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Short Commentary Open Access

Treatment Guideline for Advanced NSCLC Based on Driver Gene Mutations

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In 2004, three groups of researchers retrospectively found a close relationship between epidermal growth factor (*EGFR*) gene mutations and efficacy of the EGFR-tyrosine kinase inhibitor (TKI) used in molecularly targeted therapy in non-small cell lung cancer (NSCLC) [1-3]. Since 2009, prospective randomized Phase 3 studies clarified that progression free survival (PFS) with use of EGFR-TKI was superior to that of cytotoxic chemotherapies for advanced NSCLC patients with *EGFR* mutations [4-7]. Next, in 2007, echinoderm microtubule-associated protein-like 4-anaplastic lymphoma kinase (*EML4-ALK*) fusion gene was found to be another driver gene mutation of NSCLC, [8] and an ALK inhibitor, crizotinib, has been established to be active in terms of efficacy and PFS [9]. Both EGFR-TKI and ALK inhibitors are considered to have a positive effect on survival [10,11]. These suggest that the time for personalized treatments for advanced NSCLC has arrived. Furthermore, the results of Lung Cancer Mutation Consortium and other studies have clarified incidences of *EGFR, ALK, KRAS, Pi3KCA, BRAF* and other mutations [12], and might give chances of new targeted therapies. However, the majority of treatment guidelines for advanced NSCLC employ an old fashioned decision-tree (Figure 1A), in which the first decision step is histology (non-squamous cell carcinoma vs. squamous cell carcinoma) and, in the case of non-squamous cell carcinoma, the second decision step is detecting *EGFR* mutations and *ALK* fusion mutations.

First, biomarker tests should predict treatment benefit more precisely than a histological examination. EGFR mutation tests have proven to be reliable for use in clinical practice [13]. In particular, EGFR mutation testing as a biomarker has attained high levels of predictability, reliability, and feasibility**,** and can be performed with practical cost [14-16]. Second, histological examination is only modestly reliable; in the discrimination between non-squamous cell carcinoma and squamous cell carcinoma, inter-pathologists' correlation was found to be modest (κ=0.55) [17]. Therefore, in Japan, where approximately 50,000 patients were newly diagnosed as NSCLC in 2011, approximately 48,000 tests for *EGFR* mutations were performed, [16] indicating that most patients in Japan with NSCLC were screened**.** The cost of about 200 US dollars for the test is covered by national health insurance. In contrast, the infrastructure for testing *EML4-ALK* fusion genes is still being developed [18]. *EML4-ALK* fusion genes clearly predict clinical benefit with crizotinib treatment [9,11]. Nevertheless, there is no all-purpose testing procedure that has been established. Fluorescent in situ hybridization (FISH) and immunohistochemistry (IHC) need big tissue samples, indicating that there is some problem in terms of feasibility of sampling for advanced NSCLC, which has no indication for operation. Reverse transcription PCR (RT-PCR) for *EML4-ALK* mutations also has modest feasibility because of the need for adequate quantities of RNA immediately after getting clinical samples. Furthermore, there is some inconsistency among results by FISH, IHC and RT-PCR,[18] such as the level of reliability. Currently, FISH is more validated than IHC and RT-PCR [19]; however, FISH is the most expensive test and may not be suitable for massive screening. Therefore, the actual treatment guideline for advanced NSCLC at present in Japan as well as in Italy [20] designates *EGFR* testing as the first step, histological examination (non-squamous cell carcinoma vs. squamous cell carcinoma) as the second step, and, in the case of non-squamous cell carcinoma, testing for *ALK* fusion genes (Figure 1B) is the 3rd decision step.

In future, when we get an easy, reliable and not-expensive screening test to investigate all of the "druggable" mutations, which have specific inhibitors, a final guideline having the first step of testing druggable mutations and, thereafter, the second step of histological examination will be born (Figure 1C). The value of testing for other driver gene mutations will be more appreciated in future treatment guidelines.

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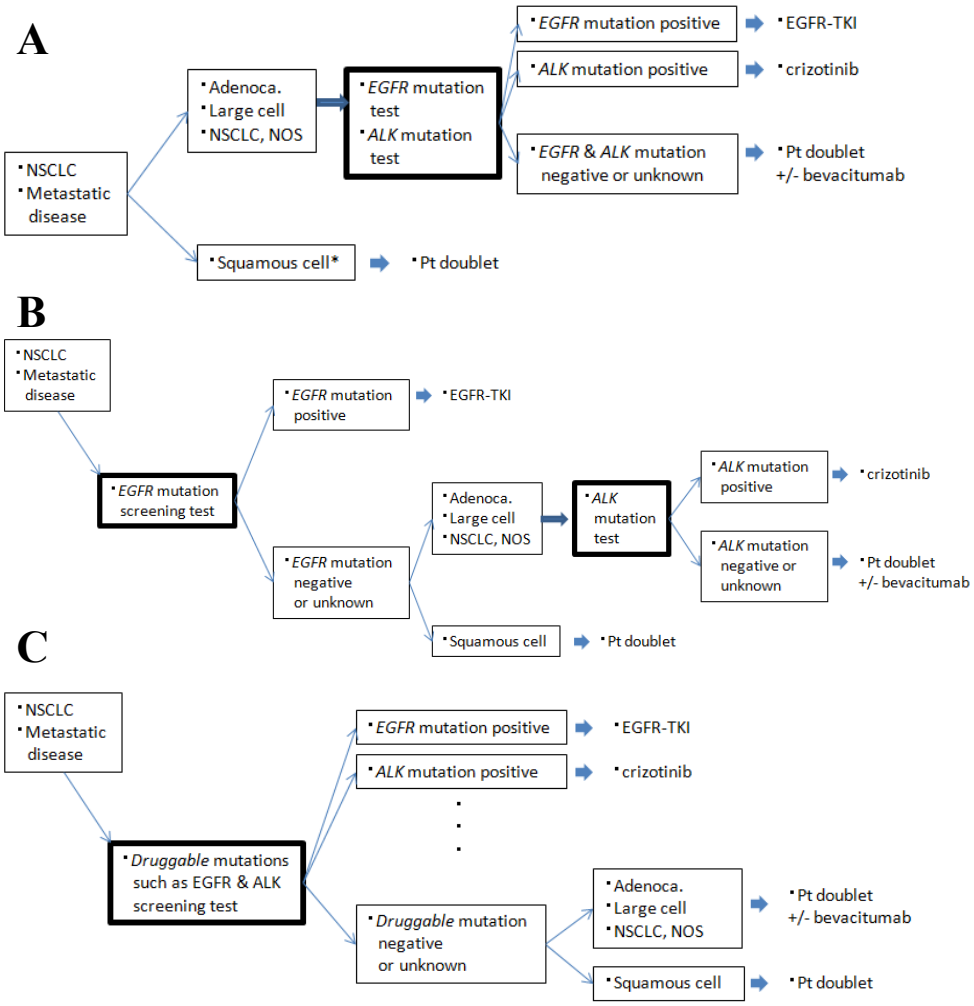

Abbreviations: NSCLC: Non-small Cell Lung Cancer; Adenoca: Adenocarcinoma; NOS: Not Otherwise Specified; EGFR: Epidermal Growth Factor Receptor; ALK: Echinoderm Microtubule-Associated Protein-like 4-anaplastic Lymphoma Kinase; TKI: Tyrosine Kinase Inhibitor; Pt: Platinum

Figure 1: A: Majority of treatment guidelines for advanced NSCLC. **B:** Present guideline for advanced NSCLC in Japan and Italy. **C:** Future guideline for advanced NSCLC based on driver gene mutations.