A Phase I Study of the Safety and Pharmacokinetics of Higher-Dose Icotinib in Patients With Advanced Non-Small Cell Lung Cancer

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TRIAL INFORMATION

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• Sponsor: Betta Pharmaceuticals Co., Ltd.
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LESSONS LEARNED

• This phase I study evaluated the maximum tolerated dose, dose-limiting toxicities, safety, pharmacokinetics, and efficacy of icotinib with a starting dose of 250 mg in pretreated, advanced non-small cell lung cancer patients. We observed a maximum tolerated dose of 500 mg with a favorable pharmacokinetics profile and antitumor activity.
• These findings provide clinicians with evidence for application of higher-dose icotinib.

ABSTRACT

Background. Icotinib, an oral epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor, has shown favorable tolerability and antitumor activity at 100–200 mg in previous studies without reaching the maximum tolerated dose (MTD). In July 2011, icotinib was approved by the China Food and Drug Administration at a dose of 125 mg three times daily for the treatment of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC) after failure of at least one platinum-based chemotherapy regimen. This study investigated the MTD, tolerability, and pharmacokinetics of higher-dose icotinib in patients with advanced NSCLC.

Methods. Twenty-six patients with advanced NSCLC were treated at doses of 250–625 mg three times daily. The EGFR mutation test was not mandatory in this study.

Results. Twenty-four (92.3%) of 26 patients experienced at least one adverse event (AE); rash (61.5%), diarrhea (23.1%), and oral ulceration (11.5%) were most frequent AEs. Dose-limiting toxicities were seen in 2 of 6 patients in the 625-mg group, and the MTD was established at 500 mg. Icotinib was rapidly absorbed and eliminated. The amount of time that the drug was present at the maximum concentration in serum (Tmax) ranged from 1 to 3 hours (1.5–4 hours) after multiple doses. The t1/2 was similar after single- and multiple-dose administration (7.11 and 6.39 hours, respectively). A nonlinear relationship was observed between dose and drug exposure. Responses were seen in 6 (23.1%) patients, and 8 (30.8%) patients had stable disease.

Conclusion. This study demonstrated that higher-dose icotinib was well-tolerated, with a MTD of 500 mg. Favorable antitumor activity and pharmacokinetic profile were observed in patients with heavily pretreated, advanced NSCLC. The Oncologist 2016;21:1294–1295d

DISCUSSION

Icotinib is a selective, oral tyrosine kinase inhibitor (TKI) targeting EGFR [1]. Its clinical investigation began in 2007, which included dose escalation and assessment of different dosing schedules [2–4]. MTD was not reached in these studies, and the recommended dose was established at 125 mg [2–6]. Oral icotinib was rapidly absorbed and eliminated in NSCLC patients, with a Tmax of 3 hours and a t1/2 of 6 hours [4, 7]. Increased drug absorption and exposure were observed when icotinib was administered with high-fat and high-calorie food [4]. Additionally, Ni et al. reported a significant relationship between drug exposure and clinical benefits [7], whereas Zhao et al. found no dose, exposure, safety/efficacy association in another study [3].

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The present study documented a relatively higher incidence of AEs in patients receiving higher-dose (250–625 mg) icotinib, with an MTD of 500 mg three times per day. The dose-limiting toxicities (DLTs) included grade 3 rash and grade 3 hand and foot syndrome (Table 1). Three patients had serious AEs (SAEs; 1 in the 500-mg group and 2 in the 625-mg group); all SAEs were ameliorated by discontinuation or dose reduction. Oral icotinib is rapidly absorbed and eliminated, which was consistent with the results obtained from previous studies assessing low-dose icotinib [2, 4, 7]. Dose-dependent increases in icotinib Cmax and area under the curve (AUC) were observed over the dose ranges of 250–350 mg and 400–625 mg, which may be due to its solubility in water (Fig. 1). This trend was also seen in a population pharmacokinetic study, in which icotinib displayed a saturated absorption rate of 204 (oral icotinib, 350 mg) and 245 (oral icotinib, 600 mg) μg per hour in healthy persons [9]. No dose, exposure, safety/efficacy relationship was found in our study.

Antitumor activity was observed over the entire dose range (250–625 mg). The overall response rate (ORR) and disease control rate (DCR) were 23.1% and 53.9%, respectively. In another phase I study evaluating icotinib, tumor response was shown from 100 to 150 mg with an ORR of 21.9% and DCR of 43.8% [2]. These results suggested that the safe and effective range for icotinib is 100–500 mg.

