Versatile ctDNA Put to the Test

ASCO 2021

Circulating tumor DNA (ctDNA) is a part of the cancer secretome (in addition to circulating tumor cells (CTC), extracellular vesicles (EV), proteins) that is a useful surrogate tool in drug development and clinical practice. Compelling evidence is steadily accumulating on its broad utility across a cancer patient's continuum.

More than 40 presentations, with ctDNA included in the analysis, were presented at ASCO 2021, representing a significant milestone validating the clinical utility of ctDNA. SmartAnalyst summarizes key evidence presented on the potential role of ctDNA in solid tumors, beyond the recognized patient enrichment strategies.

ctDNA has the potential to optimize treatment in early stage disease

Residual ctDNA detection has the potential to identify 'at risk' early stage solid tumor patients who are inadvertently 'misidentified' when using traditional imaging or biochemical techniques, in a post-definitive treatment setting.

- **In early stage NSCLC patients, presence of ctDNA reliably predicted disease recurrence ~7 mos prior to clinical progression as indicated by poor survival (shorter OS, RFS)[1]**
  - A highly sensitive and customized RaDaR assay (Inivata) that detects low levels of ctDNA (mutant allele fractions (MAF) below 0.01%) was employed in the LUCID study, in Stage I-III NSCLC (n=88) patients treated with curative intent.

- **Guardant Reveal minimal residual disease (MRD) assay was validated in NSCLC and bladder cancer patients, after proving its effectiveness as a surveillance and risk assessment tool in CRC patients[2]**
  - This assay distinguishes between cancerous tumor and non-tumor signals without the need for tissue biopsy and has the potential for favorable clinical adoption in tumors that pose challenges with tissue procurement, particularly following neoadjuvant therapy, and enables faster time to results.
  - Guardant Reveal is a single NGS custom panel for detection of differential methylation and genomic alterations in ctDNA.
  - ctDNA-based MRD was detected with >95% specificity in early stage NSCLC (n=89) and bladder cancer (n=86) plasma samples with comparable sensitivities to tissue-based approaches.

- **Clinical Genomics Pathology's COLVERA assay, earlier proven to be an improved method to detect recurrence in early stage CRC patients using ctDNA (vs. CEA/imaging), now reported optimization of actionability and clinical performance in a study[3]**
  - COLVERA assay is qPCR based to detect hypermethylation of BCAT1 and IKZF1 genes known to exist in 95% of CRC.
  - In the two CRC cohorts (n=322, n=144), COLVERA assay improved specificity (detected recurrence in 98% of patients), improved positive predictive value and high NPV (only ~4% ctDNA negative patients will have recurrence) in CRC patients where current surveillance methods (imaging and CEA levels) have limitations in being sensitive and specific.

In addition to providing predictive value, ctDNA can have multidimensional roles in advanced stages

- **ctDNA clearance can be a surrogate marker for clinical response[4]**
  - Tepotinib's VISION study in pre-treated NSCLC patients (n=99) confirmed that >75% depletion of MET exon 14 variant allele frequency (VAF) in ctDNA was associated with better clinical efficacy (ORR: 76%, mPFS: 11 mos) using Guardant360 CDx.
  - Increase of MET exon 14 VAF was associated with no response/short PFS (ORR: 0%, mPFS: 5.5 mos).

- **ctDNA can identify secondary patient populations[5]**
  - KRASG12C mutations with STK11 and/or KEAP1 mu are known to be associated with inferior outcomes than STK11/KEAP1 WT, which was also confirmed by ctDNA analysis of L1 NSCLC patients (n=63) of the BFAST (Blood First Assay Screening trial) study.
  - Evidence with G12Ci (Sotorasib/Adagrasib) suggests differential activity in the presence of co-occurring STK11/KEAP1 Mu that may drive their testing for optimizing outcomes in G12C Mu patients.

- **ctDNA can detect temporal changes in mutations to optimize treatement in progressing patients, per studies in advanced CRC[6,7]**
  - ctDNA-guided rechallenge can avoid futile treatment in ~30% clinically ineligible patients treated with prior EGFRi (identified as L1 RAS/RAF WT CRC patients, n=20).
  - The remaining 70% RAS WT patients were rechallenged with anti-EGFR (cetuximab + irinotecan, or panitumumab) that resulted in ~30% ORR, mPFS of 3-4 mos, and mOS of ~7 mos.

- **ctDNA-based predictive biomarker analysis may be superior to tissue-based for complex biomarkers such as TMB-H, across solid tumors[8]**
  - 5,610 samples from patients with different cancer types underwent clinical ctDNA testing using Guardant360 Dx assay.
  - bTMB scores trended higher than tTMB previously reported in these cancer types, reflecting ability of ctDNA to better capture tumor heterogeneity (currently a tTMB-H CDx is approved with pembrolizumab).
  - Establishes a pan-cancer benchmark for bTMB for future development

Colossal efforts to address the issues with ctDNA (low signal-to-noise ratio, concordance) and expand its utility re-affirm its potential to play a significant role in clinical practice and drug development.

References:

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SmartAnalyst is helping clients interpret the data presented at ASCO 2021 (June 4-8) focusing on key developments in cancer research.
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