

# Lung cancer in never smokers—the East Asian experience

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**Abstract:** Approximately one third of all lung cancer patients in East Asia are never-smokers. Furthermore, the proportion of lung cancer in never smokers (LCINS) has been increasing over time. Never-smokers are more often diagnosed with adenocarcinoma in East Asia, a subtype largely defined by oncogenic drivers. In this subgroup of patients, as high as 90% of patients have been found to harbor well-known oncogenic mutations and can be successfully managed with targeted therapies inhibiting specific oncogenic mutant kinases. EGFR tyrosine kinase inhibitor (EGFR-TKI) treatment has been the most important targeted therapy in lung adenocarcinoma from East Asian never-smokers as approximately 70% of these patients have the opportunity to receive EGFR-TKI treatment. Lung squamous cell carcinoma (SQCC) and small cell lung cancer (SCLC) are two common histologic types of smoking-related non-small cell lung cancer (NSCLC). The proportion of never-smokers with SQCC and SCLC in East Asian patients seems to be higher than that in Caucasian patients. Recent studies also suggest that lung SQCC and SCLC in never-smokers may be distinct subtypes. Therefore, better understanding of the biologic characteristics of these subtypes of patients may provide new insights for the treatment. In this review, we will provide an overview of East Asian experience in the treatment of advanced, never-smoking lung cancer, focusing on etiologic factors in the development of LCINS, targeted therapy for never-smokers with adenocarcinoma, distinct characteristics of never-smokers with lung SQCC and SCLC, and the role of immunotherapy in never-smokers with NSCLC.

**Keywords:** Never-smokers; East Asian; targeted therapy; immunotherapy; lung cancer

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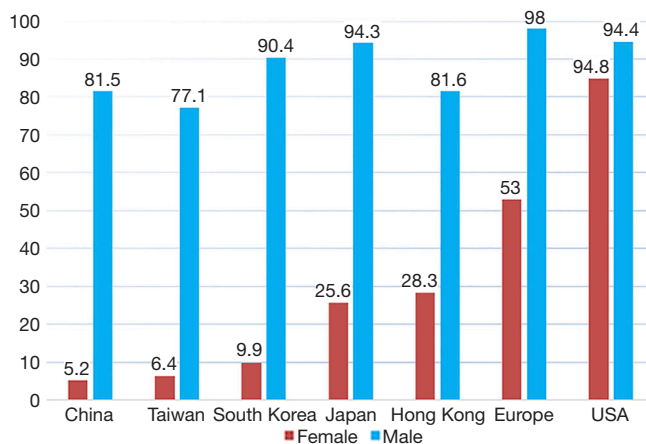
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## Introduction

Lung cancer is the leading cause of cancer-related deaths in China and accounted for an estimated 610,000 deaths in 2015 (1). The majority of lung cancers are thought to be attributed to direct tobacco exposure. However, approximately 10% to 25% of all lung cancers occur in never smokers (2,3), defined as those who smoked fewer than 100 cigarettes during their lifetime. Notably, epidemiologic studies reveal that the proportion of lung cancer in never smokers (LCINS) is higher in East Asia, including China, Japan, Mongolia, North Korea, and South

Korea, and approximately one third of all lung cancer patients are LCINS [39.7% in China (our unpublished data), 38% in South Korea (4) and 32.8% in Japan (5)]. The high proportion of LCINS is mainly due to low smoking prevalence of East Asian females with lung cancer [9.9% in South Korea, 17–25.6% in Japan, 28.3% in Hong Kong, 6.4% in Taiwan, and 5.2% in China (our unpublished data)], which was significantly lower than that in Caucasian female patients (ranging from 53% to 91%) (4-10). Meanwhile, the smoking rate of male patients with lung cancer is similar between East Asia and Western countries (*Figure 1*)



**Figure 1** Smoking prevalence of lung cancer patients by gender in East Asia, Europe and USA.

(4-10). The proportion of LCINS has been increasing over time (5). Although the reason remains unknown, a better understanding of the epidemiologic and biologic characteristics of never-smokers has become increasingly important.

Never-smokers in East Asians are more often diagnosed with adenocarcinoma, a subtype largely defined by oncogenic drivers (11). The proportion of never-smokers in lung squamous cell carcinoma (SQCC) and small cell lung cancer (SCLC) is also higher among East Asian patients than in non-Asian patients (12,13). Therefore, oncologists in East Asia have more opportunities to treat never-smoking patients with non-small cell lung cancer (NSCLC) in clinical practice. In this review, we will provide an overview of the East Asian experience in the treatment of advanced, never-smoking lung cancer.

