

# Progressive Multiple Cystic Changes in Both Lungs in a Patient Treated with Gefitinib for Lung Adenocarcinoma

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천은미



# Gefitinib

- Gefitinib (Iressa) is a selective epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor for the treatment of advanced or metastatic non-small cell lung cancer (NSCLC).

Cohen et al. Oncologist 2003

# Gefitinib – Side effects

- Manageable and non-cumulative (skin rash, diarrhea)
- ILD with an estimated incidence of approximately 1%.
- Gefitinib-induced ILD; mortality is 30%-40%.

Keam et al. Cancer Res Treat. 2013

- The case of gefitinib associated pulmonary cystic changes in NSCLC has not been reported yet.

# Case Report

- A 56-year-old female never-smoker
- **Symptoms** :persistent cough, sputum and dyspnea
- **Radiologic findings**  
:Chest CT: 2.2-cm mass in RUL with multiple small nodules in the bilateral lungs.
- **Pathology**: adenocarcinoma



# Clinical course

- Two courses of systemic chemotherapy with paclitaxel and cisplatin.
- Stopped due to paclitaxel-induced hypersensitivity
- One year later, the patient visited the ER with an abrupt onset of quadriparesis and dyspnea.

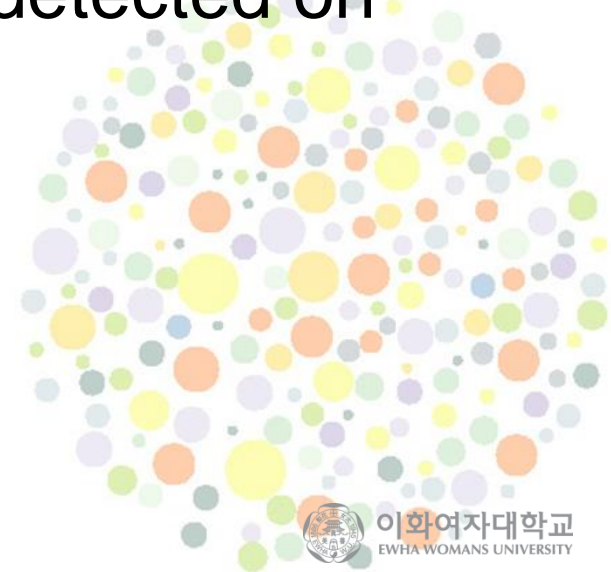
# Clinical course

- Spontaneous pneumothorax in the left lung and multiple brain metastases were noted.
- 30-Gy whole brain irradiation for brain metastases
- Gefitinib was started (a 250mg daily) and continued for the following 15 months

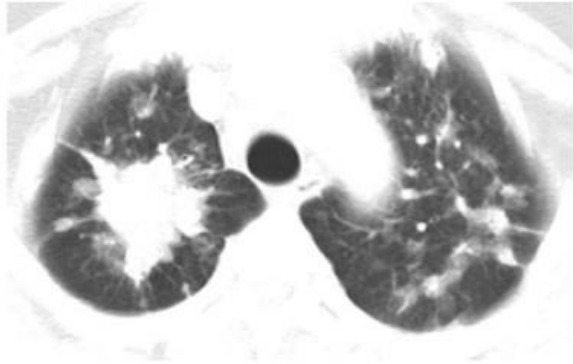


# New multiple cystic changes developed after treatment gefitinib

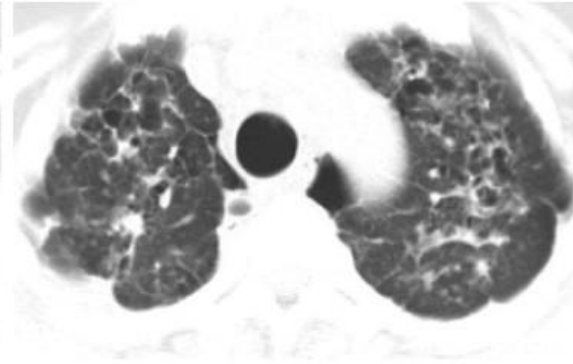
- Although the primary mass in RUL with multiple metastatic nodules decreased in size after one month gefitinib treatment, the development of new multiple cystic changes was detected on HRCT scan.



