

# Identification of a novel therapeutic target in driver-negative non-small cell lung cancer

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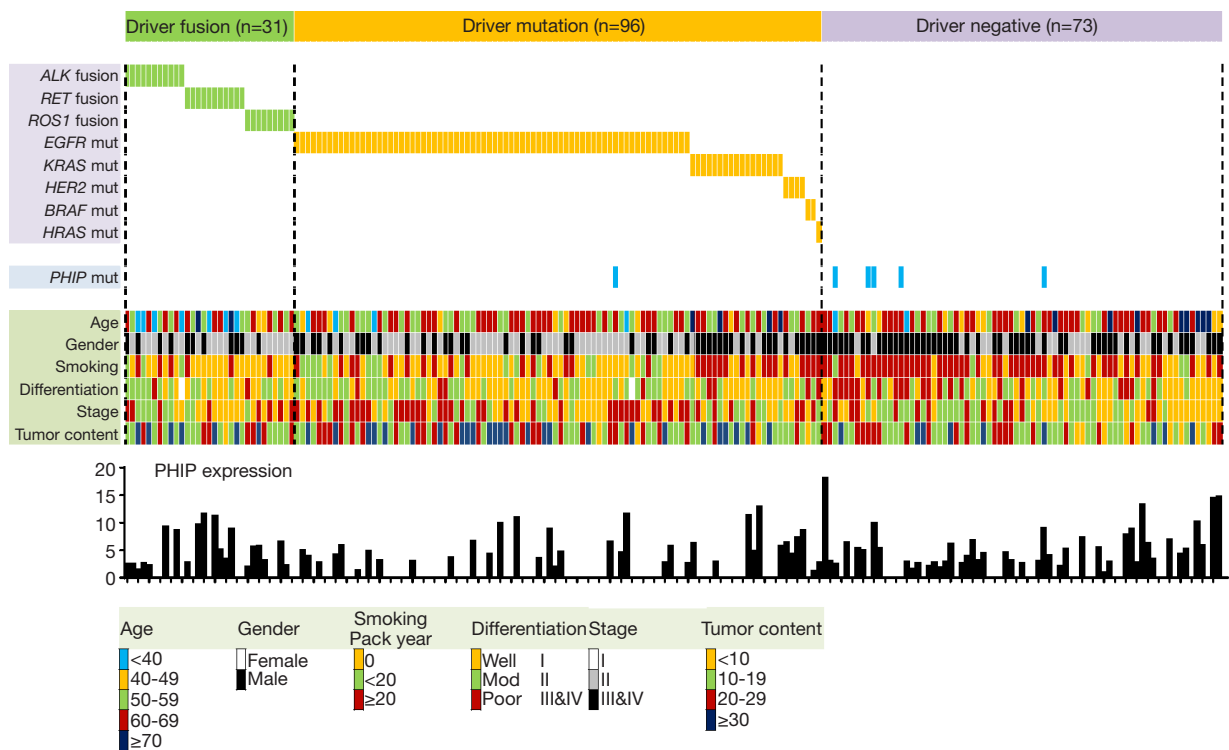
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Molecular targeted therapy against driver gene aberrations has a significantly high positive response rate compared with traditional cytotoxic chemotherapies, and has thus dramatically changed the treatment strategies for malignant tumors, including 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 *EGFR*, *KRAS*, *BRAF*, and *HER2*, and gene rearrangements involving *ALK*, *RET*, *ROS1*, and *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 *EGFR* mutations, *BRAF* mutations, *ALK* fusions, and *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 *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 *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 *EGFR* mutations are more prevalent in Asian patients, whereas *KRAS* mutations, which are not druggable, are more prevalent in European/US patients. When stratified by sex and smoking status, *EGFR* mutations are frequently detected in women and never-smokers in both Asian and European/US patients. *EGFR* mutations are more likely to be detected in Asian patients than in European/US patients, whereas *KRAS* and *BRAF* mutations occur preferentially in men and ever smokers, especially among European/US patients. On the other hand, oncogenic fusions, such as *ALK*, *RET*, and *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



**Figure 1** PHIP expression and gene mutation profile in lung adenocarcinoma according to driver aberrations with clinicopathological characteristics. PHIP expression was expressed as the FPKM (fragments per kilobase of exon per million fragments mapped) value, as previously described (17). PHIP, pleckstrin homology domain-interacting protein.