### Etiologic factors in the development of LCINS

Given the dominant role of tobacco exposure in the development of lung cancer, risk factors that contribute the pathogenesis of lung cancer have also been comprehensively investigated. The role of environmental tobacco exposure in the development of LCINS has been widely studied. A recent pooled study from 18 case-control studies in the International Lung Cancer Consortium, including 766 cases and 1,954 control who were never-smokers from Asian, has demonstrated that exposure to second-hand smoke is associated with an increased risk of lung cancer in never-smokers [odds ratio (OR) = 1.31, 95% confidence interval (CI), 1.17–1.47] (14). Moreover, the strongest association

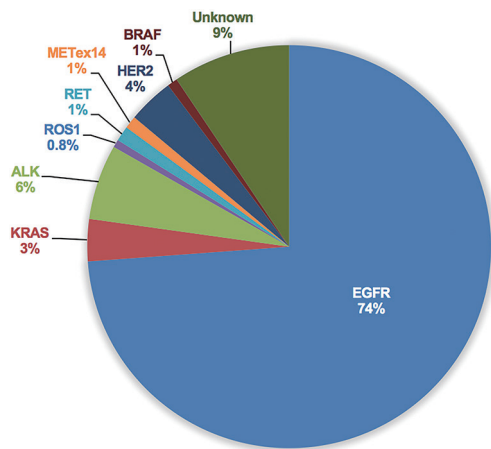
was observed in SCLC (OR = 1.26, 95% CI: 1.10–1.44 for adenocarcinoma; OR = 1.41, 95% CI: 0.99–1.99 for SQCC; OR = 1.48, 95% CI: 0.89–2.45 for large cell lung cancer; OR = 3.09, 95% CI: 1.62–5.89 for SCLC) (14). Based on data from the Global Adult Tobacco Survey (GATS) conducted from December 2009 to March 2010 (15,16), the prevalence of current smokers in adult age more than 15 years old was 28.1% in China, with an estimated more than 300 million current smokers. Due to lack of effective strategies for tobacco control for the public, exposure to second-hand smoke both at home and the workplace may play an important role in the development of LCINS in China.

Another important factor associated with an increased risk of LCINS is exposure to cooking fumes, as several case-control studies have identified cooking oil fumes as a risk factor for lung cancer among Chinese never-smoking women (17-20). A recent meta-analysis including 13 studies, with a total of 3,596 lung cancer women and 6,082 healthy controls also validated the positive relationship between cooking oil fume exposure and lung cancer among Chinese never-smoking women, with a risk ratio (RR) of 1.74 (95% CI: 1.57–1.94) (21).

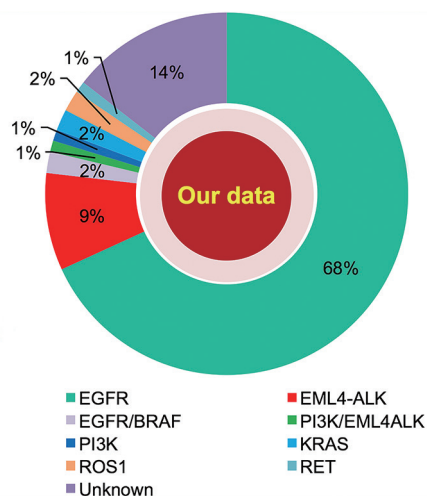
Other factors that play a role in the etiology of LCINS in non-smokers from East Asia also include inherited genetic susceptibility (22-24), occupational and environmental exposure (25), hormonal factors (26), pre-existing lung diseases (27-30), suggesting that the etiopathogenesis of LCINS is a complex process with multiple risk factors involved.

### Lung adenocarcinoma in never-smoking East Asian: a subtype largely defined by oncogenic drivers

Considerable molecular epidemiologic studies have demonstrated that lung adenocarcinoma from East Asian never-smokers is a distinct subtype that can be largely defined by targetable oncogenic drivers (11,31-35) (Figures 2,3). In this subgroup of patients, as high as 90% of patients have been found to harbor well-known oncogenic mutations and LCINS seems to be substantially driven by a single gene (11,32). On the other side, smoking-related lung cancer is a more distinct entity, with higher mutation burden, somatic single-nucleotide variations (SNVs) and higher frequency of C:G→A:T transversions (39). Smoking status may also have an impact on *EGFR* mutations, the frequency of *EGFR* mutations ranged from 22.0% to 43.5% in Chinese smokers with adenocarcinoma (40,41). Therefore, targeted therapy



**Figures 2** Pooled analysis of frequency of driver genes in adenocarcinoma from 8 studies, including 2,126 East Asian Never Smokers (11,31-33,35-38).



