Editorial

Significance of testing for *TP53* gene mutations in lung adenocarcinoma using targeted gene sequencing

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Randomized clinical trials have demonstrated the positive effects of epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) for patients with advanced or recurrent lung adenocarcinomas harboring *EGFR* gene mutations (1-3). Detecting cancer-specific gene mutations and exploring their targeted therapies for advanced non-small cell lung cancer (NSCLC) have therefore become a major topic of discussion over the past decade. Studies have shown that chromosomal rearrangements of *ALK*, *ROS1*, and *RET* genes are good targets for the corresponding TKIs (4-6) and are currently the first choice for targeted therapy for patients with the respective targetable gene rearrangements in their tumors (7). Most of these gene mutations and rearrangements are known to be mutually exclusive (8), thereby requiring more time and more samples to test them individually, which can delay treatment. The increasingly widespread use of next-generation sequencing (NGS) has helped address this issue, enabling clinicians to determine several gene alterations simultaneously from one sample (9). With the popularity of this technology, a new concept has emerged of not only detecting predesigned targetable gene alterations, but also expanding the targets to candidate genes for which targeted therapy has not yet been established, as well as searching for novel therapeutic gene targets combined with the patients' clinical and pathological features. The Lung Cancer Mutation Consortium (LCMC) has been at the forefront of these trends in multiplex genetic profiling.

LCMC1, a predecessor of the current analysis was established in 2008 as a multi-institutional, prospective, observational study to investigate the frequency of various oncogenic drivers in lung adenocarcinoma (9,10) and showed that patients with oncogenic drivers in their tumors, who were treated with the corresponding targeted therapies, achieved longer survival than those who did not undergo such therapies (9). The current analysis, a second cohort of LCMC participants (LCMC2), expanded the genes studied since 2013 because additional oncogenic drivers such as *ROS1* and *RET* that could be targeted with agents for specific gene alterations were identified. *PTEN*, *MET*, *PIK3CA*, and *TP53* gene alterations were also analyzed as candidates for future targeted therapy.

Aisner *et al.* compared the demographics, survival, and tumor's genetic status of patients and obtained similar results to LCMC1 in that patients with targetable oncogenic drivers in their tumors had significantly longer survival after undergoing the corresponding targeted therapy than those who did not undergo such therapies. However, the authors did not observe any significant differences in survival due to non-targetable gene alterations such as *PTEN*, *PIK3CA*, and *MET* (11). One of the authors' main results was that patients (even those who smoked) with *EGFR*, *ALK*, or *ROS1* alterations in their tumors had significantly longer survival times than those without these three gene alterations (11). The authors stated that their study was the first to directly compare the survival of cohorts with or without targetable gene alterations after differentiating patients who smoke from those who had never smoked. This outcome implies that patients who smoke can benefit from multiplex sequencing. The authors also showed that patients who

smoke, especially those who used to smoke, harbored gene alterations, such as *EGFR*, *ALK*, *ROS1*, *ERBB2*, and *RET*, in their tumors, though most of their frequencies were less 5%. In contrast, there were more patients who smoked harboring *KRAS* or *BRAF* mutations in their tumors than patients who had never smoked. Considering that targeted therapies for these mutations are now undergoing clinical trials (12,13), it is worth emphasizing the importance of testing a tumor's gene alterations regardless of the patient's smoking history. Previous reports have supported the statements of Aisner *et al.*, analyzing the frequency of *EGFR* mutations in patients who smoke and those who do not (14,15). The current analysis would be more interesting, however, if it included the survival rates for just the patients who currently smoke or included the trends based on the amount of cigarettes smoked as a smoking index, because patients who smoke include both of those who smoke lightly and those who smoke heavily, given that it has been reported in some studies that patients who currently smoke and/or smoke heavily gain less of benefit from gene-targeted therapy (16).

Aisner *et al.* also showed that a coexisting *TP53* mutation with *EGFR*, *ALK*, or *ROS1* gene alterations was related to a shorter survival time than without the *TP53* mutation. The authors therefore recommended the routine use of massively parallel sequencing for advanced or recurrent lung adenocarcinoma, given that detecting targetable drivers and tumor suppressor gene alterations is potentially significant for selecting the therapy and for determining the predictive markers of treatment efficacy (11). It would be interesting to test *TP53* gene mutation for all patients with advanced or recurrent lung adenocarcinoma in spite of the preliminary outcome for the *TP53* gene mutation due to the limited number of analyzed patients. It has been reported in a number of studies that *TP53* gene mutation is a poor prognostic factor for patients with NSCLC (17), while targeted therapy for *TP53* gene mutation is still under study, and no promising therapies have yet been developed (18). Therefore, the most important discussion point is whether to test these types of gene mutations by targeted gene sequencing. Unlike whole genome sequencing, targeted sequencing detects only tens or hundreds of gene mutations or alterations on predesigned panels, which consist of less than 5% of all genes. Accordingly, targeted gene sequencing is intended for use when its results enable physicians to determine whether patients can undergo a gene-mutation-specific therapy such as EGFR-TKI or whether the patients are candidates for enrolment in clinical trials due to the corresponding gene mutation. Given that LCMC1 and LCMC2 adopted targeted sequencing and that detecting *TP53* gene mutation is still far from being applied as a practical therapy, adding this mutation to the sequencing panel is inconsistent with the original purpose of targeted sequencing. However, some factors that make targeted sequencing the preferred tool for searching for prognostic factors have emerged.

The first factor is the significance and appeal of *TP53* gene mutation as a therapeutic target because mutant p53 proteins are highly expressed in many cancers and reportedly play a role in promoting cancer metastasis (19,20). Although there are still numerous challenges to overcome before this mutation can be treated, destabilizing or deactivating mutant p53 proteins (or reactivating the wild-type function in mutant p53 proteins) would have a significant effect on cancer therapy (18). The second factor is the relationship between *TP53* mutation and immune checkpoint inhibitors. Biton *et al.* determined that the combination of *TP53* mutation, *STK11*, and *EGFR* wild type had significantly higher programmed cell death 1 ligand 1, or PD-L1 expression by tumor cells and predicted the best response to anti-programmed cell death 1 (anti-PD-1) agents (21). Our data also suggested that *TP53* mutation was associated with the mutation burden in NSCLC, which was recently shown to be a favorable predictor of the response to anti-PD-1 agents (22,23). The last factor is the decrease in the running costs for NGS. The reported cost for performing high-quality whole human genome sequencing in 2006 was approximately $14 million. By late 2015, this cost dramatically plunged to $1,500, and the cost to generate a whole-exome sequence fell below $1,000 (24). Therefore, clinical studies employing NGS are expected in the search for novel genetic markers that are currently non-targetable.

In conclusion, Aisner *et al.* reported longer survival for patients with lung adenocarcinoma and an oncogenic driver mutation, who underwent effective targeted therapy, regardless of their prior smoking history. The authors suggested that all patients with lung adenocarcinoma should undergo molecular testing, regardless of their clinical characteristics. The authors also proposed the routine use of massively parallel sequencing to detect targetable driver alterations, tumor suppressor genes, and other alterations that have potential significance for therapy selection and as predictive markers for treatment efficacy. Aisner *et al.* have shown us that the practical use of multiplex genetic profiling for treating lung cancer is almost at hand.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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