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ORIGINAL ARTICLE – CLINICAL ONCOLOGY

Impact of EGFR mutation on the clinical efficacy of PD-1 inhibitors in patients with pulmonary adenocarcinoma

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Abstract

Purpose We evaluated the predictive role of EGFR mutation on the efficacy of PD-1/PD-L1 inhibitor therapy in patients with advanced pulmonary adenocarcinoma while considering clinical factors such as PD-L1 expression, gender, and smoking status.

Methods Patients were required to have available data for EGFR mutation, PD-L1 expression, and efficacy of PD-1/PD-L1 inhibitors.

Results Among 178 patients with EGFR-mutant ($n=38$) or wild-type (WT) ($n=140$) tumors, the EGFR mutation group had a lower objective response rate (ORR) (15.8% vs. 32.9%, $p=0.04$) than the EGFR WT group, similar to the pattern observed for other factors: weak/negative PD-L1 expression vs. strong PD-L1 expression (17.3% vs. 39.2%, $p=0.001$); never smokers vs. smokers (19.4% vs. 35.1%, $p=0.03$); and females vs. males (21.0% vs. 33.6%, $p=0.08$). EGFR mutation and weak/negative PD-L1 expression were associated with a significantly shorter median PFS than EGFR WT (1.9 vs. 3.0 months, $p=0.04$) and strong PD-L1 expression (1.6 vs. 3.9 months, $p=0.007$), respectively. In multivariate analysis, EGFR mutation predicted worse ORR [hazard ratio (HR) 3.15; 95% confidence interval (CI) 1.15–8.63] and PFS (HR 1.75, 95% CI 1.11–2.75), as did weak/negative PD-L1 expression (ORR, HR 3.46, 95% CI 1.62–7.37; and PFS, HR 1.72, 95% CI 1.17–2.53).

Conclusions Together with PD-L1 expression, EGFR mutation status is an important factor to predict the efficacy of PD-1/PD-L1 inhibitors in patients with pulmonary adenocarcinoma.

Keywords Pulmonary adenocarcinoma · Epidermal growth factor receptor · Programmed cell death-ligand 1 · Predictive factor

Introduction

Inhibitors of PD-1/PD-L1 have rapidly changed the treatment paradigm for advanced non-small cell lung cancer (NSCLC). PD-1/PD-L1 inhibitors have been shown to result in superior survival outcomes than chemotherapy as second-line therapy (Borghaei et al. 2015; Brahmer et al. 2015; Herbst et al. 2016; Rittmeyer et al. 2017), and first-line pembrolizumab or nivolumab monotherapies are associated with longer overall survival than platinum-doublet chemotherapy in groups with strong PD-L1 expression or high tumor mutation burden (TMB), respectively (Carbone et al. 2017; Reck et al. 2016).

Until now, PD-L1 expression and TMB have been regarded to be the most reliably predictive markers of the efficacy of PD-1/PD-L1 inhibitors. However, many patients who were expected to respond to PD-1/PD-L1 inhibitors based on these biomarkers failed to benefit from immunotherapy, and vice versa. In other words, these predictive factors for PD-1/PD-L1 inhibitors are clinically incomplete and need to be further researched. Epidermal growth factor receptor (EGFR) mutation is a good predictive factor of the efficacy of EGFR tyrosine kinase inhibitors. However, the predictive role of EGFR mutation on the efficacy of PD-1/PD-L1 inhibitors is unclear. In subgroup analyses of data from some randomized trials, PD-1/PD-L1 inhibitor

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treatment of EGFR-mutant subgroups did not yield survival benefits (Borghaei et al. 2015; Herbst et al. 2016; Rittmeyer et al. 2017). The recent ATLANTIC trial assessed the impact of EGFR mutation by enrolling patients with EGFR-mutant or EGFR wild-type (WT) NSCLC into two different cohorts (Garassino et al. 2018). Among patients with strong PD-L1 expression (PD-L1 ≥ 25%), response rates and progression-free survival in response to durvalumab treatment were 12.2% and 1.9 months, respectively, in the EGFR mutation cohort, while they were 16.4% and 3.3 months, respectively, in the EGFR WT cohort. These data suggest that EGFR mutation is associated with inferior efficacy of PD-1/PD-L1 inhibitors, even in the group with strong PD-L1 expression.

EGFR mutations are found in 32% of worldwide NSCLC cases, with 39% of tumors in those of Asian ethnicity and 17% of individuals of Caucasian ethnicity (Zhang et al. 2016). The prevalence of EGFR mutation is higher in pulmonary adenocarcinoma; 51% of pulmonary adenocarcinoma have EGFR mutations in East Asian patients (Shi et al. 2014). The high prevalence of EGFR mutation makes it more important to evaluate whether EGFR mutation is truly a negative predictive factor of PD-1/PD-L1 efficacy.

EGFR mutation is also strongly associated with several clinical factors such as lower PD-L1 expression, never-smoking status, or females (Cho et al. 2018; Yoneshima et al. 2018), which could also independently impact the efficacy of PD-1/PD-L1 inhibitors. A large meta-analysis study recently showed that immune checkpoint inhibitors were significantly less beneficial in females than males (Conforti et al. 2018). A retrospective study showed lower response rates to PD-1/PD-L1 inhibitors in never or light smokers than in heavy smokers (4.2% vs. 20.6%) (Gainor et al. 2016). In addition, the efficacy of pembrolizumab decreased in female or never-smoker subgroups in subgroup analyses of data from a large randomized trial (Brahmer et al. 2017).

