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ABBREVIATED CLINICAL STUDY REPORT

IPI-504-07

A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of IPI-504 in Combination with Trastuzumab in Patients with Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

Protocol Identification:	IPI-504-07
Investigational Product(s):	IPI-504
Indication:	Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer
Development Phase:	2
Study Design:	Multi-center, open-label, Simon's 2-stage Phase 2 trial
Study Initiation Date:	02 Mar 2009 (First Patient Consent)
Study Completion Date:	05 Oct 2010 (Last Patient Visit)
Sponsor:	Infinity Pharmaceuticals, Inc. 780 Memorial Drive Cambridge, MA 02139 USA
Responsible Medical Officer:	Pedro Santabárbara, MD, PhD Chief Medical Officer 617-453-1360
Date of Report:	September 28, 2011

This study was performed in accordance with Good Clinical Practices (GCP), including the archiving of essential documents.

Approvals

Abbreviated Clinical Study Report: IPI-504-07

A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of IPI-504 in Combination with Trastuzumab in Patients with Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

29 Sept 2011

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2 SYNOPSIS

Name of Sponsor/Company:	**Name of Drug Product**:	**Name of Drug Substance**:
Infinity Pharmaceuticals, Inc.	IPI-504 (retaspimycin hydrochloride)	IPI-504 Drug Substance

Title of Study: A Phase 2 Multicenter Study Evaluating the Efficacy and Safety of IPI-504 in Combination with Trastuzumab in Patients with Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer

Investigator(s)/Study Center(s):

- Site 001: Charles Vogel and Reshma Mahtani, Lynn Cancer Center, Boca Raton Comprehensive Cancer Center, Florida
- Site 002: Shanu Modi, Memorial Sloan Kettering Cancer Center, New York
- Site 003: Ellen Chuang, Weill Medical College of Cornell University, New York
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- Site 012: Lee Schwartzberg, West Cancer Clinic, Tennessee
- Site 013: Josep Baselga and Cristina Saura, Vall d'Hebron University Hospital, Barcelona, Spain
- Site 015: Joyce O'Shaughnessy, Texas Oncology, P.A.-Dallas, Texas
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- Site 028: Charles Henderson, Peachtree Hematology-Oncology Consultants, P.C., Georgia
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Publication (reference): Modi S, Saura C, Henderson C, Lin N, Mahtani R, Goddard J, Rodenas E, O'Shaugnessy J, Baselga J. Efficacy and Safety of IPI-504 (retaspimycin hydrochloride) in Combination with Trastuzumab in Patients with Pretreated, Locally Advanced or Metastatic Human Epidermal Growth Factor Receptor 2 (HER2) Positive Breast Cancer. Poster session presented at: General Poster Session, Breast Cancer - HER2/ER. 2011 American Society of Clinical Oncology (ASCO) Annual Meeting; 2011 Jun 3-7; Chicago, IL.

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Study Period (years): 1.6 years	**Phase of Development:** 2

Objectives: The primary objective of the study was to evaluate overall response rate, safety, and tolerability of IPI-504 plus trastuzumab in patients with pretreated, locally advanced, or metastatic HER2-positive breast cancer. The secondary objectives of the study were: 1) to evaluate the progression-free survival (PFS), time to progression (TTP) and overall survival (OS), of IPI-504 plus trastuzumab in this patient population; and 2) to evaluate the pharmacokinetics of IPI-504, its metabolites, and trastuzumab in this patient population. The exploratory objectives of the study were: 1) to evaluate the association between Hsp90 expression and other molecular characteristics of the tumor with the anti-tumor activity of this regimen; 2) to explore the potential effects of genetic variation in drug response; and 3) to evaluate the effect of IPI-504 administration on HER2 extracellular domain (ECD).