**Figure 3** Distribution of common driver genes in never-smokers with adenocarcinoma in cases from Shanghai Pulmonary Hospital, from 2012 to 2016.

inhibiting oncogenic mutant kinases plays a pivotal role for the treatment of lung adenocarcinoma in never-smoking East Asians.

### *EGFR sensitizing mutations*

*EGFR* sensitizing mutation is the most common driver gene found in never-smoker adenocarcinoma from East Asia, constituting 60–78% of this subgroup (11,32,35–37). Robust evidence has identified *EGFR* sensitizing mutation

as the most relevant predictor of response to the *EGFR* tyrosine kinase inhibitors (EGFR-TKIs) (42–44). Several randomized phase III trials have consistently demonstrated that gefitinib, erlotinib and afatinib are more effective in terms of objective response rate (ORR) and progression-free survival (PFS), and better tolerated than standard platinum-based doublet chemotherapy in advanced NSCLC patients harboring *EGFR* activating mutation. Among these trials, IPASS, LUX-LUNG 6 trial was conducted in Asian (45,46), First-SIGNAL trial was conducted in South Korea (47), OPTIMAL, ENSURE, and CONVINCED trial were conducted in China (48–50), WJTOG3405 and NEJ002 trial were conducted in Japan (51,52). To date, EGFR-TKI treatment has been the most important targeted therapy in lung adenocarcinoma from East Asia never-smokers as approximately 70% of these patients have the opportunity to receive EGFR-TKI treatment. Of note, although the above-mentioned trials did not enroll *EGFR*-mutant patients based on histologic type and smoking status, most of the enrolled patients (ranging from 87% to 100%) presented with adenocarcinoma histology. Furthermore, of the 1,416 patients enrolled in the six trials that only included *EGFR*-mutant patients (LUX-LUNG 6, OPTIMAL, ENSURE, CONVINCED, WJTOG3405 and NEJ002 trial), only 27.9% (395/1,416) were former or current smokers. A recent meta-analysis revealed that smoking status may have an adverse impact on the PFS benefit of EGFR-TKI treatment (pooled HR for PFS of never-smokers, 0.32, 95% CI: 0.27–0.37, treatment-smoking interaction P=0.02). However, current or former smokers can also derive PFS benefit from EGFR-TKI treatment (pooled HR for PFS, 0.50, 95% CI: 0.40–0.63) (53).

Although initial response is often tremendous, most patients, if not all, eventually become resistance to EGFR-TKIs. Prospective trials have investigated the role of continuation of EGFR-TKIs beyond progression (54–57). ASPIRATION trial was a phase 2, open-label, single-arm study conducted in Hong Kong, South Korea, Taiwan, and Thailand, including patients with stage IV, *EGFR*-mutant NSCLC (54). Of the 207 enrolled patients, 72.9% (151/207) were never-smokers and 97.1% (201/207) presented with adenocarcinoma histology. ASPIRATION trial demonstrated that continuing erlotinib therapy beyond progression result in a 3.1-month improvement in PFS, suggesting continuing erlotinib therapy beyond progression is feasible in Asian patients. IMPRESS trial was a phase 3 randomized trial that compared the continuation of gefitinib plus chemotherapy with placebo plus chemotherapy

in patients with *EGFR* mutation-positive advanced NSCLC after failure of first-line gefitinib (56). However, continuation of gefitinib in combination with platinum-based chemotherapy did not prolong PFS as compared with chemotherapy alone (median PFS: 5.4 *vs.* 5.4 months, HR =0.86, 95% CI: 0.65–1.13, P=0.27) (56). Recent updated OS and biomarker analyses demonstrated that continuation of gefitinib plus chemotherapy had a detrimental effect on OS when compared with chemotherapy alone (median OS, 13.4 *vs.* 19.5 months, HR =1.44, 95% CI: 1.07–1.94; P=0.016) (57). Furthermore, the detriment effect was significantly shown in patients with T790M mutation-positive plasma samples (HR =1.49, 95% CI: 1.02–2.21, P=0.0432) (57). IMPRESS trial suggested that platinum-based doublet chemotherapy remains the standard of care when acquired resistance develops and the detrimental effect of continuation of gefitinib may be driven by T790M-positive status. Our recent retrospective study also showed that patients may derive modest benefit from continuation of gefitinib in T790M mutation-negative tumors (58).