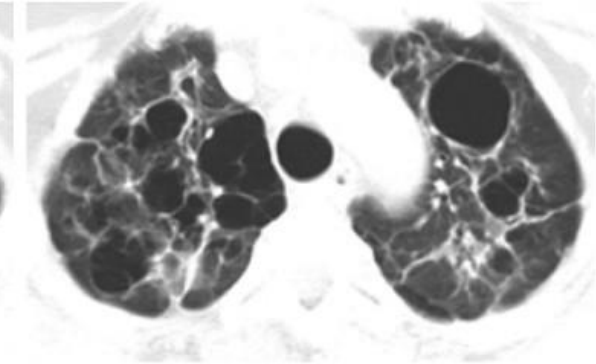
**Enhanced CT scan obtained at time point of pre-medication and 1 m, 3 m, 7m, 9 m, and 13 m after initiation of gefitinib treatment.**



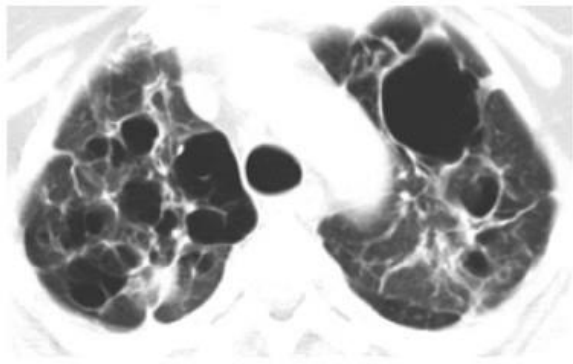
Pre



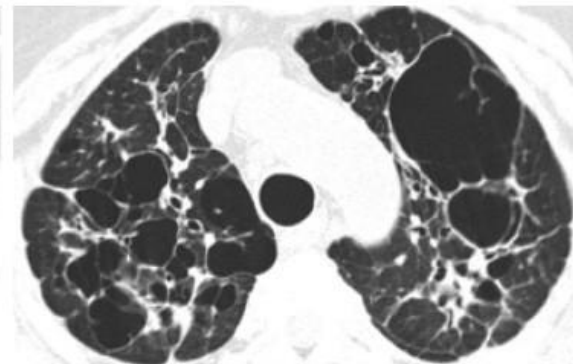
1 month



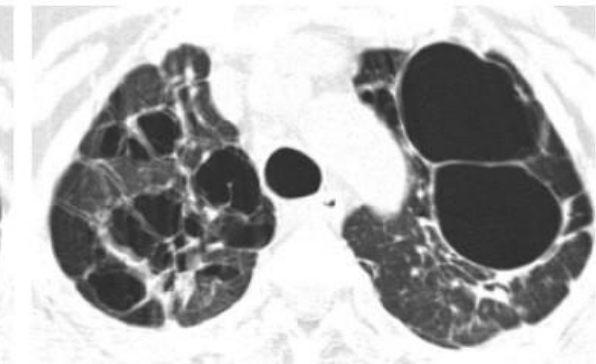
3 months



7 months



9 months

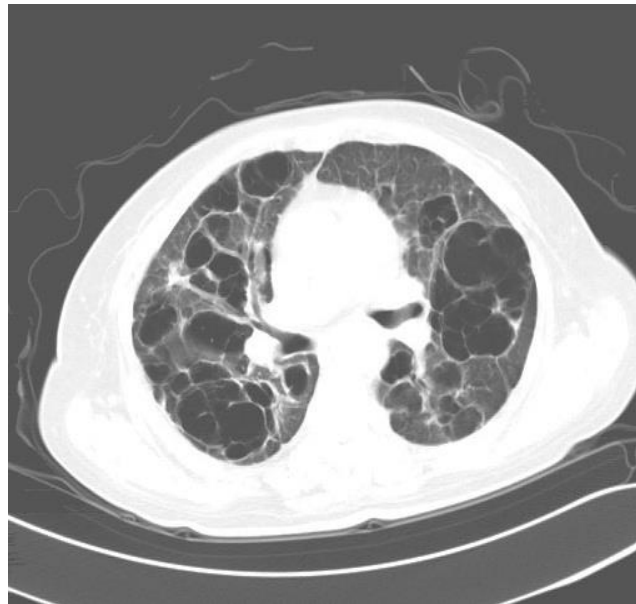


13 months





Pre state



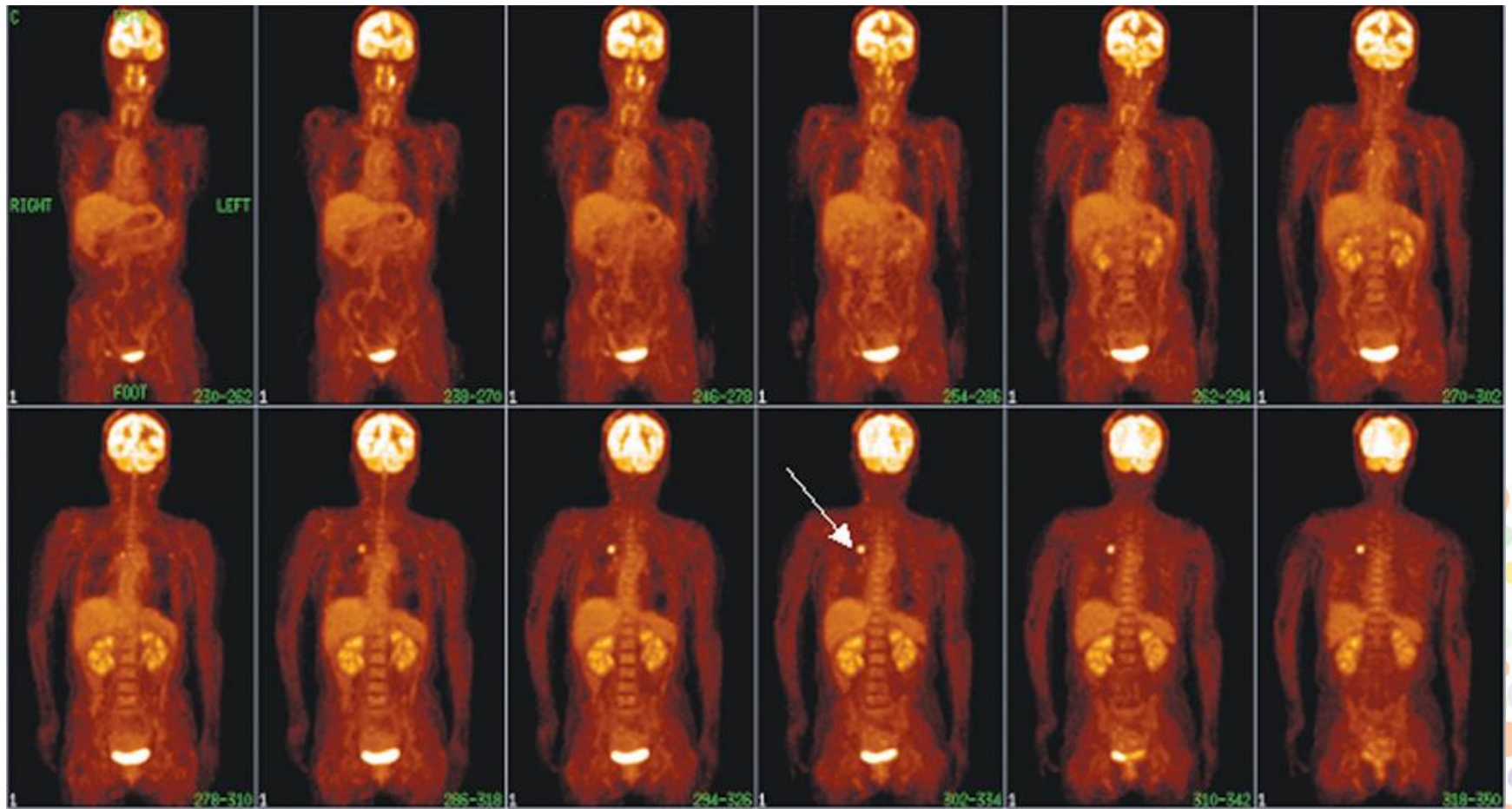
After 7 m



After 1 yr