Methodology: Study IPI-504-07 was a multi-center, open-label, Phase 2 trial designed to evaluate the safety, clinical activity, pharmacokinetics, and pharmacodynamics of 2 different dose administration schedules of IPI-504 in combination with trastuzumab in patients with pretreated, locally advanced or metastatic HER2-positive breast cancer. The study employed a Simon's 2-stage design for enrollment based on observed dose limiting toxicity (DLT) and clinical response rates.

Number of Patients:
Planned: 20 to 92 patients
Enrolled and Treated: 29 patients

Diagnosis and Main Criteria for Inclusion: All patients were to be adults with pathologically confirmed HER2-expressing locally advanced or metastatic breast cancer (Grade 3+ staining intensity on a 0 to 3 scale via immunohistochemistry or HER2 amplification on a fluorescence in situ hybridization [FISH] assay) who had received at least 2 prior regimens containing a HER2-targeted agent, (one regimen containing trastuzumab), with no limits to prior therapies, and who had Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1, acceptable baseline organ and marrow function, no clinically active brain metastases or systemic conditions that would place the patient at undue risk or interfere with the study.

Test Product(s), Dose and Mode of Administration, Lot Number(s):
Test Product: IPI-504 (retaspimycin hydrochloride)
Dose and Mode of Administration: IPI-504 at a dose of 225 or 300 mg/m^2 twice weekly by intravenous (IV) infusion or IPI-504 at a dose of 300 mg/m^2 once weekly by IV infusion, co-administered with trastuzumab every 3 weeks (8 mg/kg first dose, then 6 mg/kg) by IV infusion. Patients on the twice weekly schedule received IPI-504 for 2 weeks followed by 1 week off treatment. Patients on the once weekly schedule did not have an off treatment period. Patients whose last dose of trastuzumab was <4 weeks prior to study entry received 6 mg/kg as the first dose of trastuzumab instead of 8 mg/kg.
IPI-504 Lot Number(s): 1597479, 1945005-06, 1975005-05, 1975005-06, 021I0208, and 106I0208

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Reference Therapy(s), Dose and Mode of Administration, Batch Number(s): None

Duration of Treatment: Treatment was permitted to continue until disease progression.

Criteria for Evaluation:

Efficacy, Pharmacokinetics, and Pharmacodynamics:

- Tumor response
- Survival time and time to progression
- Plasma concentrations of IPI-504, 17-AAG, 17-AG, and trastuzumab
- Pharmacodynamic markers

Safety:

Adverse events, serious adverse events, concomitant medication use, laboratory test results, electrocardiogram (ECG) results, Eastern Cooperative Oncology Group (ECOG) performance status results, vital sign results, and left ventricular ejection fraction (LVEF)

Statistical Methods: Limited efficacy was observed during the planned interim analysis; therefore, planned efficacy analyses were not performed for the abbreviated clinical study report. Analyses were limited to disposition, demographics, exposure (including pharmacokinetics), and safety evaluations (i.e., adverse events and laboratory findings).

Summary and Conclusions:

Subject Disposition:

A total of 29 patients were enrolled and treated. Initially, 3 (10%) patients were enrolled in the study and treated with twice weekly administration of IPI-504 300 mg/m^2 and trastuzumab administered every 3 weeks. Based on safety results observed in another IPI-504 study, the protocol was amended to reduce the dose for these 3 patients to 225 mg/m^2 twice weekly, and to treat newly enrolled patients with IPI-504 300 mg/m^2 administered once weekly. Subsequently, 26 (90%) patients were enrolled in the study and treated with once weekly administration of IPI-504 and trastuzumab administered every 3 weeks. The majority (24 [83%]) of patients discontinued from the study as a result of disease progression. Adverse events in 4 (14%) patients resulted in study discontinuation, and 1 (3%) patient with stable disease was discontinued from the study by the investigator after the study Sponsor determined that the study would not proceed to Stage 2 ("other" reason).

