SYNOPSIS

Title of the study: A Phase 2 Study of XL147 (SAR245408) in Subjects with Advanced or Recurrent Endometrial Carcinoma
Coordinating Investigator: [redacted]
Study center(s): 25 study centers in the USA, Belgium, and France
Publications (reference): None
Study period: Date first subject enrolled: 29/Jan/2010 Date last subject completed: 06/Mar/2013
Phase of development: Phase 2
Objectives: The primary objectives were: • To evaluate the co-primary efficacy endpoints: 1) objective response rate (ORR: confirmed complete response [CR] or confirmed partial response [PR]) and 2) rate of 6 month progression-free survival (PFS6), the rate of progression free survival (PFS) for 183 days, in subjects receiving SAR245408 for advanced or recurrent endometrial carcinoma (EC). • To evaluate the safety and tolerability of SAR245408 in this population.
Methodology: Initially designed as a Phase 2, multi-center, single arm two-stage study to evaluate safety of SAR245408 and to evaluate the co-primary efficacy endpoints of ORR and PFS6 in subjects with advanced or recurrent EC. As of protocol amendment 3, the original 2-stage design was stopped and the primary study population was changed to limit to those patients with only 1 prior line of treatment for advanced/recurrent disease.
Number of subjects~~:~~ Planned: Up to 80 Randomized: 67 Treated: 67 Evaluated: 67 Efficacy: 67 Safety : 67 Pharmacokinetics: 67
Diagnosis and criteria for inclusion: Subjects with: a histologically confirmed diagnosis of EC (endometrioid, serous, clear cell adenocarcinoma, adenosquamous carcinoma, or mixed histology, any grade) that is advanced (ie, persistent, locally advanced) or recurrent, and is incurable by standard therapies and has received one platinum based chemotherapy regimen for EC; at least one lesion that is measurable on computed tomography (CT) or magnetic resonance imaging (MRI) scan.
Study treatments **Investigational medicinal product: SAR245408** Formulation: 100 mg capsules (prior to protocol amendment 3); 100, 150, 200 mg tablets (after protocol amendment 3) Route of administration: Oral Dose regimen: 600 mg daily (prior to protocol amendment 3); 400 mg daily (after protocol amendment 3) Lot numbers: [redacted]

Duration of treatment: In the absence of radiographic progressive disease (PD) per RECIST (Response Criteria in Solid Tumors) Version 1.1 and unacceptable toxicity, subjects may have continued to receive study treatment for up to 1 year at the discretion of the investigator and beyond 1 year with the agreement of the investigator and sponsor.

Duration of observation: Subjects were to return to the study site 30-37 days after the last dose of SAR245408 for a Post-Treatment Visit. Follow-up evaluations of safety, subsequent anti-cancer treatment, and adverse events (AEs) including any serious adverse events (SAEs), taking into account any new treatments that may confound the ability to assess the event, were to be obtained by the investigator (or designee). Subjects who discontinued study treatment before documentation of radiographic PD were to continue to undergo periodic tumor assessments until the earlier of radiographic PD, death, or the initiation of subsequent anti-cancer therapy.

Criteria for evaluation:

Safety:

Safety was assessed by evaluation of AEs, vital signs, electrocardiogram, laboratory tests, and concomitant medications. Adverse event seriousness, severity grade, and relationship to study treatment were to be assessed by the investigator. Severity grade was defined by the National Cancer Institute Common Terminology Criteria for Adverse Events v3.0 (CTCAE).

Efficacy:

Tumor assessments were to be performed within 28 days before the first dose of study drug and after Week 8, Week 16, and Week 26 following the first dose of study drug, and every 10 weeks thereafter until the earlier of documented radiographic PD, death, or the initiation of subsequent anti-cancer therapy. Response and progression was to be determined per RECIST Version 1.1. Responses were to be confirmed by repeat assessments to be performed 28-35 days after the response criteria were met.

Pharmacokinetics:

SAR245408 plasma concentrations.

Pharmacogenomics:

Blood samples were collected and genotyped. The analyses of pharmacogenomic testing along with the pharmacogenomic data used to explore the association between the main enzyme systems for SAR245408 metabolism and safety and other potential associations between genes variations and clinical outcomes will be presented in a separate report.

Pharmacokinetic sampling times and bioanalytical methods:

Sampling: Plasma samples were collected at pre-dose, and 4 hours post dose on Week 1 Day1, Week 5 Day 1, Week 9 Day 1 and Week 17 Day 1. Beginning on Week 27, a pre-dose sample was to be collected on Week 27 Day 1, and then every 10 weeks. In addition, samples were also to be collected, if possible, at the 30-day visit during the Post-Treatment Period and whenever a subject had study drug–related SAE(s) (eg, skin rash) and/or is withdrawn from the study.