# (FDG) positron emission tomography scan obtained after 12 months of treatment

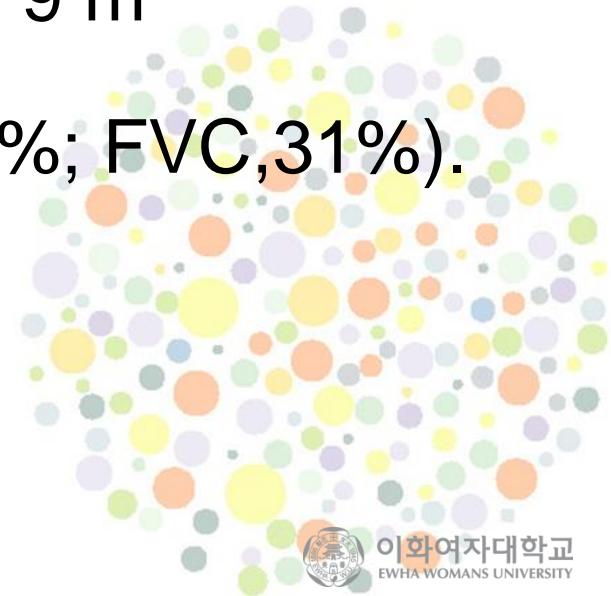


# Pulmonary function tests

- The PFT at 9 months after gefitinib therapy showed [FEV<sub>1</sub>] 36%, [FVC] 31%.
- Due to a poor performance status, histological evaluations was not available.



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- Therapy with gefitinib was continued for 15 months despite of the air cystic changes in both lungs.
  - A follow-up PFT was performed 13 m and more improvement was shown than after 9 m (FEV<sub>1</sub>,56%; FVC,53% vs. FEV<sub>1</sub>,36%; FVC,31%).



# Discussion

- The antineoplastic drug induced pulmonary toxicity occurs usually during the first 3 months.
- Preexisting pulmonary fibrosis, poor PS and prior thoracic irradiation were independent risk factors for ILD in patients with gefitinib treatment

Hota et al. Cancer J 2005

# Cases of cystic change after chemotherapy

✚ Squamous cell lung cancer is presenting as an asymptomatic pneumatocele.