Therefore, we assessed the impact of EGFR mutation on the efficacy of PD-1/PD-L1 inhibitors taking possible confounding factors such as PD-L1 expression, gender and smoking status into consideration. Here, we analyzed the clinical outcomes of PD-1/PD-L1 inhibitors in pulmonary adenocarcinoma to evaluate the predictive role of EGFR mutation on the efficacy of PD-1/PD-L1 therapy.

Materials and methods

A total of 450 patients with advanced NSCLC received PD-1/PD-L1 inhibitors (pembrolizumab or nivolumab) during their disease course at Samsung Medical Center between November 2015 and March 2018. To be eligible for this study, patients were required to be 18 years or older and have histologically documented adenocarcinoma. Other eligibility criteria were that patients had data available regarding EGFR mutation status, PD-L1 expression status, and response to PD-1/PD-L1 inhibitor therapy based on the Response Evaluation Criteria In Solid Tumors (RECIST) (Eisenhauer et al. 2009).

PD-L1 expression was assessed in formalin-fixed tumor samples obtained from core needle biopsies, excisional biopsies, or resected tissue collected at the time of diagnosis of metastatic disease. Assessment of PD-L1 expression was done by pathologist in our institution using the PD-L1 22C3 pharmDx assay (Dako, Carpinteria, CA) or/and SP263 (Ventana, Tucson, AZ). Tumor cells showing membranous staining for PD-L1 were considered PD-L1-positive cells. PD-L1 expression status was estimated as the percentage of PD-L1-positive cells out of total tumor cells. We defined strong PD-L1 expression as ≥ 50% PD-L1-positive cells for 22C3 PD-L1 antibody or ≥ 25% PD-L1-positive cells for SP263 antibody staining among total tumor cells (Garassino et al. 2018; Herbst et al. 2016; Kim et al. 2017). Conversely, tumors with fewer PD-L1-positive cells than the level defined above were considered as weak or negative PD-L1 expression.

EGFR mutations were identified by one of the following local test methods: PNA clamping, direct sequencing, and next-generation sequencing. Tumor responses were analyzed per RECIST v1.1 by the investigator (Eisenhauer et al. 2009). Progression-free survival (PFS) was defined from the time of treatment initiation to clinical/radiographic progression or death. Patients were divided according to smoking status as never smokers (< 100 lifetime cigarettes) or smokers. All statistical analyses were performed using IBM SPSS ver. 21.0 (IBM Co., Armonk, NY). A Chi-square test was used to compare categorical characteristics, response rates, and PD-L1 positivity between those with EGFR-mutant vs. EGFR WT tumors. For continuous variables, two-tailed Student *t* tests were used to compare demographic and clinical characteristics between the patient arms. Survival rates and 95% confidence intervals (CIs) were calculated using the Kaplan–Meier method. The PFS difference between groups was assessed using the log-rank test. A p value of < 0.05 was considered significant.

Correlations between PD-L1 expression statuses assessed with 22C3 and SP263 antibodies were examined using Pearson correlation coefficients. Multivariate logistic regression analysis and Cox proportional hazards models were used to define independent predictors for objective response rate (ORR) and PFS, respectively.

Results

Patient characteristics

We identified 178 eligible patients with EGFR-mutant ($N = 38$) or EGFR WT ($N = 140$) NSCLC; these patients

were treated with either nivolumab or pembrolizumab. Baseline clinical characteristics of patients are summarized in Table 1. EGFR mutation group had more never smokers (52.6% vs. 33.6%) and females (47.4% vs. 31.4%) than the EGFR WT group. The median number of prior lines of chemotherapy among EGFR WT patients was one (range 0–6), whereas that of EGFR-mutant patients was two (range 1–8). In the EGFR mutation group, all patients with the exception of two received EGFR tyrosine kinase inhibitor treatment before pembrolizumab or nivolumab therapy.

Table 1 Clinical characteristics of patients with EGFR mutation and EGFR wild type

Characteristic	EGFR mutation ($N=38$)	EGFR wild type ($N=140$)	p
Age at diagnosis			
Median	62.5	61.0	0.51
Range	40–75	33–87	
Sex, *n* (%)			
Male	20 (52.6)	96 (68.6)	0.07
Female	18 (47.4)	44 (31.4)	
Smoking history, *n* (%)			
Never smoker	20 (52.6)	47 (33.6)	0.03
Smoker	18 (47.4)	93 (66.4)	
ECOG			
0	0	5 (3.6)	0.13
1	34 (89.5)	118 (84.3)	
2	3 (7.9)	17 (12.1)	
3	1 (2.6)	0	
Prior lines of chemotherapy			
Median	2	1	0.03
Range	0–5	0–6	
EGFR mutation			
Deletion 19	17 (44.7)	N/A	N/A
L858R	16 (42.1)	N/A	
T790M + deletion 19 or L858R	3 (7.9)	N/A	
Uncommon	5 (13.2)	N/A	
PD-1 inhibitors			
Nivolumab	13 (34.2)	68 (48.6)	0.12
Pembrolizumab	25 (65.8)	72 (51.4)	
PD-L1 expression			
Strong	22 (57.9%)	75 (53.6%)	0.64
Weak or negative	16 (42.1%)	65 (46.4%)	

