ABSTRACT

Background: Icotinib is a highly selective and potent epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor. In a phase II clinical trial (IOSEIN), icotinib was shown to be well-tolerated in EGFR-TKIs, gefitinib, in progression of survival (44.9 [3.5-63.0] months vs. 34.2 [2.3-58.1] months, p=0.031). Icotinib was approved by the CDA in June 2013 for use as second- or third-line therapy for advanced non-small cell lung cancer (NSCLC) patients. Upon approval of icotinib, a phase IV study (ISEAF) was initiated in China to complete further safety and efficacy assessment of the drug.

Aims: To confirm the safety and efficacy of icotinib in the clinical setting.

METHODS: The trial was a single-arm, open-label, phase IV study, conducted in 480 hospitals in China. Advanced NSCLC patients who were eligible for treatment were administrated oral icotinib (125 mg, TID) until disease progression or intolerable toxicity occurred. The co-primary endpoints were overall survival (OS), progression-free survival (PFS), objective response rate (ORR), and disease control rate (DCR).

RESULTS: 6,076 patients were registered in the study, 5,348 were evaluable by intention-to-treat. Baseline characteristics (n=5,348): male:female 5850:492, non-smoker/ever-smoker or current-smoker 4002:1326, adenocarcinoma/non-adenocarcinoma (other) 78:175, 6:19, stage IB/IIIA/IV 76:60:22, age (95% CI) 62 (30-85), smoking status 2000 (40.7%), diabetes (9.5%), and patients experienced intermittent lung disease associated with the OS. The ORR was 30.0% and the DCR was 86.0%.

Conclusions: Through both the IOSEIN trial and phase IV safety study (ISEAF), icotinib has been shown to be both safe and effective for the treatment of patients with advanced NSCLC. Since drug approval in 2011, more than 40,000 NSCLC patients have been treated with such in China. Icotinib is currently under worldwide development, with plans to expand to the whole of Asia in the near future.

INTRODUCTION

In vivo Tumor Model

In vivo xenograft tumor model - drug administration

In vitro cell model

Drug screening

Progression-free Survival

Egfr gene status

Egfr transmembrane protein that is activated in many human cancers and leads to increased proliferation and survival of cancer cells.

EGFR mutations are short, in-frame deletions in exons 19 (delE19) and specific point mutations in exon 21 (L858R).

Mutations of EGFR is found to be oncogenic driver in many human cutaneous squamous cell carcinoma (NMSC), colorectal, and head and neck cancers.

Aromatic tyrosine kinases (RTKs) such as epidermal growth factor receptor (EGFR) and platelet-derived growth factor receptor (PDGFR) mediates a wide range of cellular processes, including mitogenic signaling, cell survival, and tumor progression.

EGFR tyrosine kinase inhibitors (TKI) are small molecules that target the ATP binding site of EGFR kinase leading to inhibition of intracellular EGFR tyrosine kinase activity.

In 2009, icotinib underwent a randomized, double-blind, phase I clinical trial (IOSEIN) where it was tested head-to-head with another EGFR-TKI, gefitinib. The results of the IOSEIN trial showed that icotinib was non-inferior to gefitinib in terms of progression free survival and overall survival. Icotinib showed a slight improvement over gefitinib in terms of overall toxicity and reported adverse events (60% vs. 70%), however it was not deemed statistically significant. Icotinib gained marketing approval from the CDA on June 7, 2011. Upon market approval, icotinib began a phase IV, safety, monitoring study (ISEAF) to determine safety and efficacy in a wider population.

PHASE I (ISAF) DATA

ENROLLMENT

Patients

Advanced NSCLC

Any number of prior therapies

EGFR status unknown

Enrollment: August 2011 - August 2012

6,076 patients accrued

Safety and efficacy: P<0.001

Overall population/Elder patients

Overall population

Elder patients

AVERAGE AGE

Gender

Male

Female

SMOKING STATUS

Non-smoker

Current-smoker

PREVIOUS CHEMOTHERAPY

Chemotherapy

1

2

EGFR status & Tumor Response

Characteristics

N (%)

Age

<70

2,489 (77.4%)

70-79

1,247 (40.7%)

80-89

403 (12.9%)

90+

135 (4.3%)

Gender

Male

1,899 (60.7%)

Female

1,177 (46.0%)

Pathology

Adenocarcinoma

4,821 (78.6%)

Non-Adenocarcinoma

935 (15.4%)

Other

369 (6.3%)

Disease Stage

I

452 (47.4%)

IV

5,480 (90.2%)

Other

139 (2.3%)

Smoking Status

Unknown

8 (0.1%)

Smokers

675 (11.1%)

Non-smokers

4,093 (67.2%)

Ex-smokers

1,319 (22.7%)

Previous Chemotherapy

Chemotherapy
t

1

2

Smoker

282 (46.5%)

64 (10.5%)

Total

356 (59.8%)

72 (12.1%)

CONCLUSIONS

Icotinib is a safe and effective EGFR tyrosine kinase inhibitor for the treatment of NSCLC.

Common adverse events in phase IV ISEAF study showed icotinib to have acceptable safety and tolerability in a broad NSCLC patient population, with low adverse events rate of 31.5%.

EGFR wild-type positive population, icotinib showed an excellent ORR of 49.2% and a disease control rate (DCR) of 62.3%.

EGFR mutation positive patients who received first-line icotinib showed an ORR of 56.3%.

Global Development

January 2014 – The United States FDA gave icotinib a “May Proceed” status.

June 2014 – The United States FDA approved icotinib.

US Phase II clinical trial enrollment to begin Q1 2015.

For more information:

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