and is characterized by higher expression of PD-1 in tumor-infiltrating lymphocytes compared to non-MSI-H (abstract #152887). Using Caris Molecular Intelligence, the investigators conducted Immunohistochemistry (IHC) and mutation analysis to profile 55 MSI-H tumors for protein aberrations, as well as potential target mutations in order to compare high (P+) versus low (P-) expression of PD-1/PD-L1 in tissue samples. Of the 55 tumors analyzed, 39 (71%) were P+ and 16 (29%) were P-. Only 27% of the P+ tumors harbored a KRAS mutation, while 62% of the P- tumors had a KRAS mutation (p=0.04). Additionally, Dr. El-Deiry noted that expression of human homologue of Groucho, transducer-like enhancer of split orthologue (TLE-3), a known inhibitor of Wnt signaling and a marker of sensitivity to taxane therapy, was 43% in P+ tumors and only 8% in P- tumors (p=0.04), a finding that suggests the potential utility of taxanes in patients with P+ MSI-H CRC in clinical trials.

“The apparent inverse association between PD-1/PD-L1 protein expression and KRAS mutation status is directly relevant to clinical trials testing immune checkpoint inhibitors in MSI-H colorectal cancer,”
commented Dr. El-Deiry. “The signaling between KRAS mutation and low or absent PD-1/PD-L1 should be further investigated, as should the role of TLE-3 expression, which may dampen beta-catenin signaling in tumors that highly express PD-1 or PD-L1.”

In a second study (abstract #4124), researchers utilized Caris Molecular Intelligence to analyze 450 pancreatic adenocarcinoma (PAC) specimens for incidence of BRCA1 and BRCA2 mutations, while also evaluating expression levels of PD-1 and PD-L1 tumor infiltrating lymphocytes (TILs). Mutations in BRCA1 and BRCA2, which are associated with increased risk of pancreatic cancer, were detected in 5% and 17% of tissues, respectively, while overexpression of PD-1 and PD-L1 TILs were also identified in 37% and 7% of PAC cases, respectively. Compared to the general pancreatic cancer population, the BRCA1-mutated cases had a higher incidence of PD-1 TILs, while BRCA2-mutated cases had a higher incidence of overexpressed PD-L1.

“The BRCA mutation patterns observed in this study are intriguing, particularly in light of recent retrospective studies describing response to platinum agents and PARP inhibitors in patients harboring these mutations,” commented David Iannitti, M.D., Chief of Hepatobiliary and Pancreatic Surgery at the Carolinas Cancer Center in Charlotte, N.C. “The different frequencies of key oncogenic drivers between the overall pancreatic adenocarcinoma population and the BRCA-mutated populations may inform driver differences and may facilitate selection of drugs and refinement of therapeutic decision-making for certain patients. Evaluating the profiles of the BRCA-mutated populations with clinical outcomes will provide valuable insights into the clinical behavior in genomically defined subsets and may facilitate development of rational combinations of targeted agents in pancreatic adenocarcinoma, a challenging disease with overall single-digit five-year survivorship.”

About Caris Life Sciences®
Caris Life Sciences® is a leading biotechnology company focused on fulfilling the promise of precision medicine through quality and innovation. Caris Molecular Intelligence®, the company's healthcare information and comprehensive tumor profiling service with more than 70,000 patients profiled, provides oncologists with the most 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 connects biomarker data generated from a tumor with biomarker-drug associations supported by evidence in the relevant clinical literature. Since 2009, Caris has tracked clinical and outcome data for certain patients undergoing tumor molecular profiling, for which Caris has observed that patients treated with drugs consistent with their molecular profile show a significant increase in overall survival. The company is developing its Carisome® TOP™ technology, a revolutionary and proprietary blood-based platform for the development of novel therapeutics, drug delivery and drug target identification. The technology is also being developed 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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