NA not applicable

Strong or weak/negative PD-L1 expression

All 178 patients enrolled in our study had been evaluated for PD-L1 expression status with either 22C3 ($n=172$) or SP263 antibodies ($n=91$). More cases showed strong PD-L1 expression with 22C3 antibodies than with SP263 (Table 2), consistent with the results of a previous study (Kowantz et al. 2018). About 52% ($n=90$) of tumors evaluated with the 22C3 antibody showed PD-L1 expression in ≥ 50% of tumor cells, while 23% ($n=21$) and 7% ($n=6$), respectively, showed PD-L1 expression ≥ 50% and 25–49% of tumor cells when tested with the SP263 antibody. To evaluate the correlation of PD-L1 expression with the expression of these two antibodies, we compared the data from 85 patients tested for both 22C3 and SP263 antibodies. In the comparison of continuous variables, the Pearson correlation coefficient was 0.76, suggesting a strong correlation between the results from two antibodies (Supplementary Fig. 1). When compared by categorical variables (strong vs. weak/negative PD-L1 expression) using Chi square test, the Cohen's kappa coefficient (κ) was 0.644, suggesting a substantial agreement (Table 3). Based on the definition of strong PD-L1 expression in our study (either ≥ 50% of tumor cells positive by 22C3 antibody or ≥ 25% tumor cells positive by SP263 antibody), a total of 97 patients were regarded to have strong PD-L1-expressing tumors while the remaining 81 patients were considered to have weak/negative PD-L1-expressing tumors.

Efficacy according to PD-L1 expression, EGFR mutation, smoking, and gender

The ORRs were 39.2% and 17.3% for the strong and weak/negative PD-L1 expression groups, respectively ($p=0.001$). PFS in the strong PD-L1 expression group was

Table 3 Correlation between PD-L1 expression as assessed by 22C3 PharmDx and SP263 antibodies using the Cohen's kappa coefficient (κ) for categorical variable

($\kappa=0.644$)	22C3 strong (≥ 50%)	22C3 weak/negative (< 50%)
SP263 strong (≥ 25%)	20 (23.5%)	6 (7.1%)
SP263 weak/negative (< 25%)	7 (8.2%)	52 (61.2%)

Table 2 PD-L1 expression status assessed by PD-L1 22C3 pharmDx assay and SP263 antibodies in the whole study population

	0	1–9%	10–24%	25–49%	≥ 50%
22C3 ($N=172$)	41 (23.8%)	15 (8.7%)	18 (10.5%)	8 (4.7%)	90 (52.3%)
SP263 ($N=91$)	31 (34.1%)	16 (17.6%)	17 (18.7%)	6 (6.6%)	21 (23.1%)

also significantly longer than in the weak/negative PD-L1 expression group (median PFS 3.9 months vs. 1.6 months, $p=0.007$) (Fig. 1a).

Objective responses were observed in 46 of 140 (32.9%) EGFR WT patients, while only 6 patients showed a partial response among the 38 patients with EGFR-mutant tumors (15.8%) ($p=0.04$). Median PFS was 3.0 months in the EGFR WT group vs. 1.9 months in the EGFR mutation group ($p=0.04$) (Fig. 1b).

Smokers showed a higher response rate than never smokers (35.1% vs. 19.4%, $p=0.03$), with a slightly longer median PFS (2.8 m vs. 2.1 m, $p=0.22$). Though male patients had an apparently higher response rate (33.6% vs. 21.0%. $p=0.08$) and longer median PFS (2.8 m vs. 2.1 m, $p=0.26$) than females, these differences were not statistically significant.

Multivariate analysis for ORR and PFS

ORR and PFS for PD-1/PD-L1 inhibitors differed significantly according to EGFR mutation status as well as PD-L1 expression status. To evaluate the independent effect of EGFR mutation on clinical outcomes of PD-1/PD-L1 inhibitor treatment, we performed multivariate analysis. Factors included into the analysis were PD-L1 expression status, smoking status, gender, ECOG performance status, and line of prior chemotherapy, which were considered possible confounding factors.

In multivariate analysis for ORR, EGFR mutation [hazard ratio (HR) 3.15, 95% confidence interval (CI) 1.15–8.63], and weak/negative PD-L1 expression (HR 3.46, 95% CI 1.62–7.37) were significant predictors of a lower ORR. In multivariate analysis for PFS, EGFR mutation (HR 1.75, 95% CI 1.11–2.75), weak/negative PD-L1 expression (HR 1.72, 95% CI 1.17–2.53), and poor ECOG performance status (ECOG 2 or 3) (HR 2.12, 95% CI 1.28–3.51) were significant predictors of a shorter PFS (Table 4).

ORR-combined analysis with PD-L1 expression, EGFR mutation status, smoking status, and gender

To determine how EGFR mutation status, smoking status, or gender affected response rates to PD-1/PD-L1 inhibitors, we compared subgroups classified by these characteristics in both strong and weak/negative PD-L1 expression cohorts.

In the strong PD-L1 expression cohort, ORRs were 22.7% and 44.0% in the EGFR mutation and WT groups, respectively ($p=0.07$) (Fig. 2a). In those patients with strong PD-L1 expression and EGFR mutation, the ORR for smokers was higher than that for never smokers (30.0% vs. 16.7%), and males had higher response rates than females (30.0% vs. 16.7%) (Fig. 2a). In patients with tumors with strong PD-L1 expression that were EGFR WT, being a smoker or male was also associated with a higher response rate than being a never smokers or a female, respectively (Fig. 2a).