The emergence of T790M secondary mutations at exon 20 remains the dominant cause of acquired resistance to EGFR-TKIs. T790M mutations occur in about half of acquired resistant cases in East Asian patients (59–61). Furthermore, T790M mutations is also the major acquired resistance mechanism of afatinib in East Asian patients, presenting in 47.6% (20/42) acquired resistant cases (62). Osimertinib (AZD9291) is an oral, potent, irreversible EGFR-TKI selective for both *EGFR* sensitizing mutations and T790M resistance mutations. Serial trials have investigated the efficacy of osimertinib in patients with T790M resistance mutations, with an ORR of 61% to 70% and median PFS of 9.6 to 12.3 months (63–65). AURA3 trial was a randomized, international, open-label, phase 3 trial that compared osimertinib with platinum-based therapy plus pemetrexed in T790M-positive patients (66). Osimertinib resulted in a significant improvement in ORR (71% *vs.* 31%, P<0.001) and PFS (10.1 *vs.* 4.4 months; HR =0.30, 95% CI: 0.23–0.41, P<0.001) when compared with standard chemotherapy. AURA17 was an open-label, single-arm, phase II study that evaluated the safety and efficacy of osimertinib in East Asian T790M-positive patients (67). Of the enrolled 171 patients, the ORR was 63% and median PFS was 9.7 months, which was consistent with the results observed from global data. To date, osimertinib has been approved for patients with T790M resistance mutations after failure of first- or second-generation EGFR-TKIs in China, Japan and South Korea.

### *ALK/ROS1/RET rearrangement*

Chromosomal rearrangement involving receptor tyrosine kinase (RTK) in lung cancer was first discovered in 2007 and currently rearrangements in three major RTKs have been identified as therapeutic targets in NSCLC.

#### **ALK**

*ALK* rearrangement defines another distinct subtype of patients with NSCLC, accounting for about 5% of all NSCLC cases (68). In never-smoker adenocarcinoma from East Asian, the frequency of *ALK* rearrangement range from 4.95% to 9.6% (11,31–35,69), which was similar with that in Caucasian. Crizotinib is an oral small-molecule TKI of *ALK*, *MET*, and *ROS1* kinases and has been approved for the first-line treatment of advanced *ALK*-rearranged NSCLC based on the results from PROFILE1014 trial (70). Nishio *et al.* recently reported a post-hoc analysis of the safety and efficacy of crizotinib in Asian populations from two global phase III trials (PROFILE1007 and PROFILE1014) (71). Consistent with the observations of overall patient populations, crizotinib also demonstrated better PFS (previously treated: 7.7 *vs.* 3.0 months, HR =0.49, 95% CI: 0.37–0.64, P<0.001; previously untreated: 13.6 *vs.* 7.0 months, HR =0.44, 95% CI: 0.30–0.65, P<0.001) and ORR (previously treated:75% *vs.* 22%, P<0.05; previously untreated: 70% *vs.* 54%, P<0.05) *vs.* chemotherapy both in previously treated and untreated Asian patients with *ALK*-positive NSCLC. The safety profile and efficacy were similar between Asian patients and non-Asian patients. PROFILE1029 trial was a randomized, phase 3 trial that compared crizotinib with platinum-based therapy plus pemetrexed in Chinese and Asian patients with *ALK*-positive tumors (72). The median PFS (11.1 months) and ORR (88%) were consistent with that observed in the PROFILE 1014 trial. To date, crizotinib has been proved as standard first-line therapy for patients with *ALK*-positive NSCLC in China, Japan and South Korea. Alectinib is a highly selective *ALK* inhibitor with high brain-penetrant that has shown high anti-tumor activity both in *ALK* inhibitor-naïve and crizotinib-resistant patients (73–75). J-ALEX trial was a randomized, open-label, phase 3 trial comparing alectinib with crizotinib in Japanese patients with previously crizotinib-naïve, advanced *ALK*-positive NSCLC (76). J-ALEX trial showed the superiority of alectinib over crizotinib in terms of PFS (not reached *vs.* 10.2 months, HR =0.34, 99.7% CI: 0.17–0.71, P<0.001). Dose interruptions due to adverse events were also significantly



reduced with use of alectinib as compared with crizotinib (29% *vs.* 74%). The results of J-ALEX trial were further confirmed in ALEX trial and suggested the superiority of alectinib over crizotinib both in Asian and non-Asian *ALK*-positive NSCLC (77).

