Comparing efficacy and safety of regorafenib versus pemetrexed in lung cancer: A preliminary clinical trial evaluating effect of inflammatory biomarkers on disease progression

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Abstract: This pilot clinical trial was designed to compare the efficacy and safety of regorafenib versus pemetrexed in Chinese patients with early stage of lung cancer. Also, the effect of inflammatory biomarkers on disease progression among Lung cancer patients who received regorafenib versus pemetrexed was evaluated in the present study. The patients who were diagnosed with early stage of lung cancer were enrolled. The eligible participants were randomized to receive regorafenib 160 mg (orally once daily for the first 21 days of each 28-day cycle) plus BSC or pemetrexed 500 mg/m^2 intravenously (Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m2 i.v. beginning 30 minutes after pemetrexed administration) plus BSC in a 1:1 ratio. Efficacy measures such as overall survival, progression-free survival and overall response were assessed after regorafenib and pemetrexed treatment. Safety of after regorafenib and pemetrexed treatment was also assessed. Blood was collected into a test tube pre-washed with chilled EDTA tubes, and then centrifuged to collect plasma sample for estimation of inflammatory biomarkers of interest. Survival time in respect to disease progression was also assessed. Also, biomarker assessments were made at each visit, to see whether inflammatory biomarker has any specific role on survival or in predicting progression of lung cancer. The present study results show that the safety and efficacy profile of regorafenib and pemetrexed was found similar in Chinese patients with early stage lung cancer. In general, regorafenib and pemetrexed treatment was well tolerated in Chinese patients with early stage Lung cancer. The results of this pilot study showed that inflammatory biomarkers such as interleukin 6 and interleukin 17A play an important role predicting progression of early stage lung cancer among Chinese patients.

Keywords: Regorafenib, pemetrexed, Chinese, early stage of lung cancer, inflammatory biomarkers.

INTRODUCTION

Lung cancer (LC) is a leading cause of cancer death in men and women worldwide (Aberle 2011). Almost 80% of lung cancers can be classified as non-small cell lung cancer (NSCLC), with 65% to 75% of cases presenting as locally advanced (Stage III) or metastatic diseases (Stage IV) that are not suitable for curative local therapy (Torre, 2012; Siege, 2016). The most important development for patients with LC is the progress of targeted therapies, recommended on a personalized approach based on molecular profiling of the tumor and the identification of predictive biomarkers. Recently, immune checkpoint inhibitors (nivolumab), oral multikinase inhibitor and new antiangiogenic agents (nintedanib, ramucirumab) emerged as new treatment options for pretreated lung cancer patients.

Pemetrexed belongs to the 'folate antimetabolites' class of chemotherapy agents. Pemetrexed inhibits cell replication and growth through the inhibition of three enzymes involved in purine and pyrimidine synthesis. Several phase II and III studies assessed the efficacy and safety of pemetrexed for first-line treatment of advanced Lung cancer (Pascale, 2016). Regorafenib, an oral multikinase inhibitor, has demonstrated promising anti-tumor activity in various solid tumors. Regorafenib has anti-proliferation effect on lung squamous cell carcinoma (LSCC) cell lines by inducing G0/G1 arrest (Matthew, 2015; Hu X, 2018). In addition, glycogen synthase kinase 3β (GSK3β) remained at the same level and Ser9 phosphorylation of GSK3β decreased with increasing incubation time and increasing regorafenib concentration in LSCC cells. GSK3β inhibition enhanced the anti-tumor activity of regorafenib (Matthew, 2015). Thus, GSK3β activation restricted the anti-cancer effect of regorafenib on LSCC. Regorafenib might be a promising drug for LSCC therapy. GSK3β might be a potential target to increase the anti-tumor effect of regorafenib in LSCC cells (Hu, 2018).