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 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

- Janku F, Stewart DJ, Kurzrock R. Targeted therapy in non-small-cell lung cancer--is it becoming a reality? *Nat Rev Clin Oncol* 2010;7:401-14.
- Cancer Genome Atlas Research N. Comprehensive molecular profiling of lung adenocarcinoma. *Nature* 2014;511:543-50.
- Ettinger DS, Aisner DL, Wood DE, et al. NCCN Guidelines Insights: Non-Small Cell Lung Cancer, Version 5.2018. *J Natl Compr Canc Netw* 2018;16:807-21.
- Kohno T, Ichikawa H, Totoki Y, et al. KIF5B-RET fusions in lung adenocarcinoma. *Nat Med* 2012;18:375-7.
- Lipson D, Capelletti M, Yelensky R, et al. Identification of new ALK and RET gene fusions from colorectal and lung cancer biopsies. *Nat Med* 2012;18:382-4.
- Takeuchi K, Soda M, Togashi Y, et al. RET, ROS1 and ALK fusions in lung cancer. *Nat Med* 2012;18:378-81.
- Saito M, Ishigame T, Tsuta K, et al. A mouse model of KIF5B-RET fusion-dependent lung tumorigenesis. *Carcinogenesis* 2014;35:2452-6.
- Drilon A, Wang L, Hasanovic A, et al. Response to Cabozantinib in patients with RET fusion-positive lung adenocarcinomas. *Cancer Discov* 2013;3:630-5.
- Yoh K, Seto T, Satouchi M, et al. Vandetanib in patients with previously treated RET-rearranged advanced non-small-cell lung cancer (LURET): an open-label, multicentre phase 2 trial. *Lancet Respir Med* 2017;5:42-50.
- Subbiah V, Gainor JF, Rahal R, et al. Precision Targeted Therapy with BLU-667 for RET-Driven Cancers. *Cancer Discov* 2018;8:836-49.
- Drilon A, Hu ZI, Lai GGY, et al. Targeting RET-driven cancers: lessons from evolving preclinical and clinical landscapes. *Nat Rev Clin Oncol* 2018;15:151-67.
- Nakaoku T, Kohno T, Araki M, et al. A secondary RET mutation in the activation loop conferring resistance to vandetanib. *Nat Commun* 2018;9:625.
- Subbiah V, Velcheti V, Tuch BB, et al. Selective RET Kinase Inhibition for Patients with RET-Altered Cancers. *Ann Oncol* 2018;29:1869-76.
- Saito M, Shiraishi K, Kunitoh H, et al. Gene aberrations for precision medicine against lung adenocarcinoma. *Cancer Sci* 2016;107:713-20.
- de Semir D, Bezrookove V, Nosrati M, et al. PHIP as a therapeutic target for driver-negative subtypes of melanoma, breast, and lung cancer. *Proc Natl Acad Sci U S A* 2018;115:E5766-E75.
- Saito M, Shimada Y, Shiraishi K, et al. Development of lung adenocarcinomas with exclusive dependence on oncogene fusions. *Cancer Res* 2015;75:2264-71.
- Saito M, Fujiwara Y, Asao T, et al. The genomic and epigenomic landscape in thymic carcinoma. *Carcinogenesis* 2017;38:1084-91.
- Socinski MA, Jotte RM, Cappuzzo F, et al. Atezolizumab for First-Line Treatment of Metastatic Nonsquamous NSCLC. *N Engl J Med* 2018;378:2288-301.
- Hellmann MD, Ciuleanu TE, Pluzanski A, et al. Nivolumab plus Ipilimumab in Lung Cancer with a High Tumor Mutational Burden. *N Engl J Med* 2018;378:2093-104.
- Gandhi L, Rodriguez-Abreu D, Gadgeel S, et al. Pembrolizumab plus Chemotherapy in Metastatic Non-Small-Cell Lung Cancer. *N Engl J Med* 2018;378:2078-92.
- Rizvi NA, Hellmann MD, Snyder A, et al. Cancer immunology. Mutational landscape determines sensitivity to PD-1 blockade in non-small cell lung cancer. *Science* 2015;348:124-8.

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