Editorial

Treatment selection with organoids in an EGFRm + TP53m stage IA1 patient with recurrence after radical surgery

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The development of molecularly targeted therapeutics and companion diagnostics targeting driver genes in cancer treatment has made rapid progress in recent years. In non-small cell lung cancer (NSCLC), individualized therapy is highly effective, and targeting mutations such as activating epidermal growth factor receptor (EGFR) mutations and anaplastic lymphoma kinase (ALK) fusions has improved progression-free survival in advanced NSCLC cases (1,2). The National Comprehensive Cancer Network NSCLC Guidelines Panel strongly advises not only EGFR and ALK gene testing but also broader molecular profiling with the goal of identifying rare driver mutations for which effective drugs may already be available. Broad molecular profiling is a key component of the improvement of care of patients with NSCLC (3). However, the implementation of many tests raises concerns about the consumption of test specimens, longer testing time, and higher testing costs. Therefore, the use of multiplex tests, especially gene panel tests using next-generation sequencing (NGS), is gaining popularity in clinical oncology (4). With the increase in NGS, multiple genetic abnormalities are being detected; this is in contrast to the "driver oncogene-centric paradigm," in which patients are matched to available targeted therapies from the identification of single genomic driver events (5).

Jia *et al.* reported a case of a 66-year-old Chinese man with metastatic recurrence of stage IA1 lung adenocarcinoma 3 years after R0 resection (6). EGFR (L858R) and TP53 (R110L) mutations were confirmed in the main tumor. Metastatic lymph nodes harbored not only the same EGFR and TP53 mutations but also the CDKN2A (H83Y) mutation. Patient-derived organoids (PDOs) were established from the lymph node of metastatic adenocarcinoma and the first-line therapy was osimertinib as determined by the drug response of PDOs. An international multidisciplinary team (iMDT) discussion was presented, and four experts, including three medical oncologists and a surgical oncologist from Germany, Italy, and Japan, participated in the iMDT.

First, the impact of co-mutation of TP53 and EGFR should be considered. Somatic mutations in TP53 represent by far the most prevalent co-alteration in EGFR-mutant lung adenocarcinoma (54.6–65%) (7,8). Genomic alterations in the *CDKN2A* gene are observed in ~24.6% of EGFR-mutant tumors. Especially, TP53 mutation is observed in both mutant and wild-type EGFR tumors, according to cBioPortal Web program from the database of 860 patients with metastatic lung adenocarcinoma treated at Memorial Sloan Kettering Cancer Center (5,9). A meta-analysis revealed poor prognosis in cases with both *EGFR* gene mutation and *TP53* gene mutation (10). A phase 3 randomized clinical trial (CTONG0901) also reported poor prognosis of TP53 exon 4 and/or exon 7 mutation in EGFR-mutant NSCLC patients compared with that of wild-type TP53 EGFR-mutant patients (11). Considering that *TP53* gene mutation is frequently detected in patients with and without *EGFR* gene mutation and that the simultaneous detection of both gene mutations makes a significant difference in prognosis, we believe that it is reasonable to search for *TP53* gene mutation at the same

time as *EGFR* gene mutation.

Four experts answered "no" to the question of whether adjuvant therapy should be given to patients with stage I lung cancer at high risk by molecular diagnosis, especially patients with lesions less than 4 cm in diameter. We also agree; however, on the basis of the results presented so far, we believe that it is appropriate to plan a clinical trial to investigate the administration of adjuvant chemotherapy to lung cancer patients with both *EGFR* and *TP53* gene mutations. In such trials, adjuvant chemotherapy with immune checkpoint inhibitors as well as EGFR-tyrosine kinase inhibitors may be considered as candidates for drug administration. In general, elevated tumor mutation burden increases the odds of generating immunogenic neoantigens, thereby inducing a response to immune checkpoint inhibitors (12), although the impact of co-mutations on the oncogene-driven NSCLC including EGFR mutations has not so far been defined regarding immunogenicity.

In response to the question of how to identify patients with early-stage lung cancer who are at high risk for recurrence, two experts (Dr. Christoph and Dr. Passaro) responded that high-risk cases should be selected using pathological features of poor prognosis that have previously been identified, such as lymphatic permeation or vascular invasion. However, these characteristics were not observed in the current case, and these characteristics alone cannot identify high-risk cases. From our experience, we believe that there may be some patterns of genetic mutations associated with poor prognosis. Multiple genetic tests would be required to detect these mutation patterns.

To the question of whether it is reasonable to use NGS for genetic mutation testing in early-stage NSCLC, two experts (Dr. Christoph and Dr. Gridelli) replied that it is not. It is true that NGS is an expensive test, and it is not practical to perform this test in all postoperative cases of early-stage lung cancer. However, as previously mentioned, it is necessary to detect patterns of genetic mutations that are associated with poor prognosis. Furthermore, a cost-effectiveness analysis from Singapore database showed that NGS is superior compared with multiple mutation tests conducted in combination (13). If detecting patterns of poor prognostic gene mutations is to be emphasized as a priority, it is essential to create an environment in which NGS can be conducted in all cases. Reducing the cost of NGS substantially so that it can be adapted in all cases is critical, and research budgets should be used for the innovations needed to achieve this goal.

Regarding the possibility of PDO as a preclinical model for drug-sensitivity screening tests, four experts supported the potential of PDOs for drug screening, especially in the era of precision medicine. Drug resistance interferes with the effectiveness of cancer chemotherapy. The initial concept was the application of *in vitro* methods to predict tumor response. The use of PDOs raises two questions. First, we must discuss when drug resistance test of PDOs should be performed. As one of the experts (Dr. Hishida) mentioned, organoid models may be useful in predicting response to conventional cytotoxic regimens and immune checkpoint inhibitors in lung cancers without driver gene mutations, because lung cancer with driver gene mutations will receive the corresponding targeted therapy, regardless of the test results. Second, we question whether this method is superior to previously reported drug-sensitivity screening tests. To determine clinical drug resistance, many different methods for assessing tumor sensitivity and resistance to chemotherapy have been developed over the past several decades (14,15). Collagen gel droplet embedded culture drug-sensitivity test (CD-DST) is one of the promising methods (16). Several trials with CD-DST in NSCLC patients revealed that drug resistance was predicted with >90% accuracy, while drug sensitivity was detected with a lower accuracy of approximately 70% (17,18). Compared with conventional methods, PDOs may allow for a more accurate determination of the effects of chemotherapy, because organoids exhibit some special function of organs, which are complex tissues composed of multiple cells. However, the crosstalk between tumor cells and stroma in the tumor microenvironment plays an important role in tumor growth (19). Because PDO do not contain stroma, this model is unlikely to reflect the influence of this crosstalk on the response to chemotherapy, which may lead to results with higher specificity but lower sensitivity, as in previous methods.

While research on effective anticancer drugs for lung cancer is advancing at an ever-increasing pace, the cost of lung cancer chemotherapy is also going up. In addition, the accurate identification of high-risk cases, prophylactic procedures to reduce the risk of recurrence, and identification of effective chemotherapy strategies are very important issues in the precision era. Research is needed to identify an appropriate lung cancer treatment method while paying close attention to cost-effectiveness.

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Footnote

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