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ORIGINAL ARTICLE

Clinical outcome of epidermal growth factor receptor-tyrosine kinase inhibitors therapy for patients with overlapping kirsten rat sarcoma 2 viral oncogene homolog and epidermal growth factor receptor gene mutations

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Abstract

Background: Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) is the second most common mutated gene following epidermal growth factor receptor (*EGFR*) mutation in Chinese lung adenocarcinoma (LADC) patients. Investigating the clinical characteristics and outcomes of patients with co-existing *KRAS* and *EGFR* mutations can provide significant information for suitable therapies.

Methods: We retrospectively investigated 2106 LADC patients who had undergone *EGFR* and *KRAS* mutation tests at the Peking University Cancer Hospital. Only advanced LADC patients who carried *KRAS* and/or *EGFR* mutations, received EGFR-tyrosine kinase inhibitors (TKIs) and/or chemotherapy, and had completed follow-up analysis were analyzed further. *KRAS* and *EGFR* mutations were tested by denaturing high-performance liquid chromatography.

Results: A *KRAS* mutation was detected in 123 out of 2106 LADC patients (5.8%) and 38 (1.8%) had a concurrent *EGFR* mutation. Seventy-two of 123 patients were advanced cases, which were divided into two sub-groups according to *EGFR* mutation status: overlapping *KRAS* and *EGFR* mutations (n = 24) and *KRAS* mutation alone (n = 48). Clinical characteristics of the two subgroups were similar. A greater ratio of patients with double mutations received EGFR-TKIs compared to *KRAS* mutation alone (75% vs. 43.8%, $P = 0.012$), and obtained a better objective response rate (38.9% vs. 9.5%, $P = 0.027$) and longer progression-free survival (8.0 vs. 1.5 months, $P = 0.028$) following EGFR-TKIs therapy. However, these differences were not observed in patients treated with platinum-based chemotherapy.

Conclusions: Overlapping *KRAS* and *EGFR* mutations occurred in 1.8% of Chinese LADC patients studied. The co-presence of *EGFR* mutations could predict a clinical benefit from EGFR-TKIs treatment for patients with *KRAS* mutations.

Introduction

Non-small cell lung cancer (NSCLC) has been well recognized as a diverse disease based on the identification of serial driver genes and the existence of intra-tumor genetic heterogeneity.[1,2] Recently, sub-clonal populations have been identified within single biopsy specimens of naïve-treatment lung cancer patients.[3–5] Yang *et al*. reported the co-existence of epidermal growth factor receptor (*EGFR*) mutations with anaplastic lymphoma kinase (*ALK*) fusion in treatment-naive NSCLC tumors.[6] Several studies (including our previous studies) have also shown that T790M may co-exist with the *EGFR* mutation in cancer cells or tumor tissue samples before EGFR-tyrosine kinase inhibitors (TKIs) treatment.[7,8] Increasing evidence has indicated that the presence of sub-clones in *EGFR*-mutated tumors may influence the therapeutic efficacy of EGFR-TKIs.[5,9,10]

The Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) mutation is the most common gene aberrance in Caucasian NSCLC patients, and the second most common somatic mutation following *EGFR* mutation in Chinese patients with lung adenocarcinoma (LADC). However, despite 40 years of

research, the prognostic and predictive roles of *KRAS* mutations with respect to EGFR-TKIs treatment and chemotherapy have been being controversial because of inconsistent results reported between trials and meta-analyses.[11] Several studies have shown that *KRAS* mutations can be a negative predictor for EGFR-TKIs therapy.[12,13] However, a retrospective study using a random-matching method based on tumor node metastasis (TNM) stage, histology, and *KRAS/EGFR* status displayed that *KRAS* mutation is a poor prognostic factor, but is not an independent predictor of response to EGFR-TKIs or chemotherapy in patients with lung cancer.[14] A recent pooled analysis of 1543 patients from four studies further indicated that neither *KRAS* wild-type nor codon 12 mutations had any predictive value to adjuvant chemotherapy, while the predictive value of *KRAS* codon 13 mutations requires further validation, which suggests that using *KRAS* status cannot be recommended for selecting patients with NSCLC for adjuvant chemotherapy.[15]