Currently, surgery is the standard care of treatment for lung cancer patients. However, 20 to 30% of patients with advanced stage of lung cancer develop relapse in spite of surgical removal of cancerous cell, thus there is a need of biomarker which helps to discriminate the stage of lung cancer among lung cancer patients (Aberle, 2011; Hoffman, 2000; Gould, 2014; Sethi, 2012). Cancer-associated tenderness and inflammation impact several characteristics of cancer pathology, which includes initiation and advancement that consist of re-production of tumor cells, and metastasis of tumor (Navarro, 2016; Rivas, 2015). Inflammatory cells which are responsible for these changes at cellular levels include different type

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of neutrophils and T cells, which are mainly associated in initiation and advancement of cancer. Further, it has been reported that tumor cells also releases different type of cytokines including chemokines, which can be easily detected in plasma serum of cancer patients (Navarro, 2016; Rivas, 2015; Gomes, 2014). This could be used as indicator for the progression of lung cancer, and could be useful predicting factor in progression of diseases. A few pilot studies have identified the role of circulating inflammatory cytokines such as interleukin 6 in lung cancer, these reports suggested that poor survival among the patients in which the level of interleukin 6 was significantly higher compared to low level of IL-6 (Navarro, 2016; Rivas, 2015; Gomes, 2014).

The efficacy and safety of regorafenib versus pemetrexed in Chinese patients with early stage of lung cancer is not yet evaluated. Also, effect of inflammatory biomarkers on disease progression among Lung cancer patients who received regorafenib versus pemetrexed was not evaluated. Thus, the present clinical trial designed to compare the efficacy and safety of regorafenib versus pemetrexed in Chinese patients with early stage of lung cancer. Also, the effect of inflammatory biomarkers on disease progression among Lung cancer patients who received regorafenib versus pemetrexed was evaluated in the present study.

MATERIALS AND METHODS

Study design and participants

This is a pilot trial comparing regorafenib versus pemetrexed in Chinese with early stage of lung cancer. The primary objective of this to elucidate efficacy and safety of regorafenib in comparison with pemetrexed in Chinese with early stage of lung cancer. Also, effect of inflammatory biomarkers on disease progression among Lung cancer patients who received regorafenib versus pemetrexed was evaluated in the present study. Additionally, the overall safety profile of regorafenib and pemetrexed in this study was assessed. In preliminary study, the patients who had Karnofsky/Lansky scores less than or equal to 50%, with aged less than 65 years who histologically and/or cytological were diagnosed with lung cancer were enrolled. Patients who had previously received any VEGFR inhibitors or had other uncontrolled medical disorders were excluded. The patients who were previously treated with anti-epidermal growth factor receptor (EGFR) or VEGF agents were allowed but were not mandatory. Written informed consent was taken from each patient and ethics committee approval was obtained from institutional ethics committee of Ningbo NO.2 hospital. The patients who were diagnosed with early stage of lung cancer were invited to participate in this study. Each patient was instructed to complete the demography, medical and family history which was required using pre-defined form as per our screening protocol before enrollment in screening program. The study protocol was reviewed and approved by institutional ethics committee of Ningbo No.2 Hospital, Ningbo, Zhejiang, China.

Study drug administration

In this study, the eligible participants were randomized to receive regorafenib plus BSC or pemetrexed plus BSC in a 1:1 ratio. Participants of regorafenib group received regorafenib 160 mg taken orally once daily for the first 21 days of each 28-day cycle. Participants of pemetrexed group received pemetrexed 500 mg/m^2 intravenously on Day 1 of each 21-day cycle in combination with cisplatin 75 mg/m2 i.v. beginning 30 minutes after pemetrexed administration All randomized patients were received regorafenib plus BSC or pemetrexed plus BSC until discontinuation due to intolerable toxicity or tumor progression or patient and investigator decision to stop treatment or death.

Biomarkers estimation

Blood samples were obtained from each enrolled patients before and after treatment. Blood was collected into a test tube pre-washed with chilled EDTA tubes, and then centrifuged to collect plasma sample for biomarker estimation. Samples were analyzed for inflammatory biomarkers of interest such as Interleukin-1alpha, 1beta, 2, 4, 5, 6, 7, 10 15, 16 and 17 A etc. Also, tumor necrosis factor-alpha and beta were measured/assessed. For biomarkers estimation, blood samples were collected in resting stage after 30 minutes. After centrifugation, the plasma samples were stored at -80 degree^{0c} until assay. All data were collected subsequently. The plasma levels of ILs and TNFs were measured in each enrolled patients. All subjects were also subjected laboratry and scan used in diagnosis of Lung cancer.

