Synopsis

NIS Code: NIS-OCN-DUM-2009/1
Date: Date：23 Nov 2014

Study title：

A non-interventional survey on the EGFR mutation status in completely resected Chinese NSCLC patients with adenocarcinoma histology (ICAN)

Participating sites：

24 sites in the mainland China

Study duration：

45 months

Date of Fist Subject Enrolled: 8 April 2010

Date of Last Subject Completing Observation: 16 Jan 2014

Objective：

Primary objective:

The primary objective of study is to explore the EGFR gene mutation status in early stage NSCLC with adenocarcinoma histology after complete resection.

Secondary objectives:

The secondary objectives of the whole study include the following items:

- To obtain the real-world practice in adjuvant setting
- To observe the clinical outcome of early stage NSCLC with adenocarcinoma histology after complete resection
- To explore the risk factors of tumour recurrence of early stage NSCLC with adenocarcinoma histology after complete resection in the real-world setting

Study design：

A descriptive observational study

Inclusion criteria：

For inclusion in the cross-sectional epidemiological study, the study subjects must fulfil the following criteria at the time of screening:

1. Patients ≥18 years old.
2. Provision of informed consent prior to any study specific procedures
3. Histological diagnosed as adenocarcinoma type of non-small cell lung cancer
4. Have completed lung cancer operation

5. The tumour EGFR gene mutation status test was performed as regular medical practice

Exclusion criteria：

For this study, patients must not enter the study if any of the following exclusion criteria is fulfilled.

(1) Patients who disagree to take participate in this study.

Number of subjects：

Of the 591 patients screened in this study, 23 patients (3.89%) were excluded from the study. A total of 568 patients were included for FAS analysis.

Efficacy variables：

Not applicable.

Safety variable：

Not applicable.

Efficacy assessment criteria：

Not applicable.

Statistical methods：

SAS 9.1.3 software was used for statistical analysis. Unless otherwise stated, all the tests were two-sided, and the significant level was 0.05, ie. If the P value is less than or equal to 0.05, the difference was considered to have statistical significance.

EGFR mutation status analysis indexes included mutation rate (mutation positive rate and 95% CI) and frequency and percentage of mutation type. Summary of mutation types include deletion of exon 19 and exon 21 mutations, as well as other transposition. For other types, according to its details, the frequency counts and percentages were descried. In this study, the same tumor tissue samples from the same patients were detected by both methods (PCR+ direct sequencing-based methods, ARMS) for gene mutation. For this kind of data, consistent percentage in mutation positive results and 95% CI were calculated, and McNemar test was used to test whether positive rates were consistent between the two methods.

For the details of postoperative adjuvant therapeies for NSCLC during the study, eg. chemotherapy, radiotherapy and other adjuvant therapy, a by-patient listing was provided.

Kaplan-Meier method was used to calculate 1, 2 and 3-year DFS rate and the 95%CI. DFS was defined as the time from operation until recurrence or death from any cause, whichever occurred first. The data were censored for the cases who were still alive at the end of 3 years. Log-rank test was used to compare 1, 2 and 3-year DFS rates among groups and to describe the DFS curves.

Multivariate Cox model was used to explore the risk factors of tumour recurrence using stepwise regression method according to the preset factors. The variables with regression coefficient test p value greater than 0.15 would be removed from the model.

Results：

Primary objective

Within the total 568 patients included in FAS, the applied detection methods of EGFR mutation were ARMS (419 patients, 73.77%), PCR plus direct sequencing (118 patients, 20.77%), mutant-enriched (23 patients, 4.05%) and (1)X-TAG- Liquid chip (2) Branch DNA-Liquid chip (8 patients, 1.41%). 313(55.11%) patients showed positive EGFR mutation (95% CI 50.91% - 59.25%), and 255 (44.89%) patients showed negative. The most common mutations were deletion and L858R point mutation seen in 139 (24.47%) and 128 (22.54%) patients respectively.

Table S2 EGFR mutation outlines

EGFR mutation results, n (%)	FAS (N=568)
Positive	313(55.11)
Negative	255(44.89)
Positive rate 95% CI	(50.91, 59.25)

The following factors were evaluated for positive EGFR mutation:
Gender as a factor showed statistical significance for positive EGFR mutation with a p-value of <0.0001, and the mutation is in favour of female (female: 66.55%, 185/278; male: 44.14%, 128/290).
Smoking as a factor showed statistically significant p-value of <0.0001 with mutation in favour of those patients who were never smoked (61.79%, 228/369). Smoking degree also showed statistically significant for positive EGFR mutation status with a p-value of <0.0001. EGFR mutation positive rate for patients never smoked plus mild smoking degree was 61.50% (254/413), and for patients of moderate and severe smoking degree was 38.06% (59/155).
EGFR mutation positive rate of patients who were postoperative pathological stage I, II, III and IV was 59.45% (173/291), 51.02% (25/49), 47.10% (65/138), and 57.14% (8/14), respectively. There is no statistical significance for the difference (P=0.1047).

