genomeweb

CRAIN June 7, 2021

Lucence Presents New Data on Liquid Biopsy for Late-Stage Cancer Monitoring, Treatment Guidance

By John Gilmore

NEW YORK – Precision oncology assay developer Lucence has shared new real-world validation data from two Asian cohorts that it believes demonstrates the ability of its AmpliMark liquid biopsy platform to detect and guide treatment decisions for late-stage cancers.

The firm's data also highlighted the assay's use in multiple cancers, supporting its expansion into cancer types beyond non-small cell lung cancer, or NSCLC.

AmpliMark uses amplicon-based next-generation sequencing and the firm's proprietary SunTzu.AI clinical analytics engine to detect alterations in up to 80 cancer-related genes, microsatellite instability, and cancer-causing viruses using cell-free DNA samples. Lucence, which has locations in Singapore and Palo Alto, California, has launched a laboratory-developed test called LiquidHallmark, based on the AmpliMark platform, for selecting targeted therapies and monitoring treatment response.

At the American Society of Clinical Oncology annual virtual meeting last week, the firm and its collaborators shared two study abstracts detailing the use of AmpliMark and LiquidHallmark to monitor treatment outcomes in NSCLC patients, as well as identify cancer-linked biomarkers in plasma samples for additional cancer types.

Wei Wu, a cancer genomics researcher at the University of California, San Francisco, shared data regarding the use of a custom 61-biomarker panel based on the LiquidHallmark assay to monitor various treatment outcomes in NSCLC patients.

Wu's team collected blood samples from 142 patients with advanced NSCLC at baseline and following immune checkpoint inhibitor, or ICI, therapy. The group characterized the mutational landscape of advanced NSCLC in the Asian cohort with LiquidHallmark, comparing the results with a Caucasian late-stage NSCLC patient dataset that his group published in a Nature Genetics study in 2017.

Wu said his team spotted several differences between the two cohorts. For example, the researchers found that concurrent KRAS and EGFR mutations were higher in the Asian cohort (4 percent) than Caucasian cohort (0.56 percent).

"We [were] trying to understand the evolution of advanced lung cancer during treatment, how the new mutation occurs, and how it's associated with drug resistance," Wu explained. "We [then] tried to understand and compare the genetic discrepancy between Caucasian and Asian populations … and how that [was] associated with treatment outcomes."

The group also found that the frequency of EGFR mutations in the samples was three times as high in Asian NSCLC patients than in Caucasian NSCLC patients. In addition, CTNNB1 and SMAD4 alterations were lower in the Asian cohort than the Caucasian cohort.

Wu and his colleagues also observed that first-line tyrosine kinase inhibitor, or TKI, responders had more genetic alterations in the EGFR-mutant cohort than non-responders. Concurrent mutated genes and copy number alterations in the advanced EGFR-mutant NSCLC cohort were enriched in RTK, PI3K-AKT, and WNT signaling pathways. Wu believes that certain individual gene mutations may therefore be redundant in the specific pathway.

"For example, if you look at the RTK gene mutations, they're not just one gene, but multiple genes in the family that have the same consequence," Wu explained. "We looked collectively at those pathway-related genes and classified genes into a specific pathway … [and therefore] you target the pathways instead of individual mutated genes."

Meanwhile, ICI therapy responders from first-line or second-line treatment exhibited a higher mutant allele frequency, or MAF, distribution, as well as fewer mutations, than non-responders.

Wu's team therefore believe that AmpliMark may be useful in identifying a high proportion of actionable biomarkers in lung cancer patients.

Based on the results of the study, Wu aims to observe differences in patient survival outcomes if disease-free survival or overall survival data is available. Noting that the reference data stemmed from a different cfDNA-based diagnostic platform (Guardant Health's Guardant360 assay), Wu aims to compare both datasets using LiquidHallmark in a follow-up study.

In a separate validation trial, Lucence's researchers gathered 1,338 plasma samples from patients in Southeast Asia with lung, breast, colorectal (CRC), pancreatic, and gynecological cancers, and cancers of unknown origin — including 86 percent with metastatic cancers — from January 2018 to November 2020.

"We had a lot of [patients] diagnosed with cancer, characterized with other tests, [that] had been on treatment but then were experiencing … progression," Yukti Choudhury, chief technology officer and cofounder of Lucence, explained. "The assay doesn't

require a lot of starting DNA material, [so] we can work with limited amounts of DNA."