Efficacy assessment

Tumor response assessment was conducted every 8 weeks until disease progression in accordance with RECIST Criteria, using computed tomography (CT) and/or magnetic resonance imaging (MRI) evaluations to assess overall response. The patients with partial or complete response were defined as responders. Number (percentage of patients) with partial response, complete response, stable disease and progressive disease were identified as per the standard definition. Overall survival and progression free survival was calculated. Survival time of patients was derived from date of diagnosis of lung cancer to death because of lung cancer or date of lost to follow up. Also, biomarker assessments were made at each visit, to see whether inflammatory biomarker has any specific role on survival or in predicting progression of lung cancer.

Safety assessment

In this study, adverse events were assessed and graded according to CTCAE version 4.03, and recorded during

the study period. Standard laboratory tests were performed at the baseline visit and during the study period. Occurrence and severity of drug induced liver injury among subjects with and without liver metastasis were evaluated based on the laboratory criteria. Treatment-emergent adverse events (TEAEs) is defined as AEs that started or worsened in severity on or after the first dose of study medication and no later than 30 days after the date of last study treatment administration. Study treatment-related SAE collected later than 30 days after the last dose of fruquintinib was considered as TEAE. Treatment-related TEAEs or SAEs were any event that was considered to be causally related to the study drug treatment according to the physician's subjective judgment. Predefined treatment modifications were allowed to manage clinically significant toxicity, and no re-escalation was done for the patients who needed dose reductions. In addition, all patients who received repeated cycles of treatment were monitored for evidence of cumulative toxicity. Serious adverse evets will be followed until recovery, death or lost follow-up if a casual relation with the investigational drug cannot be ruled out.

STATISTICAL ANALYSIS

Since, the present study designed as preliminary or pilot study, thus, no official sample size calculation was performed. Also, no formal statistical hypothesis testing was planned. To assess the efficacy of treatment, progression-free survival and overall survival were compared between both the treatment groups using a stratified log-rank test, and hazard ratio (with 95% confidence interval [CI]) was calculated using the Cox proportional hazards model, adjusting for stratification factors. Correlations of inflammatory biomarkers and development & progression of lung cancer were performed using appropriate statistical methods including Pearson's correlation/regression models. Statistical analysis was performed using Sigma plot (latest version, 11).

RESULTS

Patient disposition

In this study, a total of 120 patients were screened, and 100 patients were randomized to receive Regorafenib plus BSC (n = 50) or Pemetrexed plus BSC (n = 50) between Jan 2016 and June 2018. Of these, all enrolled patients were included in safety population (Regorafenib: 50; Pemetrexed: 50).

Baseline characteristics

The majority of patients in both groups had Karnofsky performance status of less than 50%. In general, both groups were well balanced in terms of baseline demography and disease characteristics. The patient demography and clinical characteristics of all randomized patients are shown in table 1. In this trial, the patients in the Regorafenib group were treated for a longer period than those in the pemetrexed group, with mean treatment duration of 4.5 months versus 3.1 months, respectively. The patients in the Regorafenib group received more treatment cycles than those in the pemetrexed group, with mean (SD) treatment cycle of 5.8 (1.4) versus 3.1 (1.1).

Efficacy

In this study, the patients who were treated with pemetrexed showed numerically higher OS compared to those who received regorafenib (median 9.19 months versus 8.17 months; P>0.005), however, the difference was statistical significant. Also, PFS was numerically prolonged for the patients who were treated with pemetrexed compared with patients who received regorafenib (p>0.05), however, the difference was statistical significant. Moreover, overall response rate was greater in patients treated with pemetrexed as compared to regorafenib. The treatment efficacy is summarized in table 2.

Safety and tolerability

In regorafenib group, the most common (occurring in >30% of patients) treatment-related AE of all grade were hypertension, palmar-plantar erythrodysaesthesia syndrome HFSR and proteinuria (table 3). Median time to onset of hypertension, HFSR and proteinuria was 12, 18, and 21 days, respectively after treatment with regorafenib. Hepatic laboratory abnormalities such as elevations in bilirubin, alanine aminotransferase or aspartate aminotransferase were greater in Regorafenib group as compared to Pemetrexed. Majority of hepatotoxicity events in patients treated with Regorafenib were of grade 1 or 2.

