The clinical trial information provided in this public disclosure synopsis is supplied for informational purposes only.

Please note that the results reported in any single trial may not reflect the overall potential risks or benefits of a product which are based on an evaluation of an entire research program.

Before prescribing any Takeda products, healthcare professionals should consult prescribing information for the product approved in their country.

SYNOPSIS

<table>
<tr><td>Name of Sponsor/Company:
ARIAD Pharmaceuticals, Inc</td><td rowspan="3">Individual Study Table Referring to Part of the Dossier
Volume:
Page:</td><td rowspan="3">(For National Authority Use Only)</td></tr>
<tr><td>Name of Finished Product:
Ridaforolimus (synonyms: (AP23573, MK-8669, formerly deforolimus)</td></tr>
<tr><td>Name of Active Ingredient:
Ridaforolimus Drug Product</td></tr>
<tr><td colspan="3">Title of Study: A Phase II Study of AP23573, an mTOR Inhibitor, in Female Adult Patients with Recurrent or Persistent Endometrial Cancer</td></tr>
<tr><td colspan="3">Principal Investigators:
D. Scott McMeekin, MD (United States)
Nicoletta Colombo, MD (Italy)</td></tr>
<tr><td colspan="3">Study center(s):
A total of 9 centers participated in this study: 7 centers in the United States (US), 1 center in Italy, and 1 center in Switzerland.
University of Oklahoma Health Sciences Center, Oklahoma City, OK
Yale-New Haven Hospital, New Haven, CT
Hematology & Oncology Specialists, LLC, Metairie, LA
Florida Hospital Cancer Institute, Orlando, FL
University of North Carolina Hospitals at Chapel Hill, Chapel Hill, NC
Indiana University Simon Cancer Center, Indianapolis, IN
Jack D. Weiler Hospital of the Albert Einstein College of Medicine, Bronx, NY
Instituto Europeo di Oncologia, University of Milan, Bicocca (Italy)
Istituto Oncologico della Svizzera Italiana, Bellinzona (Switzerland)</td></tr>
<tr><td colspan="3">Publications (reference):
N Colombo, S McMeekin, P Schwartz, et al. A Phase 2 Trial of the mTOR inhibitor AP23573 as a Single Agent in Advanced Endometrial Cancer . Journal of Clinical Oncology, 2007; 25 (suppl 18S): 5516.</td></tr>
<tr><td colspan="2">Studied period (years):
Date first subject/first visit: 08 August 2005
Date last subject/last visit: 29 January 2008</td><td>Phase of development:
2</td></tr>
</table>

Methodology:

This was an open-label, non-randomized, multi-center, single-arm study designed to evaluate the effect of ridaforolimus in patients with recurrent or persistent endometrial cancer. Ridaforolimus was administered intravenously (IV) at a fixed dose of 12.5 mg over 30 minutes once daily for five days (QDx5) every two weeks. A cycle of treatment was defined as a four-week period (two courses) of ridaforolimus. Target and non-target lesions were assessed every two cycles (eight weeks), and the response assigned according to modified Response Evaluation Criteria in Solid Tumors (RECIST) guidelines. Safety was assessed by routine physical and laboratory evaluations. Up to approximately 44 patients were to be enrolled into the study depending on response to treatment. Patients were expected to receive a minimum of two and a maximum of six cycles of ridaforolimus. Patients might receive additional cycles of ridaforolimus if they continued to have at least stable disease and were tolerating therapy. Patients were to be followed for 24 months after their last dose of ridaforolimus. Palliative and supportive care were permitted during the course of the study.

The following concurrent medications were prohibited during this study: any other anticancer treatment, including chemotherapy, immunotherapy, biological response modifiers, radiation therapy, and systemic hormonal therapy; any other investigational drug or device; herbal preparations or related over-the-counter preparations containing herbal ingredients that are known to affect CYP3A isoenzymes (e.g., St. John's Wort).

Number of subjects (planned and analyzed): Approximately 44 patients were to be enrolled into the study at approximately 5 to 10 centers in the US and Europe. Forty-five patients were enrolled and treated at 9 centers (7 centers in the US, 1 in Italy, and 1 in Switzerland).