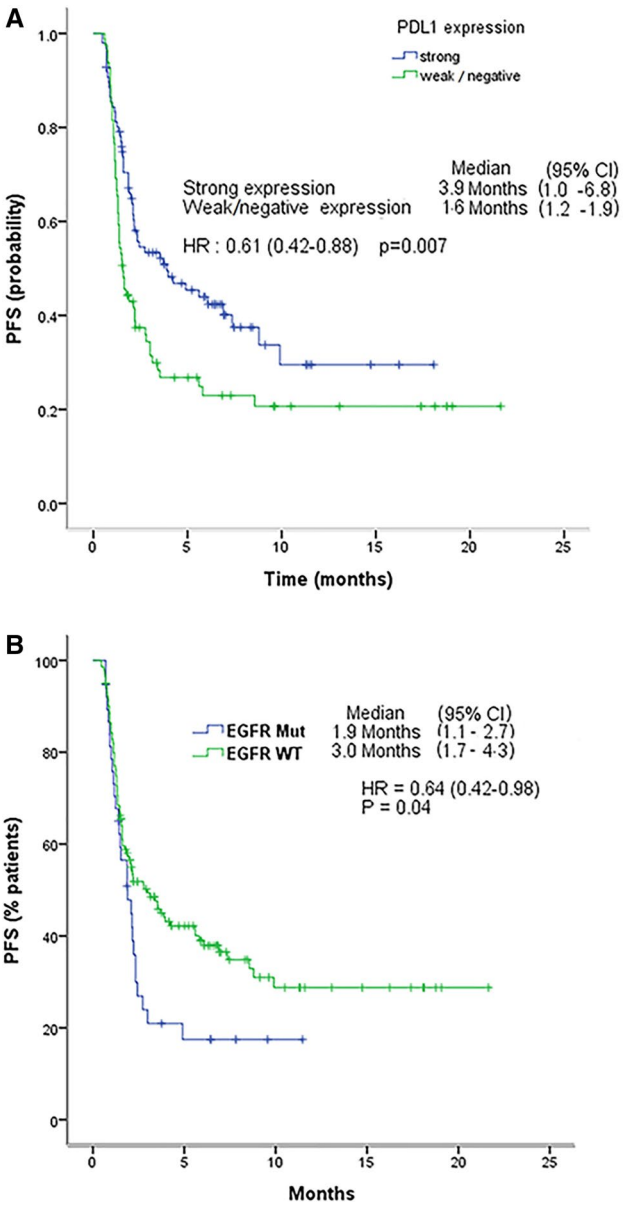

Fig. 1 Comparison of progression-free survival (**a**) in the weak/negative PD-L1 expression and strong PD-L1 expression groups. Progression-free survival (**c**) is also shown for EGFR mutation and EGFR wild-type groups

In the weak/negative PD-L1 expression cohort, ORRs were 6.3% and 20.0% for the EGFR mutation and WT groups, respectively ($p=0.28$) (Fig. 2b). In patients with weak/negative PD-L1 expression who were EGFR WT, ORR was slightly higher in smokers or males than never smokers or females, respectively (23.7% vs. 14.8%, 22.0% vs. 16.7%). However, it was hard to evaluate the effect of smoking status or gender in the group with weak/negative

Table 4 Multivariate analysis for objective response rate and progression-free survival

	No. of patients (%)	Objective response rate					Progression-free survival				
		%	Univariate	Multivariate			Median (months)	Univariate	Multivariate		
			p	HR	95% CI	*p*		*p*	HR	95% CI	*p*
Gender											
Female	62 (34.8)	21.0	0.08	0.98	0.28–3.41	0.97	2.1	0.27	1.08	0.58–2.01	0.80
Male	116 (65.2)	33.6					2.8				
PD-L1 expression											
Negative/weak	81 (45.5)	17.3	0.002	3.46	1.62–7.37	0.001	1.6	0.008	1.72	1.17–2.53	0.006
Strong	97 (54.5)	39.2					3.9				
EGFR											
Mutant	38 (21.3)	15.8	0.046	3.15	1.15–8.63	0.03	1.9	0.04	1.75	1.11–2.75	0.02
Wild type	140 (78.7)	32.9					3.0				
Smoking											
Never smoker	67 (37.6)	19.4	0.03	1.87	0.54–6.44	0.32	2.1	0.23	1.01	0.54–1.87	0.98
Smoker	111 (62.4)	35.1					2.8				
ECOG											
2–3	21 (11.8)	9.5	0.05	4.33	0.90-20.89	0.07	1.4	0.001	2.12	1.28–3.51	0.004
0–1	157 (88.2)	31.8					2.7				
Prior lines of chemotherapy											
2 or more	85 (47.8)	30.1	0.78	0.49	0.23–1.02	0.06	2.1	0.56	0.88	0.59–1.30	0.51
0–1	93 (52.2)	28.2					2.2				

HR hazard ratio, *ECOG* Eastern Cooperative Oncology Group

PD-L1 expression and EGFR mutations because of the small number of patients in this group.

EGFR-mutant tumors showing dramatic response to PD-1 inhibitor

One patient, a man aged 53 years with history of current smoking (50 pack years), was diagnosed in 2013 with stage IIIB pulmonary adenocarcinoma harboring an EGFR L858R point mutation. He received concurrent chemoradiotherapy, but new lung nodes developed 2 years after completing chemoradiotherapy. After acquired resistance to erlotinib, three lines of chemotherapy were administered to control rapidly increasing lung nodes with minimal response. Repeated biopsy was done and revealed adenocarcinoma harboring an L858R mutation without T790M and strongly expressing PD-L1 (60% positive cells by 22C3 PharmDx assay). He was treated with pembrolizumab, and the lung nodes decreased dramatically (Fig. 3a). He was being treated with pembrolizumab with response duration of 9 months at the time of this analysis.