Given that *EGFR* and *KRAS* are the two most common driver genes in Chinese lung adenocarcinoma, it is crucial to investigate their association with each other and clinical characteristics, especially as the inhibitors that target *KRAS* and its downstream pathway will be incorporated into clinical practice in the near future.[16–20]

KRAS and *EGFR* mutations were reported to be mutually exclusive in lung cancer.[21] However, Gumerlock *et al*. reported four patients with both *KRAS* and *EGFR* mutations at the American Society of Clinical Oncology annual meeting in 2005.[22] Our previous study showed coexisting *KRAS* and *EGFR* mutations in five out of 273 patients with lung adenocarcinoma.[23] In 2014, Li *et al*. reported that 30 out of 5125 Chinese patients with NSCLC concurrently harbored *EGFR* and *KRAS* mutations.[7]

Because of the low incidence of patients manifesting these double mutations, to date there are no reports comparing clinical characteristics and responses to EGFR-TKIs or chemotherapy for patients harboring *KRAS* mutations with or without *EGFR* mutations. Here, we analyzed the clinical significance of double mutations of advanced LADC with respect to EGFR-TKIs and chemotherapy.

Materials and methods

Study population

All patients included in this retrospective study were diagnosed and treated at the Peking University Cancer Hospital between 1 January 2004 and 31 December 2013. A total of 2106 LADC patients who underwent *EGFR* and *KRAS* mutation tests were screened and the analysis focused on patients who met the following criteria: (i) harboring a *KRAS* mutation with/without *EGFR* mutational status; (ii) received EGFR-TKIs and/or chemotherapy; and (iii) completed follow-up analysis. For all patients, laboratory data was obtained and recorded independently, and blinded from clinical review until final analyses.

The institutional review board of the Peking University Cancer Hospital approved the study. All patients provided written informed consent for the procurement of tumor specimens.

Mutational analysis

Epidermal growth factor receptor and *KRAS* mutations were assessed by denaturing high-performance liquid chromatography (DHPLC) based on polymerase chain reaction, which detects *EGFR* exon 19 and exon 21, and *KRAS* exon 2, as described previously.[23–25] In patients with mutated sub-types that could not be determined by DHPLC, the amplification-refractory mutation system was used for re-analysis.

Data collection

We collected clinical variables for all patients from the database, including age, gender, Eastern Cooperative Oncology Group (ECOG) performance status (PS), TNM stage, and smoking status (smoker or non-smoker). A non-smoker was defined as a patient who smoked less than 100 cigarettes in a lifetime. The patients' treatment histories were recorded, including whether they had received EGFR-TKIs (gefitinib, erlotinib or icotinib) and/or platinum-based doublet chemotherapy.[26] Patients with unknown treatment histories were excluded from therapeutic analyses.

Statistical analysis

Patient demographics (excluding age), clinical characteristics, treatment histories, and responses to treatments were compared using the chi-square test. The student's *t*-test was used for age comparison. Up to 16 May 2014, the follow-up time of patients who were still alive was calculated from the date of the first treatment to the last available follow-up date. Overall survival (OS) was defined as the date of diagnosis of advanced lung adenocarcinoma to the date of death or the last available follow-up. Progression-free survival (PFS) was defined as the time from initial treatment to the time of disease progression or the date of last follow-up. OS and PFS for EGFR-TKIs and chemotherapy were estimated using the Kaplan–Meier method and were compared across groups using the log-rank test. Cox regression univariate analysis was used to evaluate every variable to PFS and OS. The statistically significant variables in univariate analysis, age and gender were used in the proportional hazard model for multivariate analysis. SSPS 2.0 was used for statistics (IBM Corp., Armonk, NY, USA). $P<0.05$ was defined as statistically significant in regard to differences.

Results

Clinical characteristics

Among the 2106 LADC patients who underwent *EGFR* and *KRAS* analysis, 123 (5.8%) had *KRAS* mutations, including 38 patients (38/2106, 1.8%) harboring both *EGFR* and *KRAS* mutations. Most of the *KRAS*-mutated patients were diagnosed with stage IIIB and IV disease (72 of 123, 58.5%). Of the 72 patients with locally advanced and advanced LADC, the median age was 56 years (inter-quartile range, 11); 48 cases presented *KRAS* mutations alone, and 24 carried overlapping *KRAS* and *EGFR* mutations. In patients with overlapping *KRAS* and *EGFR* mutations, there were more non-smokers (62.5%) compared to those with *KRAS* mutations alone (52.1%), but the difference did not reach statistical significance (Table 1).