Diagnosis and main criteria for inclusion: Patients ≥18 years of age with recurrent or persistent endometrial cancer, histologically confirmed disease, and evidence of disease progression within the last three months, at least one measurable lesion, an Eastern Cooperative Oncology Group (ECOG) performance status ≤2, adequate renal, hepatic, and bone marrow function, and met all other criteria for study entry.

Test product, dose and mode of administration, batch number: Patients received 12.5 mg ridaforolimus (synonyms: AP23573, MK-8669, formerly deforolimus) as a 30 ± 5 minute intravenous infusion once daily for five consecutive days (QDx5) every two weeks. Each two-week dosing period constituted one course of treatment; and two courses of treatment constituted one cycle (four weeks) of therapy. The daily infusions of ridaforolimus were to occur at approximately the same time each day. In the absence of an unacceptable treatment-related adverse event or early progressive disease, each patient was expected to receive at least two cycles (eight weeks) of ridaforolimus treatment. Patients might continue to receive additional cycles of ridaforolimus until any of the discontinuation criteria were met.
IV infusion, batch number(s):
Drug Product: 221-05-003-A, 221-05-006-A, 221-03-006-A, 221-03-011, 221-05-004-A, 221-03-007-A, 221-03-007, 224-03-007, HF,141, 221-03-008, 221-03-008-A, 221-03-009, 221-03-010-A, 221-03-011-A

Diluent: 221-02-012-A, 221-02-013-A, 221-02-014, 221-02-011, 221-02-013, 221-02-011-A

Duration of treatment: The total duration of a patient's participation was expected to be approximately 30 months, including a two-week screening period, six cycles of study drug administration, and 24 months of follow-up. The actual duration of each patient's participation was expected to vary since patients might continue to receive study drug until documentation of disease progression or other discontinuation criteria were met. The total estimated duration for the conduct of the study was 36 months, including six months to accrue patients and 30 months to treat and follow-up patients.

Reference therapy, dose and mode of administration, batch number: None

Statistical methods:
All patients receiving at least one dose of ridaforolimus were to be included in the safety population. The adverse event incidence rates and the frequency of study drug related adverse events, categorized by severity grades were described. Listings of laboratory test results collected at baseline and during the study were generated. Descriptive statistics summarizing the changes in laboratory tests over time were presented.

Primary endpoint

The primary endpoint of the study was the clinical benefit response rate, which was analyzed on an intent-to-treat basis. For the purposes of this study, patients were classified as "clinical benefit responders" if they had a complete (CR), partial response (PR), or if they exhibited prolonged stable disease ≥16 weeks.

Secondary endpoints

Time to disease progression was assessed and estimated using the Kaplan-Meier procedure.

Additional endpoints included progression-free survival, overall survival, duration of response, pharmacokinetic characteristics, and quality of life (QOL) assessments.

The study employed Simon's optimal two-stage design [significance level 0.05, power = 0.90]. The study was designed to distinguish a favorable true response rate of ≥35% from a null rate of ≤15%. Initially, 19 patients were to be enrolled. If three or fewer occurrences of clinical benefit responses were observed among the 19 patients, further enrollment was to be discontinued. If four or more clinical benefit responses were observed, 25 additional patients were to be enrolled. If 11 or more clinical benefit responses were observed among 44 patients, the regimen was to be considered effective.

This design had 68% probability of stopping the enrollment early if the study drug was ineffective, 9.5% probability of rejecting the treatment if it was effective (true rate of ≥35%) and 4.8% probability of accepting the treatment if it was ineffective (true rate of ≤15%).

Summary – Conclusions

EFFICACY Summary :

Thirteen (28.9%) patients achieved clinical benefit response (CBR): 5 (11.1%) achieved a confirmed partial response (PR) and 8 (17.8%) achieved stable disease (SD) with a duration of 16 weeks or longer.

SAFETY Results:

The safety conclusions for the trial are as follows:

- All patients reported at least one treatment-emergent AE. The most common treatment-emergent events reported for 20% or more of patients were diarrhea, fatigue, nausea, anemia, constipation, vomiting, anorexia, mucosal inflammation, pyrexia, asthenia, stomatitis, peripheral edema, hyperglycemia, hypokalemia, urinary tract infection, and insomnia.
- Treatment-related, treatment-emergent adverse events were experienced by 42 (93.3%) patients.
- The most common treatment-related AEs reported for more than 10% of patients were anemia, fatigue, diarrhea, mucosal inflammation, nausea, stomatitis, vomiting, asthenia, anorexia, dysgeusia, constipation, hypertriglyceridemia, hyperglycemia, hypokalemia, and erythema.
- Twenty-four patients reported at least one Grade 3 treatment-related treatment-emergent AE and one patient reported one Grade 4 event. Grade 3 adverse events reported for 2 or more patients were anemia (10 patients [22.2%]), hyperglycemia (4 patients [8.9%]), stomatitis (3 patients

[6.7%]), asthenia, fatigue, and nausea, (2 patients [4.4%] each). One patient experienced Grade 4 hypertriglyceridemia.