Another patient, a never-smoked woman aged 51 years, was diagnosed with pulmonary adenocarcinoma with malignant pleural effusion in 2015. She was treated with pemetrexed plus cisplatin, followed by pemetrexed maintenance before it was determined that her tumor harbored a deletion in EGFR exon 19 and strong PD-L1 expression (50% positive cells by SP263 antibody). She was treated with nivolumab for 11 months as second-line therapy, and showed dramatic tumor response (Fig. 3b). She is now under treatment of erlotinib and showing a partial response.

Discussion

Though several previous studies showed that PD-1/PD-L1 inhibitors were less effective in patients with EGFR-mutant NSCLC than EGFR WT NSCLC (Borghaei et al. 2015; Herbst et al. 2016; Rittmeyer et al. 2017), other clinical factors were not considered simultaneously. We considered several possible confounding factors including smoking status, gender, performance status, and number of previous chemotherapy treatments. Never smokers and females were reported to benefit less for immunotherapy (Brahmer et al. 2017; Conforti et al. 2018; Gainor et al. 2016) and they were more likely to have EGFR-mutant tumors (Cho et al. 2018; Yoneshima et al. 2018), and those patients with a EGFR mutation were more likely to have poorer clinical outcomes with PD-1 inhibitors than those with EGFR WT. This highlights the importance of determining whether the negative impact of EGFR mutation was caused or confounded by these clinical factors. We found that EGFR mutation status

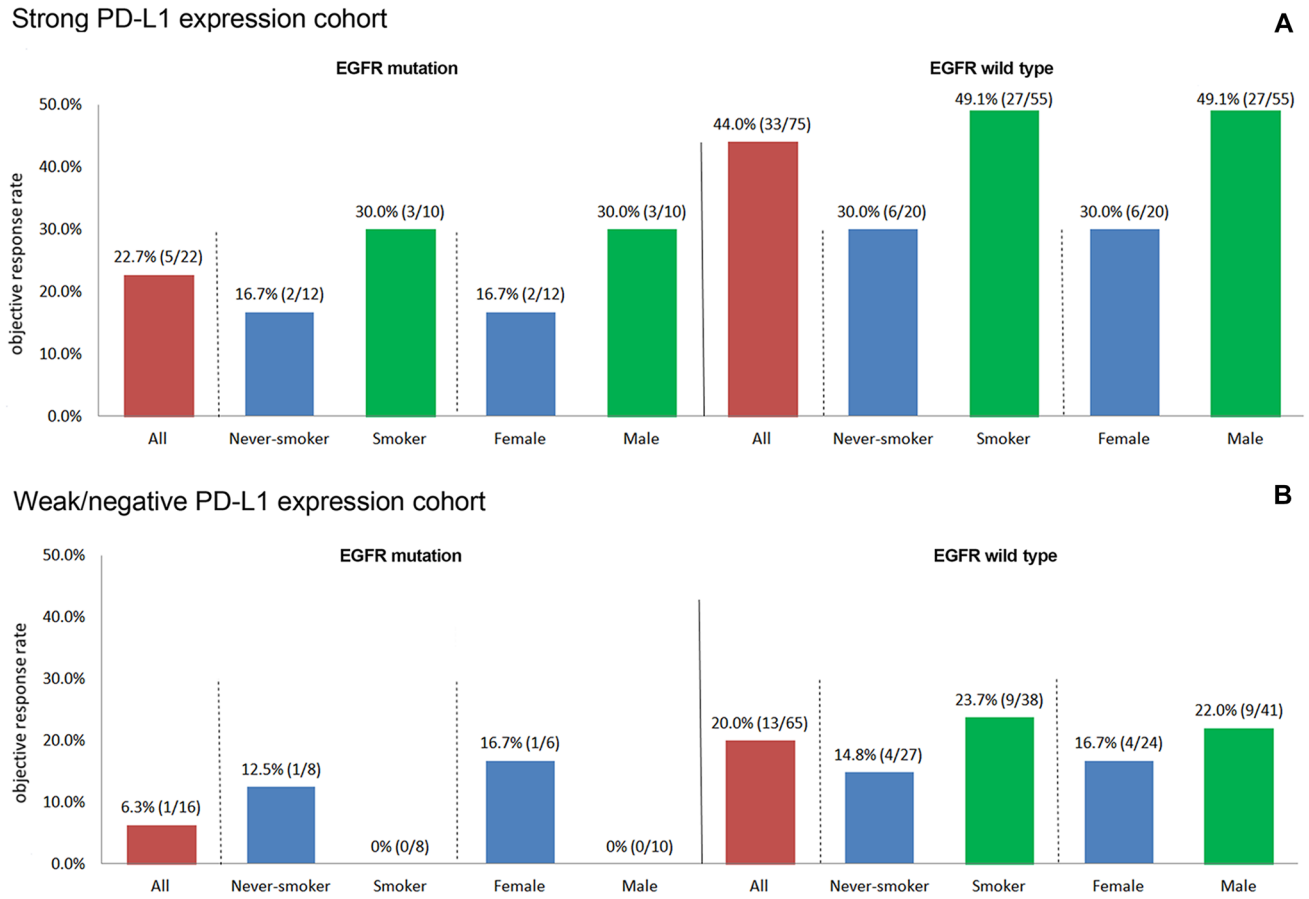

Fig. 2 Objective response rates were analyzed in the strong PD-L1 expression group (**a**) and in the weak/negative PD-L1 expression group (**b**) taking EGFR mutation status, smoking status, and gender into account

as well as PD-L1 expression independently affected the efficacy of PD-1 inhibitors.