### ROS1

*ROS1* is another RTK that shares extensive amino acid sequence homology with *ALK*. Clinical characteristics of patients with *ROS1* rearrangement are similar to those observed in patients with *ALK*-rearranged NSCLC (78,79). Although *ROS1* rearrangement was predominantly identified in never-smokers with adenocarcinoma, the alteration has also been found in patient with SQCC (80), adenosquamous (81,82), adenocarcinoma/SCLC (83), and even large cell carcinoma (84). Generally, the frequency rate of *ROS1* rearrangement was very low, with a prevalence ranging from 1% to 2% in Asian patients. Results from a phase I study (PROFILE1001) demonstrated that crizotinib was highly active in patients with *ROS1*-rearranged NSCLC; 72% (36/50) of enrolled patients responded to crizotinib and the PFS was amazing 19.2 months (85). Recently, second-generation *ALK/ROS1* inhibitor (ceritinib) (86), third-generation *ALK/ROS1* inhibitor (lorlatinib) (87) and multitarget TKIs (entrectinib and cabozantinib) (88,89) also demonstrated potent activity in patients with *ROS1*-rearranged NSCLC. In a large East Asian phase II study of crizotinib, the ORR was 69% and median PFS was 13.4 months in 127 patients with *ROS1*-rearranged NSCLC (90). In a South Korean phase II study, 32 patients with *ROS1*-rearranged NSCLC were treated with ceritinib (86). The ORR was 62% and median PFS was 9.3 months for all patients and 19.3 months for crizotinib-naïve patients.

Approximately 1% of lung adenocarcinoma are driven by oncogenic *RET* rearrangements (91). *RET*-rearranged tumors are commonly found in young never-smokers with a solid-predominant subtype of adenocarcinoma, constituting 1.4% of NSCLC and 1.7% of adenocarcinoma in Chinese patients (91). Consistently, the identified *RET*-rearranged patients in our previous study were all never-smokers (92). Independent investigators have evaluated the role of multitarget *RET* inhibitors, such as cabozantinib and vandetanib, in *RET*-rearranged NSCLC (93–95). Yoh *et al.* recently reported the activity of vandetanib in 19 patients with *RET*-rearranged Japanese NSCLC in a phase II trial (94). The ORR, median PFS, and median OS in overall patients were 47%, 4.7 months, and 11.1 months. Of note, the *CCDC6-RET* subtype showed a higher sensitivity to

vandetanib than did the *KIF5B-RET* subtype [ORR: 20% (2/10) *vs.* 83% (5/6); median PFS: 2.9 *vs.* 8.3 months; median OS: 11.1 months *vs.* not reached] (94). GLORY (the Global, Multicenter *RET* Registry) was the largest single database of patients with *RET*-rearranged lung cancers (96). When the data was carried out, 165 patients with *RET*-rearranged NSCLC from 29 centers across Europe, Asia, and the USA were accrued. Of those, 53 patients were treated with a *RET* inhibitor. The ORR, median PFS, and median OS were 26%, 2.3 months and 6.8 months, respectively. Regarding specific *RET* inhibitors, the ORR of cabozantinib, vandetanib, and sunitinib was 37%, 18%, and 22%, median PFS was 3.6, 2.9, and 2.2 months and median OS was 4.9, 10.2 and 6.8 months, respectively. Notably, the ORR and PFS or OS were not statistically significant different by various fusion subtypes (*KIF5B vs.* other partner) (96).

In summary, the epidemiologic and clinical characteristics of East Asian patients with *ALK/ROS1/RET* rearrangements were similar with those of Caucasian patients. Although clinically meaningful benefit was seen with *RET* inhibition therapy in both Asian and non-Asian patients, its activity was lower than those treated with *ALK* or *ROS1* inhibitors in patient with *ALK* or *ROS1* rearrangements. Multikinase inhibitors might not be the most effective strategy for this subtype of patients and highly *RET*-specific TKIs are needed.

### *MET 14 exon (METex14) skipping*

*METex14* skipping has been recently identified as a rare oncogenic alteration in NSCLC (97), with an overall frequency of 2.7–3.0% in Caucasian patients (97,98). Among 795 East Asian NSCLC patients, the prevalence of *METex14* skipping was 2.1% (17/795) (99). Of 45 patients with quintuple-negative lung adenocarcinoma (*EGFR/KRAS/ALK/ROS1/RET* negative), 37.8% (17/45) of patients had *METex14* skipping. The incidence of never-smokers in patients with *METex14* skipping (41.2%) was significantly lower than that in patients with *EGFR* mutations or *ROS1* rearrangements (99). In another study including 1,296 Chinese patients with NSCLC, *METex14* skipping occurred in 1% (12/1,296) of all NSCLC cases (100). Of these cases, 10 were with adenocarcinoma histology, 1 with adenosquamous, and 1 with SQCC. Among *METex14* skipping adenocarcinoma, 50% were never-smokers. The prevalence of *METex14* skipping in East Asian patients (1% to 2.1%) seemed to a bit lower than that in Caucasian patients (38,98,100). Preclinical data and case reports

suggested that patients with METex14 skipping can derive clinical benefit from MET inhibitors (crizotinib and INC280) (97,101). However, in two cases of Chinese patients with METex14 skipping treated with crizotinib, 1 patient responded to crizotinib with a PFS of 9 months and the other one experienced disease progression only 1 month later, mainly due to co-existing with *Kras* mutations (100).