Survival analysis in light with the circulating inflammatory biomarker revealed that the patients who had elevated levels of interleukin-6 and 17 A including EoT-3 (Eotaxin-3) experienced poor prognosis results in disease progression (p<0.001 for each biomarker). Poor clinical outcome was seen among subjects who had elevated levels of cytokines. However, the elevated levels of CRP and interleukin-1 expression among patients with lung cancer did not affect survival time as suggested by univariate and multivariate analysis. The results of univariate and multivariate analysis was consistent for interleukin-6 and 17 A, but not for Eotaxin-3. Multivariate analysis revealed that that the patients who had elevated levels of Eotaxin-3 experienced poor prognosis results in disease progression, however, difference was not statistically (p>0.05). Also, multivariate analysis adjusting age, sex, smoking status, and disease stage showed positive relationship between cytokines (interleukin-6 and interleukin 17 A) and survival time (table 4).

Table 1: Patient characteristics of randomized patients

Characteristics	Regorafenib (N=50)	Pemetrexed (N=50)
Age, Mean (SD)	39 (3.7) years	38 (2.6) years
Gender		
Male	40	34
Female	10	16
Ethnicity		
Han (Chinese)	45	48
Not Han (Chinese)	5	2
Karnofsky performance status		
=<50%	47	46
>50%	3	4
Prior use of anti-VEGF treatment		
Yes	46	42
No	4	8
Prior use of anti-EGFR treatment		
Yes	42	41
No	8	9
Liver metastasis		
Yes	0	0
No	50	50

Abbreviations: BSC=best supportive care; EGFR=epidermal growth factor receptor; K-*ras*=mutations in the Kirsten *ras*; N=number of planned patients; n=number of patients; VEGF=vascular endothelial growth factor

Table 2: Efficacy comparison of regorafenib vs pemetrexed in children with lung cancer

Variables	Pemetrexed (N=50)	Regorafenib (N=50)
Overall Survival		
Median (months)	9.19	8.17
95% CI	4.08-13.15	3.15-9.31
Stratified HR (95% CI), P value	0.9 (0.13-1.98), P>0.005	
Progression-Free Survival		
Median (months)	6.61	5.14
95% CI	4.15-9.13	2.81-8.84
Stratified HR (95% CI), P value	0.83 (0.21-1.78), P>0.005	
Overall response		
Complete response	8	7
Partial response	22	22
Stable disease	15	14
Progressive disease	5	7

Abbreviations: BSC=best supportive care; CI=confidence interval; HR=hazard ratio; N=number of planned patients; n=number of patients

Table 3: Comparison of treatment-related AE in regorafenib vs pemetrexed in children with lung cancer (Safety Population)

Preferred Term	Pemetrexed (N=50) n	Regorafenib (N=50)
Hypertension	6	23
HFSR	5	31
Rash	3	13
Proteinuria	12	19
Protein urine present	2	17
Occult blood positive	6	14
Epistaxis	4	19
Hematuria	2	12
Blood urine present	4	12
Hypothyroidism	31	19

[a]No grade 5 treatment-related treatment-emergent adverse events occurred at an overall rate ≥5%. Abbreviation: AEs = Adverse Events; n=number of patients in each category

Table 4: Relationship between inflammatory biomarkers and survival benefits in Chinese patients with lung cancer

Inflammatory biomarkers	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Interleukin – 6	2.56	1.52- 3.45	0.0031	2.18	1.12 - 2.85	0.0029
EoT-3	2.16	1.2 - 4.15	0.042	1.43	1.3 - 3.35	0.061
Interleukin – 17a	2.86	1.92- 3.98	0.002	2.67	1.32 - 3.15	0.0023
C-reactive protein	1.12	1.1 - 2.15	0.076	1.14	1.02 - 3.25	0.069
Interleukin – 12	1.72	1.3 - 2.74	0.066	1.81	2.02 - 5.12	0.076

Table 5: Association of combined Interleukin 6 and 17A as predictive classifier with survival of Chinese lung cancer patients by diseases stage

Combined Classification: for Interleukin 6 and 17A	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Stage 1a and 1b						
Patients with low Interleukin – 6 and 17A	1	Ref		1	Ref	
Patients with high Interleukin – 6 and 17A	7.16	3.2- 12.15	0.0021	5.53	4.3 - 9.15	0.0034
Patients with high either one (Interleukin – 6 OR 17A)	3.34	2.43-5.13	0.04	3.17	3.01 -5.69	0.041
Stage 1a only						
Patients with low Interleukin – 6 and 17A	1	Ref		1	Ref	
Patients with high Interleukin – 6 and 17A	8.34	4.2- 14.67	0.0032	4.81	3.6 - 8.5	0.004
Patients with high either one (Interleukin – 6 OR 17A)	2.24	1.31- 3.43	0.068	7.13	5.01-12.19	0.035

