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[Review]

Targeted therapy according to next generation sequencing-based panel sequencing

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Abstract

Targeted therapy against actionable gene mutations shows a significantly higher response rate as well as longer survival compared to conventional chemotherapy, and has become a standard therapy for many cancers. Recent progress in next-generation sequencing (NGS) has enabled to identify huge number of genetic aberrations. Based on sequencing results, patients recommend to undergo targeted therapy or immunotherapy. In cases where there are no available approved drugs for the genetic mutations detected in the patients, it is recommended to be facilitate the registration for the clinical trials. For that purpose, a NGS-based sequencing panel that can simultaneously target multiple genes in a single investigation has been used in daily clinical practice. To date, various types of sequencing panels have been developed to investigate genetic aberrations with tumor somatic genome variants (gain-of-function or loss-of-function mutations, high-level copy number alterations, and gene fusions) through comprehensive bioinformatics. Because sequencing panels are efficient and cost-effective, they are quickly being adopted outside the lab, in hospitals and clinics, in order to identify personal targeted therapy for individual cancer patients.

Key words : next-generation sequencing, clinical sequencing, gene sequencing panel, personalized medicine

The importance of genetic testing for cancer therapy

Recent progress in next-generation sequencing (NGS) has enabled the performance of whole genome sequencing (WGS), whole exome sequencing (WES), or RNA sequencing (RNA-Seq), as well as the identification of huge number of genetic aberrations¹⁾. Using NGS method, several large-scale investigations, such as The Cancer Genome Atlas (TCGA), have revealed genome profiles in many cancers, including gastric (GC), colorectal (CRC), breast, gynecological, and non-small cell lung (NSCLC) cancer²⁻⁹⁾. After determining the disease-specific distributions of mutational frequencies^{10,11)}, clinically actionable gene mutations are focused on among various gene aberrations¹²⁾. Several gene

mutations that may be predictive biomarkers for targeted therapy and prognostic biomarkers have also been identified.

Currently, targeted therapy is being developed based on the identification of actionable gene mutations and the development of targeted drugs. For patients with GC, anti-vascular endothelial growth factor (VEGF)- and anti-human epidermal growth factor receptor 2 (HER2)-targeted therapies have become a standard therapeutic regimen. In addition, HER2-targeted therapy for patients with HER2-positive GC has been reported to have a better therapeutic outcome than conventional chemotherapy, demonstrating that HER2-targeted therapy is a significant step forward to achieve personalized therapy. Therefore, the National Comprehensive Cancer Network (NCCN) guidelines recommend the assessment of HER2 overexpression. Genetic test-

ing for *HER2* can also assess *HER2* amplification, providing the adaptation of *HER2*-targeted therapy.

For patients with CRC, NCCN guidelines recommend investigating *RAS* (*KRAS* and *NRAS*) mutation status in advance for the use of inhibitors for epidermal growth factor receptor (*EGFR*) mutations. These guidelines also recommend investigating *BRAF* mutation status in patients with CRC, because CRC patients with *BRAF* mutations might not benefit from anti-*EGFR* therapy. Because *KRAS* is a downstream component of the *EGFR* signaling network, *EGFR* mutations can not be a therapeutic target in CRC with *KRAS* mutations.

EGFR and *KRAS* mutations are considered to be oncogenic driver mutations and are mutually exclusive in lung adenocarcinoma (LADC) (Fig. 1)¹⁹. The *EGFR* exon 19 mutation and exon 21 L858R mutation activate the tyrosine kinase domain, accelerating tumor development. Therefore, targeted therapies using *EGFR* tyrosine kinase inhibitors (TKIs) against tumors with *EGFR* mutations have remarkable therapeutic effects¹³. Similar to *EGFR* mutations, anaplastic lymphoma kinase (*ALK*) and *ROS1* fusions are treated using specific TKIs that are currently used as standard therapy (Fig. 2)^{14,15}. The current NCCN guidelines recommend genetic testing for *EGFR* mutations, *ALK* fusions, and *ROS1* fusions to determine first-line therapy¹⁶. The therapeutic effects on other actionable gene muta-

tions, such as *BRAF*, *ERBB2*, *MET*, and *RET*, are being investigated in several clinical trials¹³. After confirming the therapeutic effects of emerging targeted therapies, the NCCN guidelines will be updated the consensus of genetic testing and treatment strategy in the future.

Clinical sequencing panel

Sequencing panels can simultaneously target multiple genes efficiently, quickly and accurately to maximize the available information from a single investigation. In addition, these panels use clinical samples of both tumor and normal tissue, or tumor tissue only, and reveal gene mutations, copy number variation and gene fusions in tumors through comprehensive bioinformatics.