Subsequent analyses focused on the 72 patients who were diagnosed with advanced LADC harboring *KRAS* mutations. A total of 39 patients received EGFR-TKIs therapy, including 18 with double mutations and 21 with a single mutation, most of which (69.2%) were second-line therapies or beyond. Of the 21 patients with a single *KRAS* mutation who received EGFR-TKIs as first-line therapy, one was enrolled in an IPASS clinical trial, one refused chemotherapy, and three other patients could not tolerate the toxicity of chemotherapy. Of the total 72 patients, 65 received chemotherapy and 32 patients had both EGFR-TKIs treatment and chemotherapy. Patients with overlapping *KRAS* and *EGFR* mutations were significantly more likely to receive EGFR-TKIs treatment compared with patients harboring *KRAS* mutations alone (75% vs. 43.8%; $P = 0.012$), including seven cases who were treated with first-line EGFR-TKIs and 11 cases treated with second-line or beyond. However, no differences were observed between these two subgroups of patients for those selected to receive platinum-based doublet chemotherapies (83.3% vs. 93.8%; $P = 0.325$) (Table 1).

Table 1 The clinical characteristics of patients with advanced adenocarcinoma harboring KRAS mutation

Characteristic	*KRAS* N = 48 N (%)	*KRAS* & *EGFR* N = 24 N (%)	*P-value*
Age, median (QR)	56 (15.75)	56.5 (11)	0.537*
Gender			0.302**
Male	32 (66.7)	13 (54.2)	
Female	16 (33.3)	11 (45.8)	
PS			0.344**
0–1	42 (87.5)	24 (100)	
2–3	4 (8.3)	0	
Unknown	2 (4.2)	0	
Smoking			0.578**
Smoker	20 (41.7)	9 (37.5)	
Non-smoker	25 (52.1)	15 (62.5)	
Unknown	3 (6.3)	0	
EGFR-TKIs	21 (43.8)	18 (75)	0.012**
Chemotherapy	45 (93.8)	20 (83.3)	0.325**

**P*-value was estimated by t-test; ***P*-value was estimated by chi-square test. Age, reported in years; chemotherapy, platinum-based doublet chemotherapy; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors treatment; *KRAS*, Kirsten rat sarcoma 2 viral oncogene homolog mutation; *KRAS* & *EGFR*, *KRAS* mutation coexisting with *EGFR* mutation; N, number of patients; QR, inter-quartile range; PS, performance status.

Association of overlapping kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) and epidermal growth factor receptor (*EGFR*) mutations with EGFR-tyrosine kinase inhibitors therapy

On 16 May 2014, 49 out of the 72 patients (68.1%) had died, 15 patients were still alive, and eight patients did not maintain follow-up. The median follow-up was 18 months (inter-quartile range 19.75 months).

We analyzed ORR and PFS in the 39 patients treated with EGFR-TKIs. The ORR and median PFS were 23.1% and 5.5 months (95% confidence interval [CI], 0.40–10.60 months), respectively. For patients whose tumors carried both *KRAS* and *EGFR* mutations (n = 18), the ORR and median PFS was significantly longer after EGFR-TKIs treatment compared to those with *KRAS* mutations alone (n = 21) (ORR 38.9% vs. 9.5%, $P = 0.027$; median PFS, 8 months, 95% CI, 1.76–14.24 vs. 1.5 months, 95% CI, 0.60–2.40 months, $P = 0.028$) (Table 2 and Fig 1).

Overall survival was also analyzed according to genotype. The median OS for the 39 patients who had received EGFR-TKIs treatment was 27 months (95% CI, 23.07–30.93 months). The median OS for patients whose tumors had overlapping *KRAS* and *EGFR* mutations was longer (29.5 months, 95% CI, 5.79–53.21 months) compared with patients carrying *KRAS* mutations alone (25 months; 95% CI, 21.09–28.91 months), but there was no significant difference ($P = 0.084$).