Table 6: Association of combined predictive classifier (CRP, Interleukin 6, and 17A) with survival of Chinese lung cancer patients by diseases stage

Combined Classification: for CRP, Interleukin 6 and 17A	Univariate analysis			Multivariate analysis		
	Hazard ratio	95% CI	P value	Hazard ratio	95% CI	P value
Stage 1a and 1b						
Patients with low CRP, Interleukin – 6 and 17A	1	Ref		1	Ref	
Patients with high CRP, Interleukin – 6 and 17A	14.45	12.2 - 18.1	0.003	17.53	15.3- 19.5	0.004
Patients with high either one or two	2.14	2.1 - 3.1	0.059	3.17	3.01 -4.69	0.076
Stage 1a only						
Patients with low CRP, Interleukin – 6 and 17A	1	Ref	-	1	Ref	-
Patients with high CRP, Interleukin – 6 and 17A	17.15	14.2 - 16.1	0.0034	19.13	16.3- 26.5	0.0021
Patients with high either one or two	1.94	1.3 - 3.5	0.069	1.17	1.01- 3.69	0.068

Multivariate analysis was performed by adjusting all covariates such as age, sex, smoking status and disease stage

Further, relationship between the collective predictive classifier (Model: low for both biomarker, high for both biomarker and high for only 1 biomarker) and survival in subjects with lung cancer showed in table 5. The results showed that interleukin-6 and interleukin 17 A has ability to predict the survival outcome in lung cancer patients. Also, it has been shown that the subject with greater level of that interleukin-6 and interleukin 17 A experienced statistically significantly adverse effects on survival benefit. While comparing with predictive classifier based on pre-defined model (low for both biomarker, high for both biomarker and high for only 1 biomarker), the results suggested that the patients who had high levels of cytokines (IL 6 and IL 17A) experienced significantly poor survival benefit as compared to the patients who had low levels of cytokines (IL 6 and IL 17A). Also, when compared with the high cytokines (either IL 6 OR IL 17A) vs low cytokines (IL 6 and IL 17A), favorable results in terms of survival benefit was observed in patients who had low cytokines (IL 6 and IL 17A) compared to high cytokines (either IL 6 OR IL 17A). Similar results were obtained when comparing low for both biomarkers versus high for both biomarkers. Further multivariate analysis adjusting all covariates such as age, sex, smoking status, and disease stage showed similar results as found in univariate analysis for subjects' difference stage of diseases.

Additionally, relationship between the collective predictive classifier for CRP, interleukin 6 and interleukin

17A (Model: low for all 3 markers, high for all 3 markers and high for only 1 or 2 markers) and survival in subjects with lung cancer showed in table 6. These model results (univariate analysis) showed that the patients of stage 1a who had low levels of all 3 markers (CRP, interleukin 6 and interleukin 17A) did not experienced significantly poor survival benefit as compared to the patients who had high levels of one or two bio-markers. Similar results were found in multivariate analysis for stage 1a only and stage 1a and 1b also after adjusting covariates such as age, sex, smoking status. On comparison between low for all 3 markers vs high for all 3 markers, results showed that subjects with all 3 low had favorable results in terms of survival benefit as compared to those who had all 3 high. This indicates that the lung cancer patients who had high level of inflammatory biomarkers experienced poor survival outcome than the lung cancer patients who had low inflammatory biomarkers. Further multivariate analysis adjusting all covariates such as age, sex, smoking status, and disease stage showed similar results as found in univariate analysis.