Though EGFR mutation was a negative predictor of the efficacy of PD-1 inhibitors, some EGFR-mutant tumors showed a significant response to treatment according to PD-L1 expression, smoking, or gender status. Though only 1 (6.3%) of 16 patients with tumors harboring an EGFR mutation and weak/negative PD-L1 expression showed an objective response, 5 (22.7%) of 22 patients with EGFR-mutant tumors with strong PD-L1 expression achieved an objective response. In addition, in the strong PD-L1 expression cohort, objective responses were achieved in three of ten smokers or male patients in the EGFR mutation group. Our data are supported by a recent report from nivolumab-expanded access program performed in Italy: there were no significant differences in ORR (22.0% vs. 20.6%) and PFS (11.3 vs. 14.1 months) between smokers with EGFR WT and smokers with EGFR mutation (Lisberg and Garon 2018). Recently, however, one prospective study showed no response case to first-line pembrolizumab among ten patients with EGFR mutant, PD-L1-positive lung cancer (seven cases with strong PD-L1 expression) (Lisberg et al. 2018). However, we should not rule out the use of PD-1/PD-L1 inhibitors for EGFR-mutant tumors, because some EGFR-mutant cases have shown dramatic response to PD-1/PD-L1 inhibitors, as presented in the result section.

Immune checkpoint inhibitors are preferred to chemotherapy for patients with poor performance status, since they are less toxic. However, given that immune checkpoint inhibitors exert their anti-tumor effects using the patient's own immune system, their effects in patients with compromised immune systems have been questionable (Johnson et al. 2017). Our study showed that poor performance status was also a significant predictor for lower PFS according to multivariate analysis, which is compatible with a previous report on melanoma patients (Wong et al. 2017).

PD-L1 expression rates were higher in the current study than in previous studies (Garassino 2016; Herbst et al. 2016). Previously, out of 2222 NSCLC patients screened by 22C3 IHC pharmDx, 66% had tumors where at least 1% of tumor cells expressed PD-L1, including 28% with PD-L1 expression ≥ 50% (Herbst et al. 2016). Out of 1122 EGFR

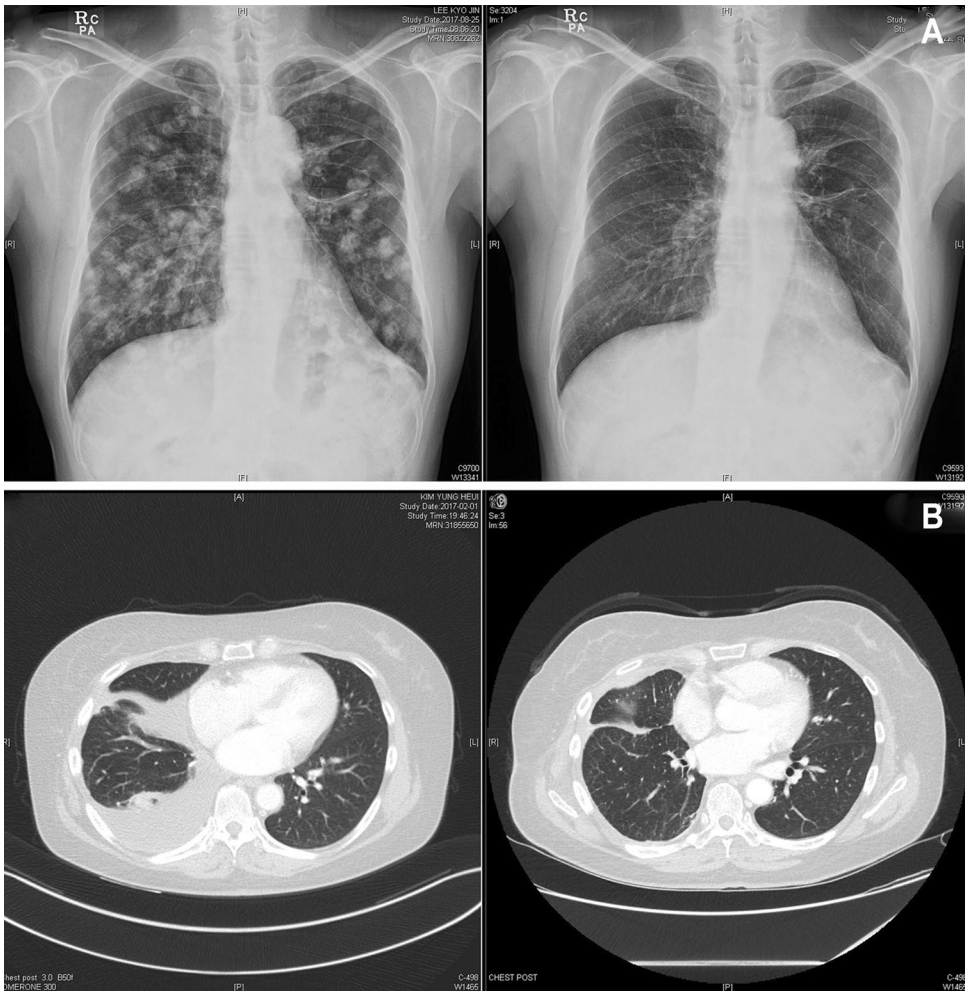

Fig. 3 **a** Multiple lung nodes disappeared after three cycles of pembrolizumab. **b** Moderate amount of pleural effusion and pleural seeding nodes were decreased after six cycles of nivolumab