The predesigned panel covers the most commonly mutated genes or candidate actionable genes in various cancers. On the other hand, custom panels or tumor-specific predesigned panels are developed to investigate the genes that are specifically focused on or found in tumor-specific mutation. While *TP53* mutations are broadly identified in various cancers, most actionable gene mutations are identified differently among different cancers. For CRC, genetic testing of *KRAS*, *NRAS*, and *BRAF* mutations is necessary, while on the other hand, for LADC, that of *EGFR*, *KRAS*, *BRAF* and *HER2* mu-

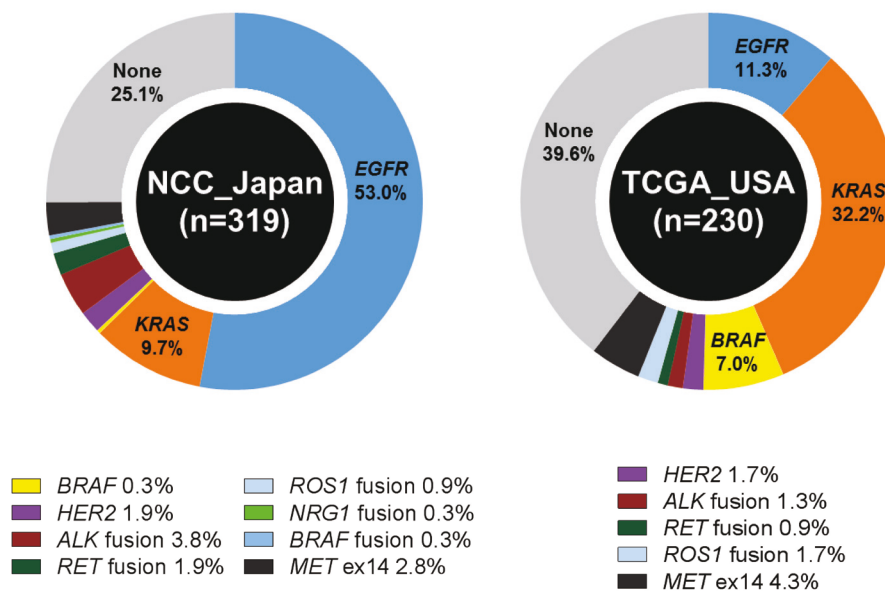


Fig. 1. Frequencies of driver gene aberrations in lung adenocarcinoma (LADC). The frequencies are shown for mutations in *EGFR*, *KRAS*, *BRAF*, and *HER2*, fusions involving *ALK*, *RET*, *ROS1*, *NRG1*, and *BRAF* and skipping of *MET* exon 14. The data were obtained from a Japanese cohort (319 cases from National Cancer Center Hospital) and a US cohort (230 cases from the TCGA study). This figure was modified from our previous reports^{13,19}.

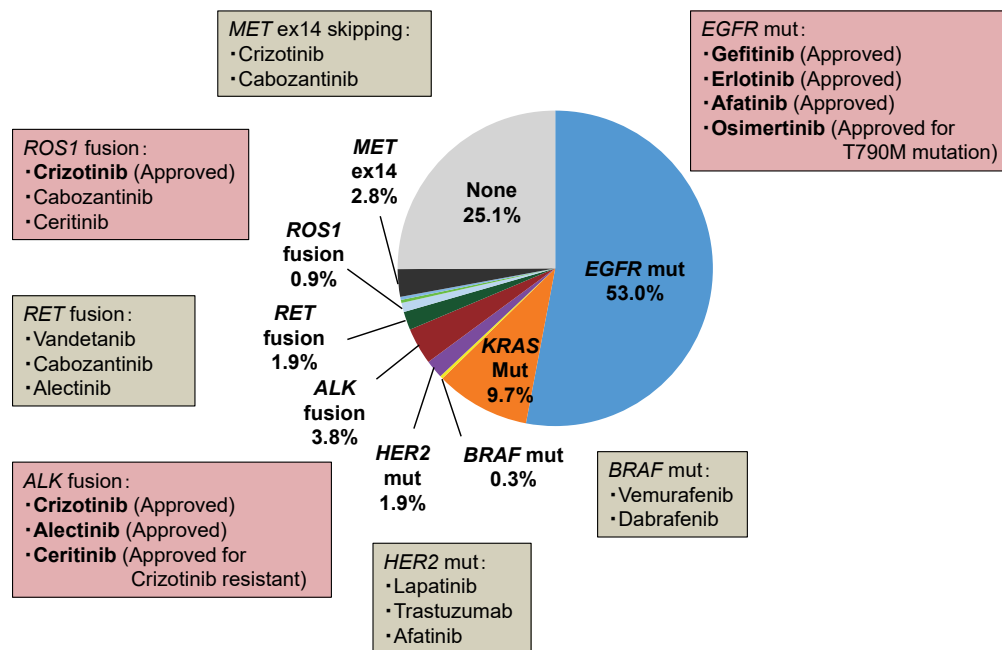


Fig. 2. Drugs approved in Japan or candidate targeted drugs against driver gene aberrations in lung adenocarcinoma (LADC). Driver gene aberrations in *EGFR*, *KRAS*, *HER2*, and *BRAF*; driver fusions involving *ALK*, *RET*, and *ROS1*; and skipping of *MET* exon 14 were examined in 319 LADC patients who had undergone surgical resection at the National Cancer Center Hospital¹³⁾