In summary, good tolerability, feasibility of prolonged treatment, antitumor activity, and pharmacological profile of higher-dose icotinib were shown in the present study, which support the application and further investigation of higher-dose icotinib.

### Trial Information

**Disease**
Lung Cancer: NSCLC

**Stage of disease / treatment**
Metastatic / Advanced

**Prior Therapy**
1 prior regimen

**Type of study - 1**
Phase I

**Type of study - 2**
3 + 3 design

**Primary Endpoint**
Toxicity

**Primary Endpoint**
Tolerability

**Secondary Endpoint**
Maximum Tolerated Dose

**Secondary Endpoint**
Pharmacokinetics

**Secondary Endpoint**
Efficacy

**Additional Details of Endpoints or Study Design**
This study was conducted between October 9, 2009, and June 15, 2011. Patients were assigned sequentially to escalating dose levels of icotinib following a 3 + 3 design with a starting dose of 250 mg three times per day. Within a 28-day cycle, a single dose of icotinib was administered orally on day 1 and day 7, followed by 24-hour blood sampling for pharmacokinetics (PK) assessments. For the remaining days, icotinib was administered three times per day.
times daily. After the first cycle, all patients received continuous icotinib until disease progression or unacceptable toxicities. The doses to be investigated were 300 mg, 350 mg, 400 mg, 500 mg and 625 mg; at least 3 patients were treated in each cohort.

DLTs were defined as any grade 3 or higher toxicity per Common Terminology Criteria for Adverse Events, version 3.0. The MTD was the lower dose after the one at which 1 of 3 or 2 of 6 patients developed a DLT. The decisions for dose escalation were based on the observed toxicities during the first treatment cycle (28 days). Dose escalation was designed to be stopped when MTD or 625 mg was achieved.

In case of DLT, icotinib could be discontinued for no more than 14 days. If DLT was not relieved after discontinuation, icotinib could be reduced no more than twice by one dose level in the same patient. EGFR mutation status was not a requirement in this study.

Investigator’s Analysis

Active and should be pursued further

| Drug Information |
|------------------|
| **Drug 1**       |
| Generic/Working name | Icotinib |
| Trade name       | Conmana |
| Company name     | Betta Pharmaceuticals Co., Ltd. |
| Drug type        | Small molecule |
| Drug class       | EGFR |
| Dose             | mg per flat dose |
| Route            | p.o. |
| Schedule of Administration | Orally administered three times daily |

| Patient Characteristics |
|--------------------------|
| Number of patients, male | 14 |
| Number of patients, female | 12 |
| Stage                     |
| TNM Staging               |
| IIIB: 5                   |
| IV: 21                    |
| Age                       |
| Median (range): 57 (34, 70) |
| Number of prior systemic therapies |
| Median (range): 2 (1, 11) |
| Performance Status: ECOG |
| 0 — 7                     |
| 1 — 19                    |
| 2 —                       |
| 3 —                       |
| Unknown —                 |
| Other                     |
| Prior treatment           |
| Chemotherapy: 26          |
| No. of previous chemotherapy |
| 1: 22                     |
| ≥2: 4                     |
| Radiotherapy: 5           |
| Surgery: 5                |
| Cancer types or histologic subtypes |
| Adenocarcinoma, 22        |
| Squamous cell carcinoma, 1 |
| Not clear, 3              |

| Primary Assessment Method |
|---------------------------|
| Control Arm: Total Patient Population |
| Number of patients enrolled |
| Number of patients evaluable for toxicity |
| Number of patients evaluated for efficacy |
| Response assessment CR |
| Response assessment PR |

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**Response assessment SD**  
$n = 8$ (30.8)

**Response assessment PD**  
$n = 12$ (46.1)

(Median) duration assessments PFS  
59 days, confidence interval (CI): 33–227

(Median) duration assessments OS  
308 days, CI: 262–516

(Median) duration assessments response duration  
227 days

### Adverse Events

**Adverse Events Legend**
All patients were evaluable for toxicity. Treatment-related AEs with incidence >5% were listed.

*No Change From Baseline/No Adverse Event

#### Serious Adverse Events

**Serious Adverse Events Legend**
Three patients experienced treatment interruption and dose reduction due to SAEs: One in the 500-mg group for grade 3 rash recovered after a 5-day discontinuation of icotinib and dose reduction to 250 mg; one in the 625-mg group for grade 3 rash relieved after dose reduction to 250 mg; one in the 625-mg group for grade 3 hand and foot syndrome relieved after dose reduction to 250 mg.