WT NSCLC patients, about 33% had tumors in which ≥ 25% of tumor cells expressed PD-L1 as assessed by SP142 antibody staining (Garassino 2016). Out of our total population, 141 patients (79.2%) had PD-L1-positive cells, and 97 patients (54.5%) had strong PD-L1 expression. The high proportion of tumors that expressed PD-L1 in our study population is easily explained by the fact that patients with PD-L1-expressing tumor cells were more likely treated with PD-1 inhibitors, and we included only patients who were treated with PD-1 inhibitors. The reimbursement system in Korea reimburses use of pembrolizumab or nivolumab only in those patients with relatively strong PD-L1 expression (≥ 50% by 22C3 or ≥ 10% by SP263); this could have further enriched the study population for those with tumors with strong PD-L1 expression. Therefore, our study should not be used as a reference for the prevalence of PD-L1 expression in NSCLC patients.

The proportion of tumors with strong PD-L1 expression (57.9%) was even more exaggerated in our EGFR mutation group considering that previous epidemiologic studies reported low rates (7.5% or 9.9%) of strong PD-L1 expression (≥ 50% of tumor cells by 22C3) in EGFR-mutant tumors (Cho et al. 2018; Yoneshima et al. 2018). However, the large number of PD-L1-expressing tumors included in our study allowed us to evaluate the effect of the interaction between PD-L1 expression and EGFR mutation status on the efficacy of PD-1 inhibitors in a relatively small number of EGFR-mutant tumors ($n = 38$).

Several reasons have been proposed to explain the low efficacy of PD-1/PD-L1 inhibitors, including high CD73 expression in EGFR-mutant tumors (Streicher et al. 2017). CD73 is a critical mediator of adenosine accumulation in the tumor microenvironment as it dephosphorylates adenosine monophosphate to adenosine. The accumulated adenosine around EGFR-mutant cells has various immunosuppressive action, thereby inhibiting the anti-tumor effects of PD-1/PD-L1 inhibitors (Vijayan et al. 2017). A targeting agent of CD73 is currently being tested in an early clinical trial (ClinicalTrials.gov). Another approach that is being attempted to overcome the poor efficacy of immunotherapy for EGFR-mutant tumors is the combination of anti-angiogenesis therapy with immunotherapy. In recent studies, immunotherapy

provided a significant survival benefit in both EGFR mutation and EGFR WT groups when atezolizumab was combined with bevacizumab plus platinum-doublet (Kowantz; Socinski et al. 2018). Vascular endothelial growth factor (VEGF) has been reported to increase regulatory T cells and also suppress dendritic cell maturation and CD8 + T cell proliferation, leading to T cell exhaustion (Khan and Kerbel 2018). Inhibitors of VEGF can prevent these immunosuppressive actions. In addition, anti-angiogenetic agents can increase tumor infiltrating lymphocytes through normalization of tumor blood vessels (Khan and Kerbel 2018).

Our study included a relatively small population of EGFR-mutant tumors. The number of patients with EGFR-mutant tumors was smaller when patients were classified according to both PD-L1 expression status and smoking status or gender. Therefore, we could not statistically compare ORRs between subgroups, and only presented arithmetic values. Although EGFR mutation adversely affected the efficacy of PD-1/PD-L1 inhibitors in our study based on various statistical analyses, further studies in larger populations are warranted.

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Compliance with ethical standards

Conflict of interest The authors have no conflicts of interest to declare.

Ethical approval All the procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional review board at Samsung Medical Center in Seoul, Korea, and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

Borghaei H et al (2015) Nivolumab versus docetaxel in advanced non-squamous non-small-cell lung cancer. N Engl J Med 373:1627–1639. https://doi.org/10.1056/NEJMoa1507643

Brahmer J et al (2015) Nivolumab versus docetaxel in advanced squamous-cell non-small-cell lung cancer. N Engl J Med 373:123–135. https://doi.org/10.1056/NEJMoa1504627

Brahmer JR, R-AD RA, Hui R, Csoszi T, Fulop A et al (2017) Updated analysis of KEYNOTE-024: pembrolizumab vs platinum-based chemotherapy for advanced NSCLC with PD-L1 TPS ≥ 50%. J Thoracic Oncol 12:S1793–S1794

Carbone DP et al (2017) First-Line Nivolumab in Stage IV or recurrent non-small-cell lung cancer. N Engl J Med 376:2415–2426. https://doi.org/10.1056/NEJMoa1613493

Cho JH et al (2018) Retrospective molecular epidemiology study of PD-L1 expression in patients with EGFR-mutant non-small cell lung cancer. Cancer Res Treatm 50:95–102. https://doi.org/10.4143/crt.2016.591

ClinicalTrials.gov MEDI9447 Alone and in combination with MEDI4736 in adult subjects with select advanced solid tumors https://ClinicalTrialsgov/show/NCT02503774. Accessed 10 July, 2018