Demographics and Baseline Characteristics:

The majority of patients (overall) were female (97%), white (79%), and between the ages of 40 and 65 years (76%). One male patient (3%) was treated. The median age of all patients was 53 years (range: 33 to 72 years) and median weight was 73.9 kg (range: 37.5 to 99.3 kg).

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Pharmacokinetic Results:

Serial plasma samples for pharmacokinetic analysis for IPI-504 and its metabolites, 17-AAG and 17-AG, were analyzed from 27 patients who received IPI-504 once weekly (N=24) or twice weekly (N=3) with or without trastuzumab co-administration on Cycle 4 Dose 1 and Cycle 1 Dose 1, respectively. Serial serum samples were collected for determination of trastuzumab pharmacokinetics in Cycle 4 (N=11). Additional sparse samples were collected at various visits throughout the study.

The concentration versus time profiles for IPI-504 and 17-AAG displayed similar shapes, with peak plasma concentrations observed at the end of the infusion. The profile for the primary metabolite, 17-AG, displayed a less pronounced distributional phase and flatter elimination phase, with peak plasma concentrations observed 30 minutes after the end of the infusion.

On Cycle 1 Dose 1, the overall mean exposure ($AUC_{0-\infty}$) to IPI-504, 17-AAG, and 17-AG was 10003, 15334, and 22975 h*ng/mL, respectively. On Cycle 4 Dose 1, the overall mean exposure ($AUC_{0-\infty}$) to IPI-504, 17-AAG, and 17-AG was 6714, 14337, and 17261 h*ng/mL, respectively. Overall, the pharmacokinetic parameters after repeated doses of IPI-504 in the presence of trastuzumab on Cycle 4 Dose 1 were similar to those after the first dose of IPI-504 without trastuzumab on Cycle 1 Dose 1.

Trastuzumab 6 mg/kg administered once every three weeks exhibited a fairly flat profile over the first day after dose administration. In Cycle 4, the mean trastuzumab exposure over the 25.5 hours following dose administration ($AUC_{0-25.5}$) was 3094 h*µg/mL. The mean terminal elimination half-life was 154 hours based on the sample collection scheme used in this study.

Safety Results:

Differences in safety parameters between the twice weekly (N=3) and once weekly (N=26) schedules were not clinically meaningful. Given the small numbers of patients treated with the twice weekly schedule (N=3), the overall (N=29) results are presented.

Overall (N=29), the median number of cycles started was 3 (range: 2 to 12) with a median number of doses of IPI-504 received of 8 (range: 3 to 35). All patients received trastuzumab every 3 weeks: 6 or 8 mg/kg as the first dose and subsequent doses of 6 mg/kg. Overall (N=29), the median number of doses of trastuzumab received was 3 (range: 2 to 11).

All patients (N=29, 100%) had a TEAE during the study. TEAEs that occurred at a frequency ≥20% (6 patients) by Preferred Term were: nausea (14 [48%] patients), diarrhoea (11 [38%] patients), vomiting (10 [35%] patients), constipation (7 [24%] patients), fatigue (16 [55%] patients), urine colour abnormal (7 [24%] patients), blood alkaline phosphatase increased (6 [21%] patients), dyspnoea (7 [24%] patients), anorexia (7 [24%] patients), headache (9 [31%] patients), and anxiety (6 [21%] patients).

The majority of patients (25 [86%]) experienced at least 1 TEAE related to IPI-504. Two

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patients also had TEAEs that were related to trastuzumab, but not IPI-504. Overall, the majority of related TEAEs were Grade 1 or 2. Related TEAEs with CTCAE Grade 3 severity occurred in 8 (28%) patients. Grade 3 related events of (by Preferred Term) aspartate aminotransferase increased occurred in 2 patients, while all other Grade 3 related TEAEs occurred in a single patient each and included: alanine aminotransferase increased, blood alkaline phosphatase increased, diarrhoea, gamma-glutamyltransferase increased, hypertension, hypokalaemia, lipase increased, nausea, and vomiting. One related Grade 4 TEAE of gamma-glutamyltransferase increased occurred in 1 (3%) patient; this patient also had Grade 3 events. of gamma-glutamyltransferase increased, alanine aminotransferase increased, and aspartate aminotransferase increased approximately 3 weeks prior to the Grade 4 TEAE.

