Liquid biopsies find distinct genomic profiles in most patients with carcinoma of unknown primary

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Bottom Line: Next-generation sequencing of circulating tumor DNA (ctDNA) identified distinct genomic profiles with potentially targetable alterations in 99.7 percent of patients with carcinoma of unknown primary (CUP) who have detectable alterations.

Journal in Which the Study was Published: *Cancer Research*, a journal of the American Association for Cancer Research.

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Background: CUP is a rare metastatic disease with no identifiable primary tumor with an incidence of 7 to12 cases per 100,000 per year. "There is a large unmet need in the CUP patient population. Response to standard platinum-based combination chemotherapy is modest at best and overall median survival is poor, about six to eight months," said Kato.

How the Study Was Conducted and Results: Using liquid biopsies from 442 patients with CUP, the researchers interrogated 54 to 70 genes in ctDNA using next-generation sequencing. They found that a total of 66 percent of patients had at least one characterized genetic mutation and 43.9 percent harbored two or more. The most prevalent variants were found in the genes TP53, KRAS, PIK3CA, BRAF and MYC. Among CUP patients found to have at least one characterized alteration, 99.7 percent of patients had theoretically actionable genetic mutations, either with off-label use of FDA-approved agents or agents currently under investigation.

Next, the researchers conducted two case studies to demonstrate the clinical relevance of their findings. In the first case, which was evaluated by Dr. Brian Leyland-Jones and colleagues who collaborated from Avera Cancer Institute, they analyzed a series of five liquid biopsies from a woman with metastatic CUP and identified dynamic changes in ctDNA that corresponded to therapeutic interventions. "This case demonstrated that cancer can change dramatically during treatment and the changes can be identified using simple blood tests to allow for customizing therapies," Kato explained.

In the second case, the investigators matched a patient, with adenocarcinoma of unknown primary with liver and abdominal lymph node metastases harboring KRAS and MLH1 mutations, to combination treatment with trametinib (Mekinist), a MEK inhibitor targeting downstream KRAS mutation, and nivolumab (Opdivo), an anti-PD1 checkpoint inhibitor. Within eight weeks, the patient had a partial response (36.4 percent tumor reduction) and a rapid decline in tumor marker CA-19-9, an antigen used to monitor treatment response.

Authors' Comments: "Our research is the first to show that we can use a simple blood test to evaluate ctDNA effectively in this difficult to diagnose patient population," said Kurzrock. "This is important because, with CUP, it has been problematic to determine how to treat patients."

"Our results show that ctDNA evaluation is feasible in CUP and that most patients have a unique

somatic profile with pharmacologically actionable mutations," she added. "Liquid biopsies can be used to guide and evaluate treatment response in patients with CUP and should be included in next-generation clinical trials."

Study Limitations: CUP diagnosis was reported by referring physicians and the database was de-identified, so it was not possible to evaluate clinical characteristics and outcomes.

More information: Shumei Kato et al, Utility of Genomic Analysis In Circulating Tumor DNA from Patients with Carcinoma of Unknown Primary, *Cancer Research* (2017). DOI: 10.1158/0008-5472.CAN-17-0628

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