tations and *ALK*, *RET*, and *ROS1* fusions is necessary. We and others have reported that gene mutation profiles differ even in different histological cancer subtypes^{17,18)}. Therefore, it is necessary to select the appropriate sequencing panel for each patient, in order to determine actionable gene mutations to perform personalized targeted therapy.

Several cancer centers all over the world have developed their own in-house platforms. For example, the Memorial Sloan Kettering (MSK) Cancer Center developed MSK-IMPACT (Integrated Mutation Profiling of Actionable Cancer Targets), a hybridization capture-based NGS panel that can detect all protein-coding mutations, copy number alterations, selected promoter mutations, and structural rearrangement in 468 cancer-associated genes. In 2017, the MSK-IMPACT test was approved by the US Food and Drug Administration (FDA) for in vitro diagnostic test for tumor profiling. To date, MSK-IMPACT has sequenced tumors from more than 20,000 patients with advanced cancer. According to a recent study that sequenced tumors from more than 10,000 patients using MSK-IMPACT, nearly 37% of patients had at least one actionable gene mutation and 11% were able to participate in clinical trials of treatments that directly targeted their genetic alterations²⁰⁾. The FDA has also approved the Oncomine Dx Target test, which targets gene muta-

tions in NSCLC. This test is used as a companion diagnosis to aid in the selection of specific drugs for individual NSCLC patients with *EGFR* mutations, *BRAF* mutations, or *ROS1* fusions.

The most impressive feature of MSK-IMPACT is that this panel can be used to analyze both tumor and matched normal tissue and blood and identifies both somatic and germline mutations²⁰⁾. Therefore, MSK-IMPACT results in accurate somatic mutation calls due to eliminate germline variants. MSK-IMPACT also accurately determines mutational signatures to reveal multiple mutational processes and tumor mutation burden to identify patients who mostly can receive the most benefit from immunotherapy. In addition, germline variants can provide therapeutic opportunity as well as cancer susceptibility²¹⁻²³⁾. The FDA approved a poly ADP ribose polymerase (PARP) inhibitors for the germline BRCA1/2-mutant ovarian cancer²⁴⁾. Furthermore, the PARP inhibitor is also approved for maintenance therapy in both germline and somatic BRCA-mutant ovarian cancer.

Clinical sequencing in Japan

The use of clinical sequencing using NGS-based multiplex gene panels has recently been started in Japan. To date, the MSK-IMPACT test is

available at Juntendo University Hospital, Tohoku University Hospital, and Yokohama City University Hospital in Japan. Tumor and non-tumor specimens are sent from these hospitals to the Memorial Sloan Kettering Cancer Center in the U.S. After being sequenced and annotated, the analyzed results are delivered to their respective hospitals in Japan. Based on the identified actionable gene mutations, each patient is recommended to undergo appropriate targeted therapies or clinical trials. Another sequencing panel, the OncoPrime test, targets 232 cancer-related genes and is used at the Kyoto University Hospital, Okayama University Hospital, and Hokkaido University Hospital. However, to date, neither MSK-IMPACT nor OncoPrime tests are covered by social insurance in Japan. Similar to other cancer centers in the world, the National Cancer Center (NCC) in Japan has developed an original sequencing panel, the NCC oncopanel, which targets 90 gene mutations/amplifications and 12 gene fusions, with the aim to identify actionable gene mutations and select suitable molecular targeted therapies²⁵⁾.

NCC Japan launched SCRUM-Japan (Cancer Genome Screening Project for Individualized Medicine in Japan), a nation-wide genome screening consortium, in March 2015. The aim of this project is to investigate the frequency of oncogenic genome alterations in Japanese patients and to facilitate the registration of clinical trials for targeted therapies. In this project, the Oncomine Cancer Research Panel (Oncomine Comprehensive Assay) is used to detect gene mutation, copy number variation and gene rearrangement²⁶⁾. The 143-gene Oncomine Comprehensive Assay is also used in the US National Cancer Institute-Molecular Analysis for Therapy Choice (NCI-MATCH) trial²⁷⁾. The NCI-MATCH trial is a phase II basket study which aims to identify actionable gene mutations.

Conclusion

The recent advances of NGS technologies have enabled the performance of gene sequencing panels for cancer patients in daily clinical practice. Personalized therapy against actionable gene mutations shows positive efficacy; therefore, we believe that the demand for this therapy will increase in all cancer subtypes.

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