### **HER2 mutations**

*HER2* is a member of the *EGFR* family of RTKs, which also includes *EGFR* (*HER1*), *HER3* and *HER4*. In the Chinese population, the prevalence of *HER2* mutations ranged from 2.4% to 5.94%, a little more common than Caucasian population (11,32,35,69,102-104). In our previous study, *HER2* mutation was detected in 4.8% (22/456) of *EGFR* wild-type lung adenocarcinoma (105). Recently, *HER2* inhibition therapy with small molecular TKIs, such as afatinib, dacomitinib, neratinib, and lapatinib, may represent a promising therapeutic option in patients with *HER2* mutations (106-110). Pyrotinib (SHR1258, discovered by Shanghai Hengrui Pharmaceutical CO., Ltd.) was a novel irreversible *EGFR/HER2* dual TKI and demonstrated robust anti-tumor activity in *HER2*-positive breast cancer both *in vivo* and *in vitro* (111). In a phase I study of pyrotinib in *HER2*-positive metastatic breast cancer, the maximum tolerated dose was established as 400 mg (112). Of 36 evaluable patients, the ORR was 50% and median PFS was 35.4 weeks. Furthermore, the ORR was impressive and 10 out of 12 (83.3%) patients achieved an objective response in trastuzumab-pretreated patients. Ren *et al.* recently reported preliminary results of a phase II study about the efficacy and safety of pyrotinib in Chinese patients with *HER2*-mutant advanced NSCLC (113). By Jul 21, 2016, 11 patients were treated with pyrotinib at a dose of 320 or 400 mg orally per day. The ORR was 54.5% (6/11) and disease control rate (DCR) was 81.1% (8/11). The median PFS was 6.2 months and side effects were mild. This trial is still ongoing (NCT02535507) and we expectantly await further results.

### **Lung SQCC or SCLC in never-smoking East Asian: potentially distinct subtypes?**

Lung SQCC and SCLC are two common histologic type of smoking-related lung cancer. The incidence of never-smoking lung cancer increased over time both in Asian patients and non-Asian patients, although the reason

remains unknown. Furthermore, the proportion of never-smokers is higher among Asian patients with lung cancer than in non-Asian patients, therefore, a better understanding of the epidemiologic and biologic characteristics of never-smokers has become increasingly important, especially in Asian patients.

Huang *et al.* recently characterized the clinical features and specific driver genes status of never-smoking lung SQCC in 597 Chinese patients (114). Overall, 14.7% (88/597) were never-smokers. The never-smokers were more likely to be female patients than ever-smokers (42.05% *vs.* 1.57%,  $P < 0.001$ ). Among the 76 never-smokers who had high quality tissue to detect oncogenic mutations, 16 harbored known oncogenic mutations, including 10 (13.16%) *EGFR* mutations, 1 (1.32%) *Kras* mutations, 2 (2.63%) *HER2* mutations, 1 (1.32%) *BRAF* mutations, 2 (2.63%) *PIK3CA* mutations and 2 (2.63%) *FGFR* fusion. The prevalence of oncogenic drivers was significantly higher in never-smokers than that in ever-smokers (21.05% *vs.* 11.05%,  $P = 0.023$ ), especially *EGFR* mutations (13.16% *vs.* 3.40%,  $P = 0.001$ ). Furthermore, never-smokers tended to have poorer OS than ever-smokers. In another study of South Korean patients, 5.0% (19/379) were never-smokers (115). Similarly, of these 19 patients, 52.5% (10/19) were females. The investigators further analyzed fifty cancer-related genes in never-smokers (12 patients) and ever-smokers (14 patients). Although the distribution of hotspot mutations in never-smokers was similar to that in ever-smokers, *EGFR* mutations were found in both never-smokers and ever-smokers. Generally, in SQCC patients with *EGFR* sensitizing mutations, *EGFR*-TKIs are generally less effective than in adenocarcinoma (116). Of note, in that study, among 4 never-smokers with lung SQCC with evaluable data, 1 achieved complete response, 1 achieved partial response, and 2 achieved stable disease (116). In another study conducted in China, among 51 non-adenocarcinoma patients with *EGFR* sensitizing mutations treated with *EGFR*-TKIs (26 with SQCC), the median PFS was longer in never-smokers than ever-smokers (5.49 *vs.* 3.78 months,  $P = 0.036$ ) (117). Several cases also observed a significantly clinical benefit from crizotinib or alectinib in patients with *ALK/ROS1*-rearranged SQCC (118-122) (Table 1). Interestingly, all these patients mentioned above were never-smokers and one patient who did not respond to alectinib was an ever-smoker SQCC (123) (Table 1). These results, at least in part, suggest that lung SQCCs in never-smokers may be a distinct subtype, and further research into lung SQCC in never-smokers is needed.