Conforti F et al (2018) Cancer immunotherapy efficacy and patients' sex: a systematic review and meta-analysis. Lancet Oncol 19:737–746. https://doi.org/10.1016/S1470-2045(18)30261-4

Eisenhauer EA et al (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 45:228–247. https://doi.org/10.1016/j.ejca.2008.10.026

Gainor JF et al (2016) EGFR mutations and ALK rearrangements are associated with low response rates to PD-1 pathway blockade in non-small cell lung cancer: a retrospective analysis. Clin Cancer Res 22:4585–4593. https://doi.org/10.1158/1078-0432.CCR-15-3101

Garassino MCV, Kim JF, Lena J, Mazieres H, Powderly J, Dennis J, P (2016) Durvalumab in ≥ 3rd-line locally advanced or metastatic, EGFR/ALK wildtype NSCLC: results from the phase 2 ATLANTIC study. WCLC

Garassino MC et al (2018) Durvalumab as third-line or later treatment for advanced non-small-cell lung cancer (ATLANTIC): an open-label, single-arm, phase 2 study. Lancet Oncol 19:521–536. https://doi.org/10.1016/S1470-2045(18)30144-X

Herbst RS et al (2016) Pembrolizumab versus docetaxel for previously treated, PD-L1-positive, advanced non-small-cell lung cancer (KEYNOTE-010): a randomised controlled trial. Lancet 387:1540–1550. https://doi.org/10.1016/S0140-6736(15)01281-7

Johnson DB, Sullivan RJ, Menzies AM (2017) Immune checkpoint inhibitors in challenging populations. Cancer 123:1904–1911. https://doi.org/10.1002/cncr.30642

Khan KA, Kerbel RS (2018) Improving immunotherapy outcomes with anti-angiogenic treatments and vice versa. Nat Rev Clin oncol 15:310–324. https://doi.org/10.1038/nrclinonc.2018.9

Kim H, Kwon HJ, Park SY, Park E, Chung JH (2017) PD-L1 immunohistochemical assays for assessment of therapeutic strategies involving immune checkpoint inhibitors in non-small cell lung cancer: a. comparative study Oncotarget 8:98524–98532. https://doi.org/10.18632/oncotarget.21567

Kowantz MSM, Zou W, McCleland M, Yang N, Chavez AL, Spira A, Mazieres J IMpower150: Efficacy of atezolizumab (atezo) plus bevacizumab (bev) and chemotherapy (chemo) in 1L metastatic nonsquamous NSCLC (mNSCLC) across key subgroups. Presented at: American Association for Cancer Research Annual Meeting 2018; April 16, 2018: Chicago, IL

Lisberg A, Garon EB (2018) The Italian Nivolumab expanded access program confirms the limitations of single-agent PD-1 inhibition in EGFR-mutant and never-smoking patients with NSCLC. J Thorac Oncol 13:1058–1059. https://doi.org/10.1016/j.jtho.2018.06.003

Lisberg A et al (2018) A phase II STUDY OF PEMBROLIZUMAB in EGFR-Mutant, PD-L1+, tyrosine kinase inhibitor naive patients with advanced NSCLC. J Thoracic Oncol 13:1138–1145. https://doi.org/10.1016/j.jtho.2018.03.035

Reck M et al (2016) Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med 375:1823–1833. https://doi.org/10.1056/NEJMoa1606774

Rittmeyer A et al (2017) Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label multicentre randomised controlled trial. Lancet 389:255–265. https://doi.org/10.1016/S0140-6736(16)32517-X

Shi Y et al (2014) A prospective, molecular epidemiology study of EGFR mutations in Asian patients with advanced non-small-cell lung cancer of adenocarcinoma histology (PIONEER). J Thoracic

Oncol Off Publ Int Assoc Study Lung Cancer 9:154–162. https://doi.org/10.1097/JTO.0000000000000033

Socinski MAJR, Cappuzzo F, Orlandi FJ, Stroyakovskiy D, Nogami N, Rodriguez-Abreu D (2018) Overall survival (OS) analysis of IMpower150, a randomized Ph 3 study of atezolizumab (atezo) + chemotherapy (chemo) ± bevacizumab (bev) vs chemo + bev in 1L nonsquamous (NSQ) NSCLC. Journal of clinical oncology: official journal of the American Society of Clinical Oncology 36

Streicher K et al (2017) Increased CD73 and reduced IFNG signature expression in relation to response rates to anti-PD-1(L1) therapies in EGFR-mutant NSCLC. J Clin Oncol 35:11505–11505. https://doi.org/10.1200/JCO.2017.35.15_suppl.11505

Vijayan D, Young A, Teng MWL, Smyth MJ (2017) Targeting immunosuppressive adenosine in cancer. Nat Rev Cancer 17:709–724. https://doi.org/10.1038/nrc.2017.86

Wong A et al (2017) Clinical and palliative care outcomes for patients of poor performance status treated with antiprogrammed death-1 monoclonal antibodies for advanced melanoma Asia. Pac J Clin Oncol 13:385–390. https://doi.org/10.1111/ajco.12702

Yoneshima Y et al (2018) PD-L1 expression in lung adenocarcinoma harboring EGFR mutations or ALK rearrangements. Lung Cancer 118:36–40. https://doi.org/10.1016/j.lungcan.2018.01.024

Zhang YL et al (2016) The prevalence of EGFR mutation in patients with non-small cell lung cancer: a systematic review and meta-analysis. Oncotarget 7:78985–78993. https://doi.org/10.18632/oncotarget.12587