- No patient died during ridaforolimus treatment. Twenty four (53%) patients were reported to have died after ridaforolimus discontinuation and during the trial follow-up period. Four (16.7%) of the 24 patients died within 30 days of receiving the last dose of ridaforolimus. Out of these, two patients were reported to have died due to progressive disease; one patient died of bowel obstruction that was assessed by the Investigator as not related to study drug; finally, one patient, died of respiratory failure, also not considered as related to the study drug.
- Seven (15.6%) patients experienced treatment-related serious adverse events during the trial. Three patients experienced a treatment-related SAE of anemia (two Grade 3 and one Grade 2) that were assessed by the Investigator as probably or possibly related to ridaforolimus. One patient each experienced deep vein thrombosis (Grade 3), vomiting (Grade 2), dehydration (Grade 3), and stomatitis (Grade 2). All of these events resolved with one exception: one case of anemia led to clinical sequelae.
- There was one patient (033-001) who experienced a treatment-related (assessed probably related), Grade 3 TEAE that led to study discontinuation (worsening of interstitial lung disease). Three (6.7%) patients discontinued study drug due treatment-emergent AEs unrelated to study drug treatment: infection and endometrial cancer (both Grade 2) in one patient, and sepsis and mood altered (both Grade 3) in one patient each.
- Fifteen (33.3%) patients experienced at least one treatment-related AE that led to dose modification. Seven (15.6%) patients reported at least one Grade 3 event stomatitis (3 events), and mucosal inflammation, anemia, thrombocytopenia, neutropenia, and interstitial lung disease (one event each).
- Four (8.9%) patients reported Grade 3 treatment–related oral lesions. There were no reports of Grade 4 treatment-related oral lesions.
- Six patients (13.3%) experienced metabolic abnormalities that were Grade 3 or 4 and were considered treatment related by the Investigators. Four patients (8.9%) experienced Grade 3 treatment-related hyperglycemia. No Grade 4 treatment-related hyperglycemia events were reported. There was one case (2.2%) each of treatment-related Grade 3 and Grade 4 hypertriglyceridemia.
- Two patients experienced electrocardiographic abnormalities. One patient had QT prolongation that was assessed by the Investigator as possibly related to ridaforolimus. This event resolved without medical intervention. A second patient was reported to have an arrhythmia (ectopic beat) that was assessed by the Investigator as unrelated to ridaforolimus.

CONCLUSION:

Patients with endometrial cancers in the second-line setting or beyond have few effective treatment options. Ridaforolimus demonstrated evidence of antitumor activity in pre-treated patients with endometrial cancer. The patient population was heavily pre-treated with 29 (64%) of the patients treated with 2 or more prior regimens. Thirteen (28.9%) of 45 enrolled and treated patients achieved clinical benefit response and 5, a partial response (11.1%). Compared to the results achieved in multiple trials in second and later lines endometrial cancer, these results are promising.

Ridaforolimus was generally well tolerated with few patients experiencing dose delay, dose reduction or drug discontinuation due to adverse events. The mean (SD) ratio of actual to expected cumulative dose was 0.9 (0.2); the median (range) ratio was 1 (0.2 to 1).

Three patients discontinued study drug due treatment-emergent events unrelated to study drug

treatment: infection and endometrial cancer (both Grade 2) in one patient, and sepsis and mood altered (both Grade 3) in one patient each. There was only one patient who discontinued the study due to a treatment-related event, a Grade 3 worsening of interstitial lung disease. The adverse event profile is consistent with that observed in other clinical trials with ridaforolimus and with other mTOR inhibitors used in cancer treatment.

The evidence of antitumor activity in patients with few treatment options along with acceptable tolerability indicates that the use of ridaforolimus in endometrial cancer warrants further study.

Date of the report:
17 March 2010