SYNOPSIS

NAME OF SPONSOR/COMPANY: Johnson & Johnson Pharmaceutical Research & Development, L.L.C. NAME OF FINISHED PRODUCT: ZARNESTRA™ (tipifarnib) NAME OF ACTIVE INGREDIENT(S): tipifarnib (R115777)	INDIVIDUAL STUDY TABLE REFERRING TO PART OF THE DOSSIER Volume: Page:	(FOR NATIONAL AUTHORITY USE ONLY)

Protocol No.: R115777-INT-11

Title of Study: A Phase III, Double-blind, Placebo-controlled Trial of Gemcitabine Plus Placebo Versus Gemcitabine Plus R115777 in Patients With Advanced Pancreatic Cancer

Principal Investigator: D. Von Hoff, MD
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Publication (Reference): None

Studied Period (years): DATE STUDY INITIATED: 4 November 1999 DATE STUDY COMPLETED: 15 September 2001	**Phase of development:** 3

Objectives: Primary: Determine whether the addition of R115777 to standard gemcitabine therapy improved overall survival time in comparison with gemcitabine plus placebo. Secondary: Estimate 6-month and 1-year survival rates; compare objective response rate, progression-free survival, duration of objective response and quality of life between the 2 treatment groups; assess safety based on laboratory and clinical parameters; and determine the incidence of ras mutations in subjects.

Methodology: This was a Phase 3, multicenter, randomized, double-blind, placebo-controlled study in subjects with advanced pancreatic cancer. Subjects (688) enrolled in 126 sites were randomized to receive R115777 (200 mg b.i.d.) + gemcitabine (1000 mg/m^2) or placebo + gemcitabine (i.v., 1000 mg/m^2). R115777 and placebo were administered in a double-blind fashion and gemcitabine was administered in an open-label, unblinded fashion.

Dose modification criteria were different for gemcitabine and R115777/placebo. Gemcitabine causes hematologic and nonhematologic toxicity. Gemcitabine doses were not increased above 1000 mg/m^2 at any time during the trial. Dose adjustments for hematologic toxicity were based on the blood counts obtained in preparation for that day of treatment and were relative to the dose of gemcitabine received in the previous week. All nonhematologic toxicity had to improve to grades 1 or 2 or return to baseline prior to retreatment. Dose adjustments for the next cycle of therapy were based on the worst toxicity observed during the previous cycle of therapy and were relative to the start dose of gemcitabine received in the previous cycle. Gemcitabine treatment was delayed at least a week for subjects who had not recovered from toxicities associated with the previous cycle. Failure to recover after 3 weeks caused the subject to be discontinued from the study. R115777 or placebo dose modifications were made based on drug- and disease-related adverse events. This blinded study medication was temporarily held for hematologic and nonhematologic adverse events if the investigator considered them to be related. When treatment with blinded study medication was reinstituted, after being temporarily held for toxicity, a dose reduction was performed. Two dose reductions were permitted. At the first dose reduction, the dose was again reduced by 100 mg per day: the morning dose was 100 mg; the evening dose remained 200 mg. At the second dose reduction, the dose was again reduced by 100 mg per day: a daily dose of 100 mg b.i.d. was given. Subjects developing unacceptable drug-related toxicity had their treatment discontinued.

Duration of treatment and study: Gemcitabine (1000 mg/m2) was administered intravenously weekly for 7 consecutive weeks followed by 1 week of rest. Subsequent gemcitabine was given weekly for 3 consecutive weeks followed by 1 week of rest. R115777 or placebo was given orally (2 dosage units, b.i.d.) continuously until disease progression or the development of unacceptable toxicity. All subjects were followed until death.

SYNOPSIS (CONTINUED)

Criteria for Evaluation:

Main Inclusion Criteria

1. Pathological confirmation of locally advanced, unresectable or metastatic adenocarcinoma of the pancreas.
2. At least 18 years old.
3. An ECOG Performance Status 0 to 1.
4. Written informed consent.

Main Exclusion Criteria

1. Significantly abnormal hematologic status: absolute neutrophil count (ANC) <1500/mm3; platelet count <100,000/mm3
2. Newly diagnosed disease that had the potential for curative surgical resection.
3. Prior therapy with any chemotherapy or any systemic therapy for pancreatic cancer, even as a sensitizer with the exception of 5-FU used as a radiation sensitizer.
4. Serum bilirubin >2.0 mg/dL; transaminase greater than 5 times normal; creatinine >1.5 mg/dL.
5. The use of any investigational drugs concomitantly or in the last thirty days.
6. Uncontrolled or severe cardiovascular disease.

Statistical Methods: Median, mean, 95% CI percentiles for demographics and other baseline characteristics. Adverse events were examined with respect to incidence, severity and relationship to study medication.

Survival Time: Overall survival time was calculated from the date of randomization to the date of death, or to the last follow-up date for the subjects who were still alive at the clinical cutoff date. Treatment comparison of survival time was performed using a two-sided log-rank test with two stratification factors: performance status (ECOG 0 vs. 1 vs. 2) and presence or absence of metastatic disease. The survival probabilities over time were based on Kaplan-Meier estimates. The hazard ratio of placebo/gemcitabine over R115777/gemcitabine and its 95% confidence interval were estimated by using the stratified Cox regression model.