Using two to three 10-ml tubes of plasma per sample, Choudhury's team analyzed genomic alterations in the circulating tumor DNA, or ctDNA, in each patient's sample using LiquidHallmark with 80 genes that she said were "relevant in specific cancer types." The group established limits of detection of 0.1 percent variant allele frequency, or VAF, for single-nucleotide variants and indels, 0.5 VAF for gene fusions, 5 percent tumor fraction for microsatellite instability, and two viral particles per ml.

LiquidHallmark detected about 70 percent of total ctDNA in each of the cancer types (1,272 samples), from about 76 percent of metastatic and 25 percent of localized tumors, with an analytical specificity of 99 percent, Choudhury said. Among the 2,117 detected alterations, the assay had a median VAF of about 1.4 percent.

Choudhury pointed out that LiquidHallmark had a high sensitivity for actionable mutations, as roughly 75 percent (484) of ctDNA-positive lung cancers had at least one or more mutations. The team also saw that almost 30 percent of lung cancers treated with either EGFR TKI therapy or osimertinib (AstraZeneca's Tagrisso) harbored resistance mutations, including EGFR amplifications, PIK3CA alterations, and KRAS alterations.

Choudhury acknowledged that the analytical sensitivity of about 70 percent in lung cancer samples "skews the overall average" because most of the mutations were found in lung cancer. In contrast, her team did not find as much ctDNA in certain cancers due to their low mutation rate, such as nasopharyngeal and liver cancers.

"Those [cancers] would be characterized by methods like viral biomarker [detection], which is one aspect of the assay," Choudhury said. "But it's still very informative, since the cancers are characterized by viral infections using the liquid biopsy assay."

However, Choudhury's team did find that viral targets in the plasma samples allow for cancer monitoring, even in "low genetic biomarker prevalence settings."

LiquidHallmark detected PIK3CA and ESR1 mutations in 44 percent of hormone receptor-positive, HER2-negative breast cancers, which Choudhury pointed out are treatable with alpelisib (Novartis' Piqray). The firm also identified anti-EGFR resistance mutations in 50 percent (112) of all CRC plasma samples.

"We need to characterize the mutation to understand what [drugs] they are sensitive to," Choudhury said. "This is a benefit that liquid biopsy affords, [but] it needs to be a sensitive enough method to pick up and look at a broad range … of changes that can emerge post treatment."

Choudhury also highlighted that her team was able to narrow down the potential source of about 20 samples from individuals with cancers of unknown origin.

"Some mutations are characteristic of tumor type … for example, if it's a particular KRAS mutation, we can narrow it down to pancreatic and colorectal cancer," Choudhury explained. "If you look at a specific mutation, that can help characterize which primary tumor the error came from."

Based on the mutational profiles that can be gathered using the assay and other clinical information, the researchers believe the assay can potentially help clinicians narrow down cancer diagnoses and make appropriate treatment decisions for patients.

"We are able to use an amplicon-based liquid biopsy assay [that] is sensitive … and that is highlighted by the fact that [in] the sum total of all the mutations found, the median of the [MAF] is quite low," Choudhury said. "If we didn't have these ultrasensitive methods, a lot of these mutations would be missed, which means a lot of the clinically actionability inherent to these mutations would not be found."

Choudhury's team anticipates submitting the full and updated results of the trial, as well as "detailed analytical orthogonal validation results" using the technology, by the end of the year.

Meanwhile, Wu expects to gather more data from the Asian NSCLC cohort and eventually publish a study comparing the overall genetic discrepancies in NSCLC mutations between the Asian and Caucasian populations.

"The assay is able to detect these meaningful mutations in the clinical setting, with which clinicians can make decisions, whether it's just post-diagnosis during the course of treatment," Choudhury added.

Min-Han Tan, CEO and cofounder of Lucence, said in an email that the studies highlight the firm's liquid biopsy capabilities in profiling lung cancer mutations. Oncologists can currently order the assay through Lucence's CLIA labs in Singapore and the Bay Area to help guide treatment in patients with certain cancer types, and Tan said that the firm will continue to explore the test's diagnostic and minimal residual disease performance in hematological cancers.

"Our long-term commercial plans involve the development of sequencing and cell-based liquid biopsy testing for early cancer detection and treatment selection," Tan said. "We expect this to proceed sequentially from lung cancer progressively to other major cancers, such as breast, colon, and hematological cancers."

Outside North America, Tan said that Lucence expects to grow LiquidHallmark's reach progressively in the next two years into South America, Asia, Africa, and Europe.