**Table 1** Cases of East Asian patients with squamous cell carcinoma harboring *ALK/ROS1* fusions

Author	Year	Race	Gender	Age (years)	Pathology	Smoking status	Stage	Molecular alteration	treatment	Best response	PFS (months)	Reference
Wang <i>et al.</i>	2014	Chinese	Female	55	SQCC	Never	IV	ALK fusion	Crizotinib	Partial response	5.8+	(118)
Zhang <i>et al.</i>	2015	Chinese	Female	55	SQCC	Never	IV	ALK fusion	Crizotinib	Partial response	6	(119)
Wang <i>et al.</i>	2016	Chinese	Female	37	SQCC	Never	IIIB	ALK fusion	Crizotinib	Partial response	9+	(120)
Mamesaya <i>et al.</i>	2017	Japanese-Brazilian	Female	52	SQCC	Never	IV	ALK fusion	Alectinib	Partial response	11+	(121)
Li <i>et al.</i>	2017	Chinese	Female	47	SQCC	Never	IV	ALK-ROS1 fusion	Crizotinib	Partial response	5	(122)
Tamiya <i>et al.</i>	2015	Japanese	Male	78	SQCC	Ever	Unknown	ALK fusion	Alectinib	Stable disease	1.5+	(123)

PFS, progression-free survival; SQCC, squamous cell carcinoma.

The prevalence of never-smokers with SCLC in Caucasian patients is very low, accounting for 2.0% to 2.5% of all SCLC cases (124,125). Two recent studies showed that the proportion of never-smokers with SCLC in East Asian patients was higher than that in Caucasian patients (12,13). In the study by Sun *et al.*, 13% (50/391) were never-smokers in South Korean patients. In our study, 22.8% (69/303) were never-smokers in Chinese patients (12). Furthermore, more than 80% of never-smokers were females. Both studies demonstrated that never-smokers with SCLC had better survival than ever-smokers (12,13). Of 28 genetically evaluable never-smokers, *EGFR* mutations were detected in four cases (14.3%), and other molecular alterations included *TP53* in 26 cases (92.9%), *RB1* in 7 cases (25%), *PTEN* in 5 cases (17.9%), *MET* in 4 cases (14.3%), and *SMAD4* in 3 cases (10/7%) in the study by Sun *et al.* (13). Although *EGFR* mutations can be found in SCLC phenotypically transformed from adenocarcinoma as an acquired resistance mechanism to *EGFR*-TKIs, these 4 cases were found in patients with *de novo* SCLC. A recent case revealed that one never-smoking patient with *de novo* SCLC harboring *EGFR* exon 19 deletion but had no response to erlotinib (126). However, due to the high proportion of never-smokers among Asian SCLC patients, better understanding of the biologic characteristics of these subtypes of patients may provide new insights for the treatment strategies that have not changed for decades.

### Immunotherapy in never-smoking East Asian: can a patient population not always be blessed?

Immunotherapy with immune checkpoint blockade

targeting the programmed-death 1/programmed-death ligand 1 (PD-1/PD-L1) axis represents a novel approach for the treatment of patients with advanced NSCLC (127). Several randomized trials have demonstrated a significant survival advantages of PD-1/PD-L1 antibodies over docetaxel as second-line therapy (128-132). Furthermore, pembrolizumab has been approved as first-line therapy for advanced NSCLC patients with PD-L1 positive tumors ( $\geq 50\%$ ) based on the results of KEYNOTE-024 trial (133). Of note, the current obstacle to the wide use of anti-PD-1/PD-L1 antibodies is lack of biomarker to identify beneficial patient population because only about 20% of patients with NSCLC respond to anti-PD-1/PD-L1 antibodies. Tumor mutation burden (TMB) has recently been identified as a promising biomarker for response to immune checkpoint inhibitors (134). Patients with high nonsynonymous burden had higher ORR (63% *vs.* 0%,  $P=0.03$ ) and better PFS (14.5 *vs.* 3.7 months, HR =0.19, 95% CI: 0.05–0.70,  $P=0.01$ ) than those with low nonsynonymous burden. High TMB can increase the number of neoantigens, which are recognized by T cells, therefore enhancing tumor immunogenicity and leading to an antitumor immune response (134). These preliminary findings have been confirmed in an exploratory analysis of CheckMate-026 trial (135). In CheckMate-026 trial, although nivolumab did not prolong the PFS as compared with chemotherapy in patients with previously untreated advanced NSCLC with PD-L1-positive tumors ( $\geq 5\%$ ), the ORR (47% *vs.* 28%) and PFS (9.7 *vs.* 5.8 months, HR =0.62, 95% CI: 0.38–1.00) were significantly improved with the use of nivolumab in patients with high TMB (135). Genomic analysis has demonstrated that smokers had a significantly higher number of mutations