Pharmacokinetics: Analysis of variance (ANOVA) for calculation of 90% confidence intervals. General linear model including factors of subjects, dose, and treatment for comparison of combination versus monotherapy. Mean treatment ratio and associated 90% confidence intervals for log-transformed Cmax and AUC using mean square error from ANOVA.

SYNOPSIS (CONTINUED)

ASSESSMENTS

Screening: registration and informed consent, medical history, urine β-HCG, PE/vitals, performance status, CBC, clinical chemistry, urinalysis, ECG, disease assessment, tumor biopsy, ophthalmic examination, quality of life (QOL; +Day 1 of every cycle), DNA sampling
Cycle 1: Days 1, 8, and 15; PK samples
Subsequent cycles: Days 1, 8, 15, and 22: review diary, adverse events (all cycles), CBC
Treatment Termination: PE/vitals, performance status, CBC, clinical chemistry, urinalysis, ECG, disease assessment, tumor biopsy, ophthalmic examination, QOL
Post treatment follow-up: adverse events, disease assessment, QOL
Body weight is measured at every physical exam and before every infusion of gemcitabine.

SUMMARY - CONCLUSIONS

SUBJECT SAMPLE

A total of 688 subjects (394 [57.3%] men and 294 [42.7%] women) with a median age of 62 years and a median weight of 66 kg were enrolled and randomized in the study. The sex and age distribution were typical for this indication.

EFFICACY RESULTS:

Primary analyses: Overall survival was calculated from the date of randomization to the date of death. At the clinical cutoff date, 500 subjects had died and the incidence was similar between groups (72% in the placebo + gemcitabine group and 73% in the R115777 + gemcitabine group. The median overall survival time was 182 days in the placebo + gemcitabine group and 193 days in the R115777 + gemcitabine group. There was no statistically significant difference in overall survival between the two groups. The most frequently reported cause of death, disease progression was reported in 61% of the placebo + gemcitabine group and in 64% of the R115777 + gemcitabine group.

Secondary analyses: The prognostic factor analysis stratified for performance status and presence of metastatic disease, showed a statistically significant difference ($p=0.010$) for weight loss ($p<0.001$ for time to weight loss), with the subjects who had not experienced weight loss having the better survival. There was a marginally statistically significant difference ($p=0.091$) between the overall survival between subjects who had the Whipple procedure and those who had not. Subjects who had undergone the procedure had the better survival.

The Cox Regression Model adjusted for the prognostic factors showed a significant difference for weight loss ($p=0.006$), therefore, weight loss can be considered as a prognostic factor. For all other parameters (age, sex, Whipple procedure and jaundice ≤6 months prior to randomization), the prognostic factor analysis showed no significant differences, and when the overall treatment comparison was corrected for all factors (age, sex, Whipple procedure, jaundice and weight loss), the intergroup difference was not statistically significant ($p=0.785$).

SAFETY RESULTS:

Adverse events (AEs) were reported by almost all of the subjects in both treatment groups with similar frequencies. The most frequently reported AEs were gastrointestinal, constitutional (fatigue and fever), and hematological (reported more frequently in the R115777 + gemcitabine group). The hematological AEs reported most frequently were anemia, thrombocytopenia and granulocytopenia (reported more frequently in the R115777 + gemcitabine group). The nonhematologic AEs (nausea, vomiting, diarrhea, abdominal pain, anorexia, fever and constipation, mild to moderate in severity) where similar in both groups. Peripheral neurotoxicity was noted in 55 subjects in the R115777 + gemcitabine group and 30 subjects in the placebo + gemcitabine group. For thrombosis-related AEs, a high incidence was observed for deep venous thrombosis and pulmonary embolism in the two treatment groups, reflecting hypercoagulability in pancreatic cancer. One hundred sixty-four of the treated subjects (24%) died during treatment or within 30 days after the last administration of study medication. AEs leading to withdrawal were reported by 96 (28%) subjects in the placebo + gemcitabine group and in 120 (36%) subjects in the R115777 + gemcitabine group. In the withdrawal group, AEs were considered the primary reason for treatment discontinuation.

SYNOPSIS (CONTINUED)

PHARMACOKINETIC RESULTS:

The individual concentrations of R115777 varied from below the limit of quantification (2 ng/mL) to 2662 ng/mL. In agreement with other studies, R115777 is rapidly absorbed following oral administration and the highest concentrations were generally observed between 2 to 4 hours.

CONCLUSIONS:

- R115777 at a continuous dose of 200 mg b.i.d. with standard dosing of gemcitabine did not improve the overall survival of subjects with advanced pancreatic cancer as compared with gemcitabine only.
- The toxicity profile of the combination treatment was considered acceptable and similar in the two groups.
- The treatment group difference in evaluation over time in QOL was considered not clinically significant.
- The pharmacokinetic profile was in agreement with other studies.

Date of the report: August 29 2003

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