Molecular targeted therapy against driver gene aberrations has a significantly high positive response rate compared with traditional cytotoxic chemotherapies, and has thus dramatically changed the treatment strategies for malignant tumors, including non-small cell lung cancer (NSCLC) (1). Lung adenocarcinoma (LADC) can be treated with targeted therapy against driver gene aberrations using tyrosine kinase inhibitors (TKIs). A large genomic sequencing study showed that mutations of $\text{EGFR}$, $\text{KRAS}$, $\text{BRAF}$, and $\text{HER2}$, and gene rearrangements involving $\text{ALK}$, $\text{RET}$, $\text{ROS1}$, and $\text{MET}$ exon 14 skipping are mutually exclusively identified as driver gene alterations in LADC (2). The National Comprehensive Cancer Network (NCCN) Guidelines Insights focus on recent updates in targeted therapy against driver genes for patients with advanced NSCLC (3). According to the NCCN guidelines, testing for $\text{EGFR}$ mutations, $\text{BRAF}$ mutations, $\text{ALK}$ fusions, and $\text{ROS1}$ fusions, and assessing PD-L1 expression levels are recommended in patients with advanced NSCLC before the initial treatment. The guidelines recommend first-line specific TKIs for driver-positive patients and immunotherapy and/or chemotherapy for driver-negative patients. Efforts to confirm the therapeutic utility of TKIs and to identify resistance mutations leading to the development of novel TKIs for overcoming acquired resistance are continuous. For example, oncogenic $\text{RET}$ fusions were discovered in LADC (4-6) and confirmed as a promising target (4,7). The efficacy of vandetanib and cabozantinib in patients with $\text{RET}$ fusions (8,9) promoted the design of clinical trials to evaluate the efficacy of a novel RET-specific inhibitor that was developed to overcome the weak points of multikinase inhibitors (10,11). A recent report describes the mechanism underlying acquired resistance to vandetanib (12), and a novel RET-inhibitor was developed to suppress acquired resistance associated with mutations (13).

We recently demonstrated that the frequency of driver gene aberrations in LADC differs according to ethnicity, sex, and smoking, which leads to differences in treatment efficacy (14). In this report, comparison of Asian and European/US cohorts showed that $\text{EGFR}$ mutations are more prevalent in Asian patients, whereas $\text{KRAS}$ mutations, which are not druggable, are more prevalent in European/US patients. When stratified by sex and smoking status, $\text{EGFR}$ mutations are frequently detected in women and never-smokers in both Asian and European/US patients. $\text{EGFR}$ mutations are more likely to be detected in Asian patients than in European/US patients, whereas $\text{KRAS}$ and $\text{BRAF}$ mutations occur preferentially in men and ever smokers, especially among European/US patients. On the other hand, oncogenic fusions, such as $\text{ALK}$, $\text{RET}$, and $\text{ROS1}$ fusions, are frequently detected in women never smokers in both cohorts. Lastly, driver-negative cases are more prevalent among smokers in both cohorts. There are currently no targeted therapies against driver-negative cases, underscoring the need to identify new druggable targets.

Recently, de Semir et al. reported that pleckstrin homology domain-interacting protein (PHIP) could be a
A novel therapeutic target for driver-negative malignancies including NSCLC (15). These authors demonstrated that PHIP plays a role in promoting the progression of driver-negative NSCLC. PHIP knockdown and overexpression in vitro revealed that increased expression of PHIP promotes tumor cell proliferation and invasion. In clinical specimens, PHIP is upregulated in the bronchioid subtype of LADC without EGFR mutations, KRAS mutations, and ALK fusions. This study demonstrated the possible therapeutic utility of anti-PHIP bromodomain inhibitors for the treatment of patients with elevated PHIP expression.

To explore the therapeutic potential of PHIP inhibitors, we extracted data on PHIP expression from 200 LADC cases that were previously included in a comprehensive genetic analysis performed by our group (16). This study included activating mutations in the EGFR, KRAS, HER2, BRAF, and HRAS oncogenes (n=96), oncogenic ALK, RET, or ROS1 fusions (n=31), and driver-negative cases (n=73). As shown in Figure 1, LADC cases with significant PHIP upregulation were preferentially detected among driver-negative cases, suggesting the therapeutic utility of PHIP targeting in LADC, especially in driver-negative cases. Analysis of PHIP mutations showed that they were more frequent in the driver-negative group (5/73, 6.8%) than in the other two groups (1/127, 0.8%). These results suggest that PHIP gene aberrations preferentially occur in driver-negative patients with LADC with accumulated non-synonymous mutations. As indicated by de Semir et al., identifying new targetable mutations and adapting immunotherapies are critical issues in driver-negative tumors. In driver-negative cases, MET amplification, RIT1 mutations, MEK1 (MAP2K1) mutations, and loss of functional NF1 mutations were identified and considered therapeutic targets (2,14). In addition, truncating mutations of SMARCA4/BRG1 and ARID1A are prevalent in driver-negative tumors and targetable using a synthetic lethal approach (14). Currently, the most promising additional personalized therapy for driver-negative cases is immunotherapy (18-20). Because mutation burden is associated with anti-programmed death (PD)-ligand 1 (PD-L1) drug sensitivity (21), immune checkpoint blockade of PD-1 and PD-L1 is expected to be effective in driver-negative cases.
negative LADC cases. PHIP or other targeted therapy and immunotherapy will hopefully lead to the development of effective targeted therapies providing a survival benefit in patients with NSCLC.

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

References