Association of overlapping *KRAS* and *EGFR* mutations with chemotherapy

We then analyzed PFS in the platinum-based doublet chemotherapy population. The ORR and median PFS for the 65 patients who received platinum-based doublet chemotherapy were 23.1% and four months (95% CI, 2.61–5.39 months), respectively. For patients who harbored both *KRAS* and *EGFR* mutations, the ORR and median PFS were 30% and 4.5 months (95% CI, 2.49–6.51 months), respectively, and were comparable to those without *EGFR* mutations (ORR 20%; median PFS 3 months, 95% CI, 1.60–4.40

Table 2 Analysis of PFS in patients treated with chemotherapy or EGFR-TKIs and OS for all patients by Kaplan–Meier

	Platinum-based doublet chemotherapy N = 65				EGFR-TKI N = 39				All patients N = 72			
Variables	N (%)	PFS	95% CI	*P*	N (%)	PFS	95%CI	*P*	N (%)	OS	95% CI	*P*
Age				0.054				0.261				0.239
Age≤56	34 (52.3)	5	2.33–7.68		19 (48.7)	1.5	0.00–4.34		37 (51.4)	24	17.62–30.38	
Age>56	31 (47.7)	3	1.44–4.56		20 (51.3)	6.5	3.21–9.79		35 (48.6)	20.5	11.09–29.91	
Gender				0.742				0.338				**0.015**
Female	22 (33.8)	4	2.25–5.75		18 (46.2)	5.5	1.34–9.66		27 (37.5)	29.5	19.78–39.22	
Male	43 (66.2)	3	1.04–4.96		21 (53.8)	4.5	0.00–11.98		45 (62.5)	21	12.43–29.57	
PS†				0.059				0.117				**0.001**
PS≤1	60 (92.3)	3	1.15–4.85		38 (97.4)	5.5	2.48–8.52		66 (91.7)	23.5	19.05–27.95	
PS>1	3 (4.6)	1	0.00–0.00		1 (2.6)	1	0.00–0.00		4 (5.6)	6	0.00–0.00	
Smoking‡				0.323				0.660				0.109
Non-smoker	33 (50.8)	3	1.89–4.11		26 (66.7)	5.5	3.00–8.00		40 (55.6)	26.5	19.60–33.40	
Smoker	29 (44.6)	4.5	2.51–6.49		11 (28.2)	2	0.00–6.86		29 (40.3)	21	19.44–32.56	
Mutation				0.829				**0.028**				0.067
KRAS	45 (69.2)	3	1.60–4.40		21 (53.8)	1.5	0.60–2.40		48 (66.7)	23	13.76–32.24	
KRAS & *EGFR*	20 (30.8)	4.5	2.49–6.51		18 (46.2)	8	1.76–14.24		24 (33.3)	24	14.37–33.63	

P-value estimated by Kaplan-Meier. Bold type indicates *P*<0.05. †The performance status in two cases was unknown. ‡The smoking status in three cases was unknown. Age, reported in years; chemotherapy, platinum-based doublet chemotherapy; CI, confidence interval; EGFR-TKIs epidermal growth factor receptor-tyrosine kinase inhibitors treatment; *KRAS*, Kirsten rat sarcoma 2 viral oncogene homolog mutation; *KRAS* & *EGFR*, *KRAS* mutation coexisting with *EGFR* mutation; N, number of patients; OS, overall survival; PFS, progression-free survival; PS, performance status.

Figure 1 Kaplan–Meier estimates of progression-free survival (PFS) curve in the epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKIs) treated populations. The red dotted line represents the PFS of patients with both *EGFR* and Kirsten rat sarcoma 2 viral oncogene homolog (*KRAS*) mutations (median PFS 8 months); the dark blue full line represents the PFS of patients with *KRAS* mutations alone (median PFS 1.5 months), *P*-value =0.028 estimated by the Kaplan–Meier method. ▬, KRAS+; ▬ ▪ ▬, EGFR+ & KRAS+.

months) ($P = 0.829$). The median OS for the total 65 patients who accepted platinum-based doublet chemotherapy was 23 months (95% CI, 19.28–26.72 months). The median OS for the double-mutated patients was similar to that of patients with *KRAS* mutations alone (24 months, 95% CI, 19.64–28.36 vs. 23 months, 95% CI, 13.24–32.76, $P = 0.122$).

