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precision medicine for all

ASCO 2016 Abstracts

Lyle S, Powers W, Xu J, et al. Comparison of a large NGS panel to hot-spot testing and small panels for the ability to accurately stratify advanced colorectal cancer patients to appropriate treatment pathways. J Clin Oncol 34, 2016 (suppl 4S; abstr 510). http://meetinglibrary.asco.org/content/160314-173

Importance: It is well established that KRAS mutations confer resistance to anti-EGFR therapy for colorectal cancer patients. More recently, other RAS mutations (NRAS and BRAF) have been determined to cause similar resistance and treatment guidelines are changing to incorporate testing of these genes as well. In addition, evidence suggests that mutations outside of hot-spot regions (Codons 12 and 13 of KRAS and NRAS; BRAF V600E) can also mediate therapeutic response. Recent data also suggest that other genes are relevant for treatment planning.

Results: 40% of samples contained a KRAS hot-spot mutation. When expanded to NRAS and BRAF hot-spots, an additional 8% of patients were identified as resistant to anti-EGFR therapy. An additional 15% of clinically significant variants were captured by full-gene sequencing of these 3 genes. Thus, > 25% of mutations lie outside traditional hot-spot regions. The majority of BRAF mutations were not V600E. The 415 gene panel identified clinically significant driver mutations in 99% of patients, while in smaller panels missed a significant number of actionable changes. In very few patients were actionable changes limited to KRAS, NRAS and BRAF hot-spots.

Conclusions: Hot-spot testing and small gene panels can miss clinically significant genomic alterations. The detection of mutations outside of small panels and hot-spots may lead to more appropriate and successful treatment of colorectal cancers.

Jiang J, Eifert C, Lyle S, et al. Clinical next generation sequencing in lung cancer: Beyond personalized medicine. J Clin Oncol. 2016; 34, 2016 (suppl; abstr e23128). http://meetinglibrary.asco.org/content/171001-176

Importance: NSCLC adenocarcinoma is the most common subtype of NSCLC lung cancer occurring in 40% of these patients. Recently approved targeted treatment options show prolonged survival. Key drivers of NSCLC adenocarcinoma are well described, and several targeted therapies are either FDA approved or under clinical evaluation for patients with advanced cancers. Thus there is an increasing need to better molecularly characterize the tumor of each patient to apply appropriate therapy.

Personalized medicine has become a reality with the availability of rapid and actionable clinical NGS-based genomic profiling, which is now strongly endorsed by the NCCN through its issued guidelines.

Results: As expected, the CANCERPLEX test has identified mutations in EGFR that predict response to FDA approved anti-EGFR therapies. Among 28% of patients, we found a number of KRAS mutations which are negative predictors of response to the EGFR TKIs, erlotinib and gefitinib. We found that the majority of patients have alterations in STK11 that is impacting the mTOR signaling. Predictably, several ALK-EML4 translocations have been detected. The EML4-ALK gene fusion is a strong, independent driver of NSCLC and as such these tumors are highly sensitive to ALK targeted inhibitors crizotinib and ceritinib. We also found a significant number of mutations in DNA repair enzymes that may sensitize these tumors to PARP inhibition. Lastly, there are 8.2% cases with high mutation burdens, which predicts likely positive response to immune-checkpoint inhibition therapies.

Conclusions: Tumor specific sequencing analysis using the CANCERPLEX panel leads to appropriate and successful targeted treatment of lung cancers as supported by the literature.

Wakai T, Nagahashi M, Shimada Y, et al. Large-scale genomic sequencing of colorectal cancer in the Japanese population. J Clin Oncol 34, 2016 (suppl; abstr e15121). http://meetinglibrary.asco.org/content/163111-176

Importance: The advent of whole genomic sequencing has greatly facilitated the identification and characterization of cancer-relevant genes. Given the potential genetic and environmental differences between ethnic populations, it is unclear if the underlying oncogenic drivers detected by genomic profiling will be consistent across populations. CANCERPLEX is a large panel genomic test of 400-plus genes associated with cancer. Here we demonstrate alignment of CANCERPLEX with TCGA database and validate the utility of the platform.