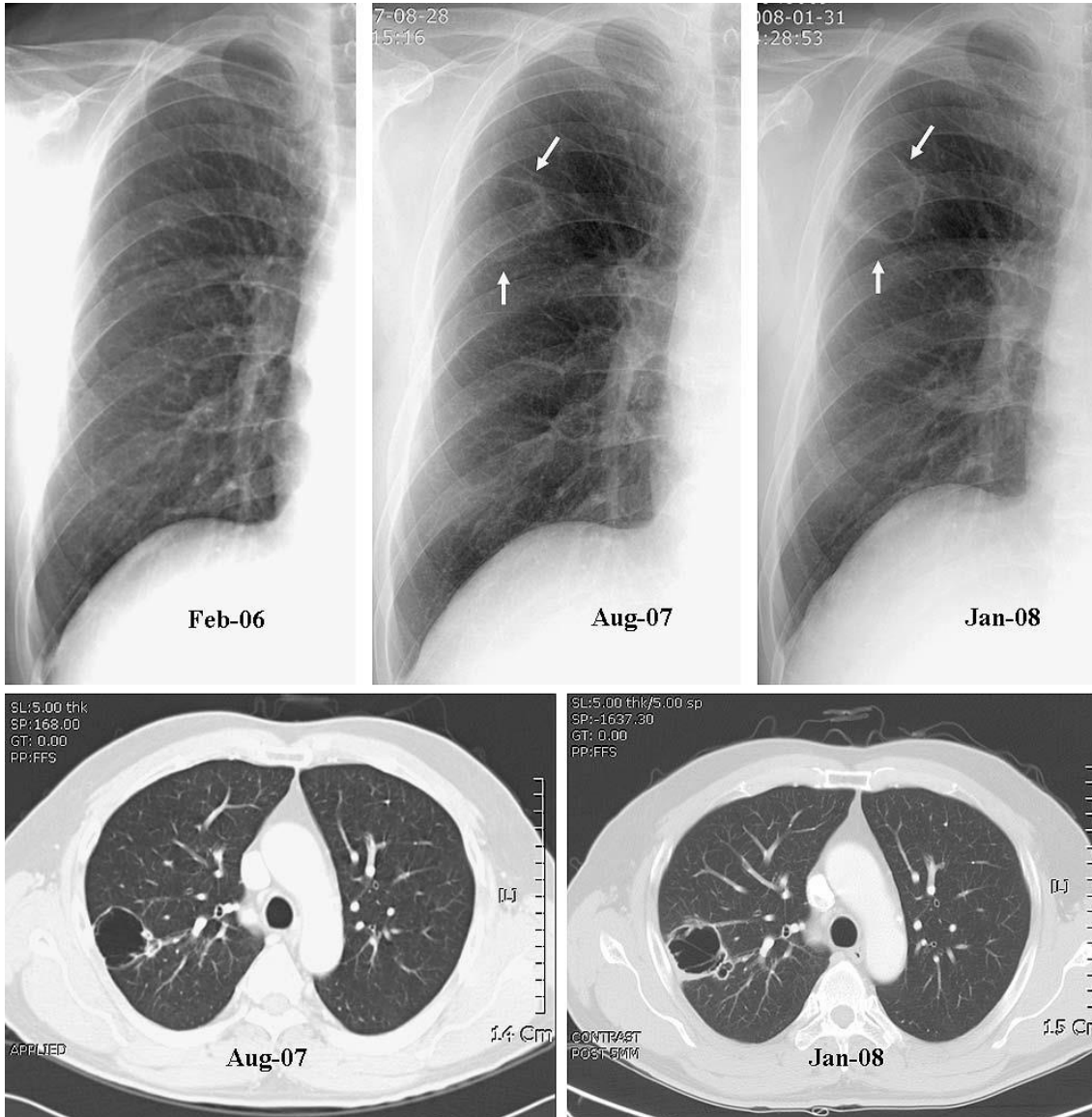
Lee et al. Intern Med 2008

✚ Fatal cystic change in the brain metastasis after gefitinib therapy.