Univariate and multivariate analyses

Finally, we evaluated each clinical and genetic variable, including gender, age, PS, smoking status, and *KRAS* and *EGFR* mutations, to determine their impact on survival outcomes. In univariate Cox regression analysis, gender and PS (0–1/2–3) were associated with OS (hazard ratio [HR] 0.467, 95% CI, 0.25–0.88; $P = 0.018$ and HR 0.159, 95% CI, 0.04–0.59; $P = 0.006$, respectively); however, only *EGFR* mutation was associated with PFS (HR 0.497, 95% CI, 0.26–0.97; $P = 0.040$) in EGFR-TKIs treated patients (Table 3).

Notably, in univariate analysis, none of these factors (age, smoking, PS, *EGFR* mutation) were observed to have a significant association with PFS in patients treated with platinum-based doublet chemotherapy (Table 3).

Multivariate Cox regression models were used to assess the predictive effect on OS of each clinical parameter (age,

Table 3 Clinical variables and *EGFR* mutation associated with PFS in chemotherapy or TKIs treatment and OS: Univariate analysis

	PFS (chemotherapy) N = 65			PFS (EGFR-TKI) N = 39			OS (All Patients) N = 72		
Variables	HR	95%CI	*P*	HR	95%CI	*P*	HR	95%CI	*P*
Age (age ≤56/ > 56)	0.695	0.41–1.19	0.184	1.426	0.74–2.74	0.287	0.711	0.40–1.26	0.244
Gender (female/male)	0.915	0.52–1.61	0.757	0.736	0.38–1.42	0.363	0.467	0.25–0.88	**0.018**
PS (PS≤1/ > 1)	0.359	0.11–1.18	0.091	0.247	0.03–1.95	0.185	0.159	0.04–0.59	**0.006**
Smoking (non-smoker/smoker)	1.297	0.75–2.25	0.355	0.857	0.42–1.77	0.676	0.626	0.35–1.12	0.115
Group (*KRAS* & *EGFR*/*KRAS*)	0.943	0.53–1.66	0.839	0.497	0.26–0.97	**0.040**	0.570	0.309–1.05	0.072

P-value estimated by univariate cox regression analysis. Bold type indicates $P < 0.05$. Age, reported in years; chemotherapy, platinum-based doublet chemotherapy; CI, confidence interval; EGFR-TKIs, epidermal growth factor receptor-tyrosine kinase inhibitors treatment; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma 2 viral oncogene homolog mutation; *KRAS* & *EGFR*, *KRAS* mutation coexisting with *EGFR* mutation; N, number of patients; OS, overall survival; PFS, progression-free survival; PS, performance status.

gender, PS, and smoking status) and molecular marker (*EGFR* mutation) in 72 *KRAS*-mutated patients. Female gender (HR 0.515, 95% CI, 0.27–0.97; $P = 0.040$) and good performance status (PS 0–1) (HR 0.180, 95% CI, 0.05–0.67; $P = 0.010$) tended to be associated with longer OS (Table 4). In the 39 patients who had received EGFR-TKIs, only *EGFR* mutation (HR 0.330, 95%CI, 0.151–0.725; $P = 0.006$) was associated with longer PFS following treatment.

Discussion

Coexisting *EGFR* and *KRAS* mutations have been reported by several investigators in a minority of the NSCLC population, although previous reports have indicated that these two genes were mutually exclusive.[21] From 2005 to 2014, there were 12 case reports involving 60 patients with overlapping *EGFR* and *KRAS* mutations, and 25 cases who underwent EGFR-TKIs treatment. Seven patients presented a positive response with partial or complete remission, while others did not benefit from EGFR-TKIs treatment. However, the number of patients in these reports was too small to make any relevant analysis.[7,23,27–36]

In our study, we analyzed the data of 38 (38/2106, 1.8%) lung adenocarcinoma patients with overlapping *KRAS* and *EGFR* mutations, which, to the best of our knowledge, is the largest cohort to date. We analyzed the clinical outcomes of 24 advanced adenocarcinoma patients with co-existing *EGFR* and *KRAS* mutations and 48 patients with *KRAS* mutations alone who had received EGFR-TKIs treatment or/and platinum-based doublet chemotherapy. The results showed that more patients with double mutations received EGFR-TKIs treatment, and obtained a better response with longer PFS and OS compared with those carrying *KRAS* mutations alone. However, these differences were not observed in patients treated with platinum-based doublet chemotherapy between *KRAS*-mutated patients with or without *EGFR* mutations.