Results: Actionable mutations were identified in > 99% of the Japanese colorectal patients. Sequencing data obtained from CANCERPLEX identified 60% of Japanese cases with alterations in the RTK/RAS pathways, similar to that determined in CRC cases by TCGA. Of these, 26 Japanese cases had BRAF mutations, in which only 13 harbored the V600E mutation. Additionally, 83% of Japanese cases presented with alterations in the DNA double strand break repair pathway, comparable to data obtained from TCGA demonstrating alterations in 70% cases.

Conclusions: Large panel genomic profiling of CRC patients captures the actionable genomic driver mutations in the Japanese population, validating its utility in stratifying patients for therapy. In addition, significant differences in the BRAF mutation profile were detected, supporting the use of full-gene sequencing vs hot-spot testing.

Ichikawa H, Shimada Y, Nagahashi M, et al. Large panel genomic profiling using CANCERPLEX to reveal candidates for HER2 targeted therapies in colorectal cancer. J Clin Oncol 34, 2016 (suppl; abstr e13125). http://meetinglibrary.asco.org/content/163212-176

Importance: Human epidermal growth receptor type 2 (HER2) overexpression/amplification is associated with the efficacy of HER2 targeted therapies in breast and gastric cancers, where candidates for its targeted therapies are selected by immunohistochemistry (IHC) and/or fluorescence in situ hybridization (FISH) testing. However, the HER2 status in colorectal cancer (CRC) has not been fully investigated to date. CANCERPLEX is a comprehensive next-generation sequencing-based test that evaluates 400-plus genes for mutations and copy number changes, including HER2.

Results: HER2 positive cases were observed in 8% patients (IHC3+ in 6% and IHC2+ and FISH positive in 2% patients). CANCERPLEX results demonstrated that 6% had HER2 amplification, 15% had HER2 mutations, and 1% had both HER2 amplification and mutation. Additionally, CANCERPLEX detected the other mutations of MAPK pathway (KRAS, NRAS, HRAS, and BRAF). The Fisher's exact test revealed a significant association between HER2 status and HER2 amplification detected with CANCERPLEX ($P< 0.001$), however, there was no significant association between HER2 status and HER2 mutation.

Conclusions: We found 8 of 100 (8%) Japanese CRC cases are HER2 positive. There is a significant association between HER2 status and HER2 amplification detected with CANCERPLEX. CANCERPLEX is a comprehensive testing tool for detecting gene alterations including not only mutations of MAPK pathway (KRAS, NRAS, HRAS, and BRAF), but also HER2 amplification, which is a possible useful predictor of the candidates for HER2 targeted therapies in CRC.

Nagahashi M, Wakai T, Shimada Y, et al. Mutation burden and microsatellite instability in colorectal cancer in Japan and US. J Clin Oncol 34, 2016 (suppl; abstr e15103). http://meetinglibrary.asco.org/content/162909-176

Importance: It has been previously documented that high somatic mutational rates in cancer as determined by whole genome sequencing correlates with high microsatellite instability (MSI-H) and mutations in the DNA mismatch repair (MMR) pathway quantified by electrophoretic mobility shift with five mononucleotide repeat markers and immunohistochemical staining. Here we demonstrate that the CANCERPLEX large-scale genomic sequencing platform can accurately and precisely identify patients with high mutational burden and MSI-H. Further, we demonstrate concordance among independent datasets obtained from either

Japanese colorectal patients or US colorectal patients as compared with each other and with the publicly available TCGA database.

Results: CANCERPLEX identified 17/201 Japanese cases as hypermutated as determined by mutational burden. This highly correlates with MSI-status and DNA repair defects. These data are similar to those obtained by the TCGA on US patients. These data are also in concordance with CANCERPLEX data obtained from US clinical cases demonstrating the applicability of a large gene panel to Japanese patients.

Conclusion: Given the important differences in treatment strategies for patients with MSI tumors and the emerging utilization of immune checkpoint inhibitors for hypermutated tumors, it is becoming imperative to accurately identify all patients with hypermutated tumors. Large panel genomic profiling offers comprehensive analysis of mutation burden and MSI-status.