per Mb (median 10.5, range 4.9–17.6) than never-smokers with NSCLC (median 0.6, range 0.6–0.9) (134). Therefore, smokers are more likely to induce greater TMB and derive clinical benefit from checkpoint inhibitors than never-smokers. Interestingly, Kinoshita *et al.* found that non-smokers with adenocarcinoma can generate an immunosuppressive tumor microenvironment and inhibit CD8<sup>+</sup> T-cell activation, suggesting checkpoint inhibitors may not be effective in this subtype of patients (136). However, in a recent meta-analysis, the treatment benefit for checkpoint inhibitors was independent of smoking history (current and former smokers *vs.* never smokers: HR for death, 0.69 *vs.* 0.79; interaction,  $P=0.40$ ) (137). Actually, it is the molecular smoking signature rather than self-reported smoking history that is significantly related to the clinical benefit from checkpoint inhibitors (134). Therefore, there is currently lack of robust evidence to select the beneficial population by smoking history for checkpoint inhibitor therapy.

As mentioned above, the vast majority of never-smoking East Asians with NSCLC have adenocarcinoma, a subtype largely defined by oncogenic drivers. Although tremendous efficacy has been achieved in these patients with the administration of targeted therapy, the survival outcomes are not satisfactory. Whether checkpoint inhibitors can generate a durable response of these patients, therefore, becomes of great importance. However, recent randomized trials and meta-analysis revealed that patients with *EGFR* mutations did not derive survival benefit from checkpoint inhibitors (128-132,138). A recent retrospective study also demonstrated that *EGFR* mutations or *ALK* rearrangement was associated with low response to checkpoint inhibitors (3.6%, 1/28) (139). The poor response to checkpoint inhibitors in patients with *EGFR* mutations or *ALK* rearrangement may result from a potentially immunosuppressive microenvironment in these patients (139). *EGFR* mutation was also correlated with uninflamed phenotype and weak immunogenicity, with decreased PD-L1 expression, lack of T-cell infiltration, and lower TMB (140). A recent report showed that High CD73 expression in *EGFR*-mutant NSCLC may be another cause that contribute to the reduced benefit from checkpoint inhibitors, which can alter immune cell function and is correlated with low PD-L1 expression (141). Sabari *et al* recently reported preliminary results of immunotherapy in NSCLC with METex14 skipping (142). However, only 1 patient (6.7%, 1/15) responded to checkpoint inhibitors and median PFS was only 2.3 months. TMB was lower in

patients with METex14 skipping and no partial response was observed even in patients with high TMB (142). Current evidence suggests that never-smoking adenocarcinoma from East Asia, the potentially beneficial population of targeted therapy, do not seem to be the same beneficial population of immunotherapy.

Notably, although this review focuses on East Asia, most of the data comes from China, Japan, and South Korea and we have little information about Mongolia and North Korea. Furthermore, China is a huge country with a diverse ethnic population. Almost all the reported data in Chinese targets Han population. As the ethnic minorities have distinct life-styles, growing backgrounds, diets and living conditions compared with Han population, the genetic profiles may also differ. For example, Uyghur population, mainly living in North-west of China, had significantly lower *EGFR* mutation rate than Han population (12% *vs.* 55.1%) (143). Therefore, these experiences and treatment strategies cannot be directly generalized to other East Asians, namely Mongolians and North Koreans, and Chinese ethnic minorities, and further studies are still needed in these populations.

## Conclusions

In summary, approximately one third of all lung cancer patients in East Asia are LCINS. Never-smokers are more often diagnosed with adenocarcinoma in East Asian, a subtype largely defined by oncogenic drivers. In this subgroup of patients, as high as 90% of patients have been found to harbor well-known oncogenic mutations and can be successfully managed with targeted therapy inhibiting specific oncogenic mutant kinases. Lung SQCC and SCLC are two common histologic type of smoking-related NSCLC. The incidence of LCINS also increases over time in East Asian patients. Recent studies suggest that lung SQCC and SCLC in never-smokers may be distinct subtypes, and better understanding of the biologic characteristics of these subtypes of patients may provide new insights for the treatment of these patients. Although Immunotherapy with immune checkpoint blockade generates durable response in some patients with advanced NSCLC, lung adenocarcinoma from East Asian never-smokers do not seem to be the beneficial population. These findings may reflect the considerably lower total mutation burden (and thus fewer neoantigens) in never smokers. However, there is currently lack of robust evidence to guide checkpoint inhibitor treatment by smoking history.



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## Footnote

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