Table 4 Clinical variables and *EGFR* mutations associated with overall survival: Multivariate analysis

Variable	HR	95% CI	*P*
PS (0–1/ 2–3)	0.18	0.05–0.67	0.01
Gender (female/male)	0.515	0.27–0.97	0.04

P-value estimated by Cox-regression. Multivariate analysis by Cox regression, included age (age≤56/ > 56), gender (female/male), performance status (PS) (0–1/2–3), smoking (non-smoker/smoker), and group (KRAS & EGFR/KRAS). CI, confidence interval; *EGFR*, epidermal growth factor receptor; HR, hazard ratio; *KRAS*, Kirsten rat sarcoma 2 viral oncogene homolog mutation; *KRAS* & *EGFR*, *KRAS* mutation coexisting with *EGFR* mutation.

Our study showed that ORR, PFS, and OS in patients with co-existing *KRAS* and *EGFR* mutations after EGFR-TKIs treatment were superior to those with *KRAS* mutations alone. Interestingly, the median PFS and OS (8 and 29.5 months, respectively) in this subgroup were similar to the results of serial prospective clinical studies in which *EGFR*-mutated patients received EGFR-TKIs therapy (PFS 9.2–13.1 months, OS 19.3–30.9 months), but ORR (38.9%) was inferior to the results of these studies.[37–41] A possible reason for the lower ORR might be that most patients in this subgroup received EGFR-TKIs as second-line or further therapy. Several clinical trials have shown that EGFR-TKIs as second or third-line therapy presented a response of 30–60% in *EGFR*-mutated patients, which may be attributed to the dynamic alteration of *EGFR* mutations after chemotherapy in heterogeneous tumors.[26,29,42–44] Further investigations are, therefore, needed.

Multivariate analysis revealed that gender and PS status were independent prognostic factors in patients with overlapping *KRAS* and *EGFR* mutations, which is consistent with the historical data observed in NSCLC.[45] For the specific genotype of patients with overlapping *KRAS* and *EGFR* mutations, *EGFR* mutation, but not *KRAS* mutation, was associated with an efficient response to EGFR-TKIs therapy, suggesting that *EGFR* mutations are more effective in predicting a clinical benefit from EGFR-TKIs treatment in this genotype of patients with concurrent *KRAS* and *EGFR* mutations.

Despite initial studies reporting *KRAS* as a potential predictive marker to chemotherapy resistance, these studies were small and frequently did not have untreated control arms. Several randomized clinical trials involving adjuvant platinum-based chemotherapy versus untreated control arms in completely postoperative NSCLC analyzed the impact of *KRAS* mutation on chemotherapy, and negative results were observed.[15] The present study has shown that patients with co-existing *KRAS* and *EGFR* mutations had a similar PFS and ORR after platinum-based doublet chemotherapy to those harboring *KRAS* mutations alone. Thus, neither *EGFR* nor *KRAS* mutations predicts longer PFS in patients with NSCLC receiving platinum-based doublet chemotherapy.

Limitations of this study included small sample size and the retrospective nature, with a large span of therapeutic time. In addition, a portion of these patients were treated from January 2004 to December 2008, during which time an *EGFR* mutation was not identified as a strong predictor for EGFR-TKIs therapy. Patients with certain clinicopathological characteristics, such as women, non-smokers, and adenocarcinoma, were thought to be a population favorable to EGFR-TKIs therapy. This is the main reason why patients with *KRAS* mutations received EGFR-TKIs therapy. In addition, enrollment in a clinical trial (IPASS) or intolerance of chemotherapeutic toxicity also suggested that patients with a single *KRAS* mutation should receive EGFR-TKIs treatment.

Conclusions

Our results indicate that *EGFR* and *KRAS* mutations can co-exist in LADC tumors. Furthermore, the co-existing *EGFR* mutation in *KRAS*-mutated patients is a predictive factor for a better response and prolonged PFS following EGFR-TKIs treatment. However, this is not the case for platinum-based doublet chemotherapy in advanced LADC patients.

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Disclosure

No authors report any conflict of interest.

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