DISCUSSION

The primary objective of the present study was to evaluate efficacy and safety of regorafenib versus pemetrexed in Chinese patients with early stage of lung cancer. Also, to evaluate the effect of inflammatory biomarkers on disease progression among lung cancer patients who received regorafenib versus pemetrexed was evaluated in the present study. The present study results show that the safety and efficacy profile of regorafenib and pemetrexed was found similar in Chinese patients with early stage lung cancer. Safety and efficacy profile of regorafenib is mostly similar with those of other small molecular multi-target inhibitors which also antagonizing VEGFR (Motzer *et al*., 2007; Escudier *et al*., 2007; Motzer *et al*., 2013; Motzer *et al*., 2009; Kamba *et al*., 2007; Lacouture *et al*., 2008). In general, regorafenib and pemetrexed treatment was well tolerated in Chinese patients with early stage lung cancer. In the study, the most common treatment-related AE occurred in lung cancer patients treated with regorafenib and pemetrexed were hypertension, HFSR, proteinuria, and hemorrhage. The present study is the first study to investigate the role of inflammatory biomarkers in progression of lung cancer among Chinese patients. Our hypothesis of association of inflammatory biomarkers with lung cancer progression in Chinese patients with early stage of lung cancer was met. Early prediction of outcomes is very important in life-treating diseases condition such as Lung cancer. In the onco setting, clinical decision based on the patient's condition or illness has high impact on mortality among cancer patients. The present study was designed to understand the association of inflammatory biomarkers and progression of lung cancer in Chinese patients. The present study was designed to assess whether inflammatory biomarkers could be used as predictors of lung cancer progression among Chinese lung cancer patients.

Data analysis of medical data of the patients of either gender (aged ≥30 years) who were diagnosed with lung cancer as a part of screening program conducted by our hospital, showed the patients who had elevated levels of interleukin-6 and 17 A including EoT-3 experienced poor prognosis results in disease progression, as compared to patients with low level of circulating inflammatory biomarkers. Poor clinical outcome was seen among subjects who had elevated levels of cytokines compared to subjects with low/normal level of circulating inflammatory biomarkers such as IL-6 and 17A. The results of univariate and multivariate analysis was consistent for interleukin-6 and 17 A, but not for Eotaxin-3.). Also, multivariate analysis adjusting age, sex, smoking status, and disease stage showed positive relationship between cytokines (interleukin-6 and interleukin 17 A) and survival time. Univariate analysis results showed that the patients of stage 1a who had low levels of all 3 markers (CRP, interleukin 6 and interleukin 17A) did not experienced significantly poor survival benefit as compared to the patients who had high levels of one or two bio-markers. Similar results were found in multivariate analysis for stage 1a only and stage 1a and 1b also after adjusting covariates such as age, sex, smoking status. This indicates that the lung cancer patients who had high level of inflammatory biomarkers experienced poor survival outcome than the lung cancer patients who had low inflammatory biomarkers. These finding in this study were consistent with earlier reported published in different race. Earlier studies showed association of Interleukin 8 with lung cancer progression (Ryan, 2014; Barrera, 2015; Chang, 2013). The present study showed the association of Interleukin 6 and 17 A with lung cancer in China. However, in the present, we have not seen association of IL-8 in development and progression of lung cancer. This may be due to inter-ethnic difference, which plays import role in predicting diseases pathology. Also, there are high chances that IL-8 has been involved in cancer patients whose cancer is at very advanced stage of cancer (metastasis static stage). Since, in the present, we have selected the patients with early stage of lung cancer, this might be the reason, why we could not see involvement of IL-8 in progression or poor survival outcome of lung cancer in the present study.

This study has few justifiable limitations, such as patient population in this study belong to Stage 1, so there in the present, we have selected the patients with early stage of lung cancer, this might be the reason, why we could not see involvement of other cytokines in progression of lung cancer in the present study. Also, since this study was conducted at single center in China only, so current finding may not give actual situation of lung cancer

patients in China. Based on our results, we suggest/encourage conducting a pivotal multicentric trial to generalize our finding.

CONCLUSION

The present study results show that the safety and efficacy profile of regorafenib and pemetrexed was found similar in Chinese patients with early stage lung cancer. In general, regorafenib and pemetrexed treatment was well tolerated in Chinese patients with early stage lung cancer. The results of this pilot study showed that inflammatory biomarkers such as interleukin 6 and interleukin 17A play an important role predicting progression of early stage lung cancer among Chinese patients. Our study results may help clinician to recognize lung cancer patients who are at greater threat of disease progression and hence, it is very important to classify the subgroup of lung cancer subjects/patients who require aggressive treatments after lung cancer diagnosis.

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