Two patients, 007-001 and 013-002, who received study drug on the once weekly dose schedule died as a result of TEAEs involving respiratory failure and aspiration, respectively. Both patient deaths were unrelated to IPI-504 and trastuzumab and were assessed as related to progressive disease by the Investigators.

Overall (N=29), 13 (45%) patients experienced a serious TEAE. No serious TEAEs occurred in patients receiving IPI-504 on the twice weekly schedule. The most frequently occurring serious TEAEs were vomiting and pneumonia, each occurring in 2 (7%) patients, overall. All other serious TEAEs occurred with a frequency of 1 patient, each. Serious TEAEs of Grade 1 diarrhoea and Grade 3 hypokalemia that were related to IPI-504 and trastuzumab occurred in 1 patient (004-001). A serious TEAE of ventricular extrasystoles that was related to trastuzumab, but not related to IPI-504, occurred in 1 patient (028-003). All other serious TEAEs were not related to either IPI-504 or trastuzumab.

TEAEs related to treatment with IPI-504 or trastuzumab led to study drug withdrawal and study discontinuation of 4 patients:

- Patient 001-002: Grade 2 blood alkaline phosphatase increased (related to IPI-504)
- Patient 004-001: Grade 3 lipase increased (related to IPI-504 and trastuzumab)
- Patient 013-008: Grade 3 ALT increased, AST increased, and GGT increased (all related to IPI-504)
- Patient 015-002: Grade 2 ejection fraction decreased (related to IPI-504 and trastuzumab)

Transient fluctuations in mean and median levels for all clinical laboratory parameters were observed between all study timepoints. No clinically meaningful trends in mean or median values for any clinical laboratory results were observed. Shifts from normal or a lower CTCAE Grade to CTCAE Grade 3 or higher were infrequent across all clinical laboratory parameters. A non-serious, related TEAE and a serious, unrelated TEAE of anaemia occurred in 1 patient. TEAEs and related TEAEs associated with abnormal clinical chemistry laboratory values that occurred in at least 3 (10%) patients (overall) were blood alkaline phosphatase increased (6 [21%] patients; 5 [17%] patients), aspartate

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aminotransferase increased (4 [14%] patients; 4 [14%] patients), alanine aminotransferase increased (3 [10%] patients; 3 [10%] patients), and hypokalaemia (3 [10%] patients; 1 [3%] patient).

Transient fluctuations in mean and median values for all vital sign and ECG parameters were observed between all study timepoints. Mean and median baseline, minimum, and maximum values for all parameters were within normal limits. Changes from baseline mean and median values to mean and median maximum and minimum post-baseline values in all parameters were not clinically significant. TEAEs that were related to IPI-504 and that involved vital sign parameters were non-serious pyrexia in 3 patients, body temperature increased in 1 patient, and non-serious hypertension in 1 patient. Treatment-emergent changes in ECG values occurred in 8 (28%) patients with normal PR durations at baseline and PR durations >200 msec post-baseline, and in 7 (24%) patients with normal QTcF durations at baseline and whose post-baseline QTcF durations were >450 msec or had increased >30 msec from baseline. A serious, CTCAE Grade 3 event of ventricular extrasystoles occurred in 1 patient with a history of mitral valve incompetence, hypertension, deep vein thrombosis, and hypercholesterolemia, and was related to trastuzumab but not related to IPI-504.

Conclusions:

Overall, the combination of weekly IPI-504 in combination with trastuzumab was well-tolerated in patients with breast cancer, with no unexpected or overlapping toxicities. Limited efficacy responses were observed at the studied dose levels, prompting study termination.

Date of Report: September 28, 2011