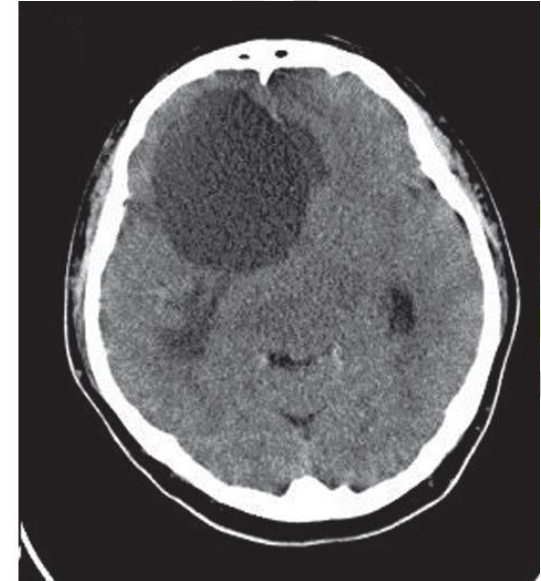
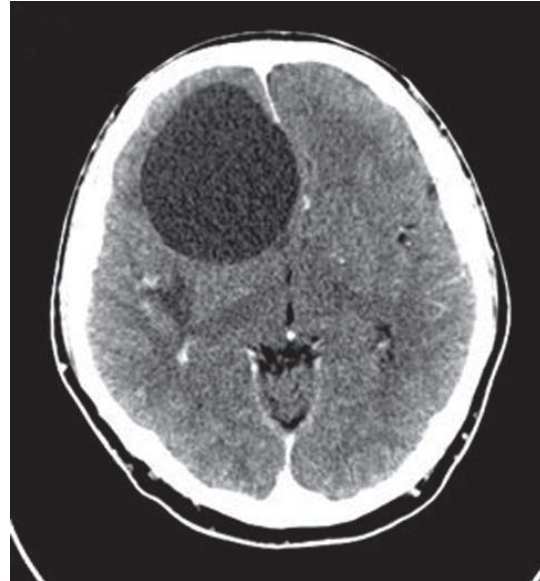
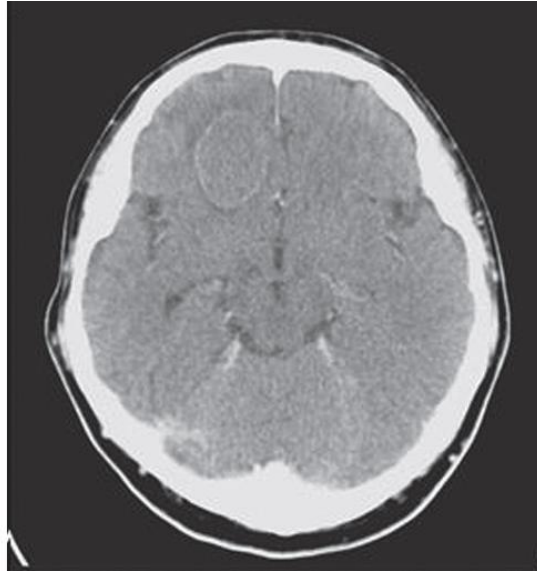
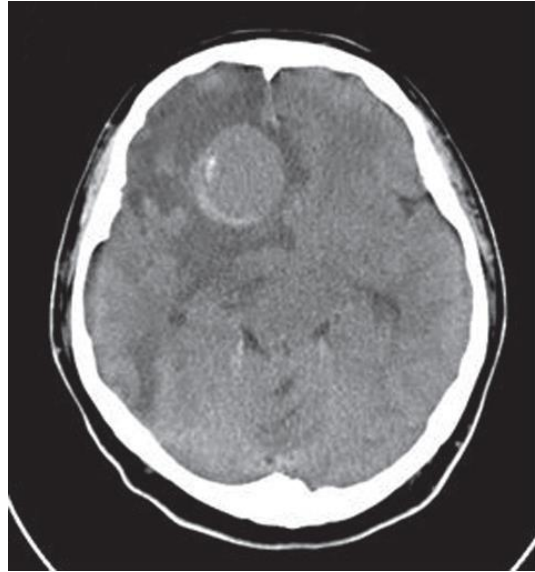
✚ The cytology of cystic mass of the brain was negative for malignancy.

Zee et al. J Clin Oncol 2008

# 1) Lung Cancer Presenting as an Asymptomatic Pneumatocele



## 2) Fatal Cystic Change of Brain Metastasis After Response to Gefitinib



# Postulation of cystic changes

- Tumor necrosis due to tumor killing effects & tumor infiltrations of air-containing spaces with a check-valve

Topal et al Indian J Radio Imaging 2007

- Tumor lysis and necrosis caused by the targeting property of gefitinib towards to cancer cells.
- EGFR inhibitor, gefitinib, may impair normal repair and thereby exacerbate any lung injury

Danson et al. Drug Saf 2005

# Presenting case : discussion

- Size of the main lesion with metastatic nodules were decreased and cystic changes were developed.
- The improvement of lung function as the effect of decrease of tumor burden as well as rehabilitation.
- Cystic changes of the presented case may be postulated by an unknown rare side effect of gefitinib.

# Incidence of ILD by gefitinib

- The incidence of ILD in Japanese was reported between 2.4% and 5.4%.
- In Korean patients, studies reported (1.3%- 3.7%)
- Lower albumin level(< 3g/dL) was associated with ILD(OR, 3.91; 95% CI, 1.20 to 12.1).
- ILD (80%) occurred during the first 8 weeks

Beom et al. Cancer Res Treat. 2016

# Mechanism of ILD by gefitinib

The mechanism of ILD by gefitinib is unclear.

- Decreased EGFR phosphorylation ?

Suzuki et al Cancer Res 2003

- Methotrexate resulting from hypoalbuminemia could enhance drug induced pulmonary toxicity.

Lateef Expert Opin Drug Saf 2005

- High erlotinib and metabolite levels result in severe adverse pulmonary reactions.

Ter Heine et al. Lung Cancer 2012

- Lower albumin level might lead to higher levels of free gefitinib and enhance pulmonary toxicity.

Beom et al. Cancer Res Treat. 2016



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