Secondary objectives

Adjuvant therapy

There were 50.70% of patients who received adjuvant therapy after operation, in which 37.50% patients only received chemotherapy, 0.53% patients only received radiotherapy and 1.76% patients received only TKI therapy, respectively.
The proportions of patients with postoperative pathological stage I, II, III and IV received adjuvant therapy after operation were 37.46% (109/291), 61.22% (30/49), 67.39% (93/138), and 50.00% (7/14), respectively.

DFS

One-year, 2-year and 3-year DFS rates were 82.15%, 68.91% and 61.68%, respectively. Multivariate Cox model analysis was used to explore the risk factors of tumour recurrence. The risk factors included age group (<65 or ≥65 years), gender, smoking history (never/ever/current smoker), smoking degree (pack years), operation type (pneumonectomy/ lobectomy/others), operation method (open survey/VATS), postoperative pathologic stage

and adjuvant treatment (with/without; for patients with adjuvant treatment, also to compare chemotherapy only vs. other adjuvant treatments), and EGFR mutation status (negative/common mutation/uncommon mutation). Smoking degree and postoperative pathologic stage, which were not included in the original analysis plan, were added as a post-hoc analysis.

The results of the first year data showed that the risk factors of tumour recurrence were: male ($HR_{F/M}$=0.556, 95%CI=[0.354,0.874]), with open operation ($HR_{VATS/open}$=0.548, 95%CI=[0.296,1.014]) and postoperative pathologic stage (HR=1.813, 95%CI=[1.455,2.259]).

The results of the second year data showed that the risk factors of tumour recurrence were: male ($HR_{F/M}$=0.694, 95%CI=[0.501,0.963]), with pneumonectomy ($HR_{lobectomy/pneumonectomy}$ =0.602, 95%CI=[0.375,0.968]) or others operation type ($HR_{others/\ lobectomy}$ =5.303, 95%CI=[1.298,21.669]), with open operation ($HR_{VATS/open}$=0.567, 95%CI=[0.367,0.876]) and postoperative pathologic stage (HR=1.678, 95%CI=[1.423,1.978]).

The results of the third year data showed that the risk factors of tumour recurrence were: male ($HR_{F/M}$=0.661, 95%CI=[0.452,0.966]), ever-smoker ($HR_{current/ever}$=0.576, 95%CI=[0.349,0.952]), with pneumonectomy ($HR_{lobectomy/pneumonectomy}$ =0.492, 95%CI=[0.321,0.753]) or others operation type ($HR_{others/\ lobectomy}$ =5.319, 95%CI=[1.298,21.796]), with open operation ($HR_{VATS/open}$=0.672, 95%CI=[0.461,0.979]) and postoperative pathologic stage (HR=1.610, 95%CI=[1.383,1.874]).

Consistency Analysis of the Results between Two Detecting Methods

Among the 568 patients included in FAS, PCR plus direct sequencing and ARMS were both applied to 419 patients. Among the 419 patients, 48.93% of patients reported positive mutation by both detecting methods, and 36.52% of patients reported negative mutation results by both detecting methods. Different results from two detecting methods were reported by 14.56% of patients. The difference between the two detecting methods is no statistical significance (P=0.0548).

Of the 223 male patients detected by both methods, 42.60% of patients with PCR + direct sequencing and 46.64% of patients with ARMS reported positive results. As for the 196 female patients, 67.86% of patients with PCR + direct sequencing and 70.92% of patients with ARMS reported positive results.

Of the 293 never-smoked or mild-smoking-degree patients, 61.43% of patients with PCR + direct sequencing and 65.87% of patients with ARMS reported positive results. As for the 126 moderate or severe-smoking- degree patients, 38.10% of patients with PCR + direct sequencing and 39.68% of patients with ARMS reported positive results.

Of the 262 never-smoked patients, 61.45% of patients with PCR + direct sequencing and 66.03% of patients with ARMS reported positive results. Of the 97 Ex-smoked patients, 46.39% of patients with PCR + direct sequencing and 47.42% of patients with ARMS reported positive results. As for the 60 current smoking patients, 36.67% of patients with PCR + direct sequencing and 40.00% of patients with ARMS reported positive results.

Of the 219 stage I patients, 60.73% of patients with PCR + direct sequencing and 63.01% of patients with ARMS reported positive results. Of the 33 stage II patients, 45.45% of patients with PCR + direct sequencing and 48.48% of patients with ARMS reported positive results. Of the 98 stage III patients, 47.96% of patients with PCR + direct sequencing and 55.10% of patients with ARMS reported positive results. As for the 9 stage IV patients, 55.56% of patients with PCR + direct sequencing and 44.44% of patients with ARMS reported positive results.

Among the 419 patients who received both detecting methods, positive results were reported by 54.52% of patients with PCR+ direct sequencing and 58.00% of patients with ARMS. Consistent detecting results between the two methods in regarding of all EGFR mutation types were reported by 321 patients, counting for 76.61%. Regarding of the individual mutation type, the consistent detecting results between the two methods were reported by 408 patients (97.37%) on exon 18 mutation, 384 patients (91.65%) on exon 19 mutation, 394 patients (94.03%) on exon 20 mutation and 376 patients (89.74%) on exon 21 mutation.