### Pharmacokinetics/Pharmacodynamics

| Dose level | Dose of drug: icotinib | Number enrolled | Number evaluable for toxicity | Number with a dose-limiting toxicity | Dose-limiting toxicity information |
|------------|-------------------------|-----------------|-------------------------------|-------------------------------------|----------------------------------|
| 1          | 250 mg                  | 5               | 5                             | 0                                   |                                  |
| 2          | 300 mg                  | 3               | 3                             | 0                                   |                                  |
| 3          | 350 mg                  | 3               | 3                             | 0                                   |                                  |
| 4          | 400 mg                  | 3               | 3                             | 0                                   |                                  |
| 5          | 500 mg                  | 6               | 6                             | 1                                   | Grade 3 rash                     |
| 6          | 625 mg                  | 6               | 6                             | 2                                   | Grade 3 rash/grade 3 hand and foot syndrome |

### Assessment, Analysis, and Discussion

**Completion**  
Study completed

**Investigator’s Assessment**  
Active and should be pursued further
This phase I study demonstrated that oral icotinib was well tolerated at the dose range of 250–500 mg in pretreated, advanced NSCLC patients. The MTD was established at 500 mg. Incidence of AEs was higher than seen in prior studies evaluating normal dose (125 mg three times daily) without a new safety signal [1, 2]. In addition, favorable antitumor activities and PK profile was also documented.

Phase I studies of icotinib began in 2007 and consisted of dose-escalation and assessment of different dosing schedules in both healthy persons and patients with solid tumors [3–5]. Icotinib was well tolerated in healthy persons with a single dose ranging from 75 to 1,025 mg, even at the highest dose [5]. In NSCLC patients, mild and manageable AEs were seen when icotinib was orally administered at a dose of 75–150 mg three times daily [3]. The most frequently occurring AEs were rash (16 of 36 [44.4%]) and diarrhea (8 of 36 [22.2%]); the only 2 grade 3 AEs (grade 3 hepatic aminotransferase elevation and grade 3 mouth ulceration) were recorded in the 500- and 625-mg group, with no other grade 3 or higher AEs. MTD was not reached, and the recommended dose was established at 125 mg [3].

Another phase I study assessed the safety and activity of icotinib in 40 NSCLC patients with different dosing schedules (150 and 200 mg twice daily and 125 mg three times daily) [4]. The safety profile was similar to that in other studies, with an overall incidence of 65%. However, an interstitial lung disease (ILD) was recorded in the 200-mg twice-daily group [4].

Icotinib was rapidly absorbed and eliminated in healthy persons with a Tmax of 2 hours and a t1/2 of 6 hours [5]. Increased drug absorption and exposure of icotinib were observed when the drug was administered with high-fat and high-calorie food [5]. Similar PK patterns of icotinib were documented in cancer patients. A 3-hour Tmax and a 6-hour t1/2 were seen after oral icotinib at 75–150 mg three times daily [3]. Steady state was reached within 15 days. Similar values for Tmax and t1/2 were demonstrated in a study performed in NSCLC patients with icotinib at 150 and 200 mg twice daily [6]. Both studies revealed increased drug exposure with rising dose. Additionally, Ni et al. reported a significant relationship between drug exposure and clinical benefits [7], whereas Zhao et al. found no dose, exposure, safety/efficacy association in another study [3].

The present study documented a relatively higher incidence of AEs in patients receiving higher-dose (250–625 mg) icotinib, with an MTD of 500 mg three times per day. Most toxicities were mild to moderate, and only 2 grade 3 rash and 1 grade 3 hand and foot syndrome were recorded (Table 1). The most frequent AEs were grade 1 and 2 rashes (14 of 26 [53.8%]), diarrhea (6 of 26 [23.1%]), and mouth ulceration (3 of 26 [11.5%]). Three patients had SAEs (1 in the 500-mg group and 2 in the 625-mg group), and all SAEs were relieved after discontinuation or dose reduction. No changes in icotinib safety profile were observed during prolonged administration. PK analysis indicated that single-dose oral icotinib is rapidly absorbed and eliminated, which was consistent with the results obtained from previous studies assessing low-dose icotinib [3, 5, 6].
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(C/A) Consulting/advisory relationship; (RF) Research funding; (E) Employment; (ET) Expert testimony; (H) Honoraria received; (OI) Ownership interests; (IP) Intellectual property rights/inventor/patent holder; (SAB) Scientific advisory board

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