Bioanalytical methods: Plasma concentrations of SAR245408 were determined using a validated liquid chromatography coupled with tandem mass spectrometry (LC-MS/MS) method with a lower limit of quantification (LLOQ) of 1.00 ng/mL.

Statistical methods: The co-primary efficacy endpoints are: 1) ORR, defined as the proportion of subjects for whom the best response is a confirmed CR or confirmed PR, and 2) PFS6, defined as the proportion of subjects who survive and are progression free at least 183 days after the date of the first dose of study drug.

Prior to protocol amendment 3, the study was designed to test the following hypotheses:

- H0: ORR is ≤5% and proportion with PFS6 is ≤15%
- HA: ORR is ≥20% or proportion with PFS6 is ≥30%

The sample size estimate of 71 subjects evaluable per protocol was based on a single-arm, two-stage design by Sill and Yothers (2008) with a nominal alpha of 0.07 and power of 90%.

Based on the stopping rule defined in the original protocol (2-stage design), the study met the futility criteria for the overall study population. As of protocol amendment 3 , the primary analysis population was changed to the subset of patients with only 1 prior line of treatment for advanced/recurrent EC, and Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 1, with the primary analysis of interest being the estimate of co-primary endpoints (ORR and PFS6) with corresponding 90% confidence intervals.

Summary: Overall, 67 patients with advanced or recurrent EC enrolled, with 30 patients enrolled prior to protocol amendment 3 and 37 patients enrolled after protocol amendment 3. Study patients were women aged 46 to 89, with a median age of 64.0 years. The most common histologies of EC were endometrioid (38.8% of all patients), serous carcinoma (35.8%), and mixed (14.9%). The mean duration of study treatment was 16.2 weeks (median of 8.0 weeks, range: 0.4-150.1). The mean duration of study treatment was 16.2 weeks (median of 8.0 weeks, range: 0.4-150.1). The primary reason for the majority of patients to discontinue treatment was disease progression (71.6% of all patients), assessed either objectively by RECIST v1.1 or by clinical assessment. Discontinuation of treatment due to an AE was reported for 14 patients (20.9%).

All patients reported at least 1 TEAE, with 82.1% of patients (55 of 67) reporting a TEAE that was considered related to study treatment. The most commonly reported TEAEs (>20% of patients), regardless of relationship to study drug, were diarrhea, rash, fatigue, nausea, vomiting decreased appetite, abdominal pain, and edema peripheral. The most commonly reported AEs assessed as related to study drug (related in >10% of patients were rash, diarrhea, fatigue, nausea, hyperglycemia, and decreased appetite.

Overall, 26 patients (38.8%) died, with 17 of the 26 deaths directly attributed to disease progression. None of the reported deaths was assessed as related to study drug. Of the 9 other deaths, 8 were attributed to the AEs of general health deterioration (2 patients), multi-organ failure (2 patients), cardio-pulmonary arrest (1 patient), cerebral infarct (1 patient), sepsis (1 patient), and gastrointestinal hemorrhage (1 patient). The remaining death was attributed to a fall with subdural hematoma approximately 8 weeks after the patient's last dose of study drug. Of the 26 deaths, 14 were reported more than 30 days after the patient's last dose of study drug, with the other 12 deaths being within 30 days of the last dose of study drug.

Treatment-emergent SAEs were experienced by 36 patients (53.7%). Of these, 10 patients (14.9%) experienced an SAE that was considered at least possibly related to study drug. The mostly commonly reported SAE preferred terms (PTs) regardless of relationship were general health deterioration (9.0% of patients), dehydration (7.5%), and abdominal pain (7.5%). The only PT which was reported as serious and related in more than 1 patient overall was diarrhea, assessed as a related SAE for 2 patients.

There were 14 patients (20.9%) who experienced AEs leading to discontinuation of study drug. The only PTs that were reported as leading to discontinuation in more than 1 patient overall were rash, reported in 4 patients (6.0%), and abdominal pain and diarrhea, each reported in 2 patients (3.0%).

Liver toxicities were reported in 14 patients (20.9%), with liver toxicities of Grade 3+ in 8 patients (11.9%). In assessment of other laboratory parameters, gamma-glutamyl transferase increased of Grade 3 was reported in 10.4% of patients and hyponatremia of Grade 3 was reported in 7.5% of patients. Most other reported hematological and chemistry abnormalities were of Grade 1 or 2. There were no safety issues identified in the data from vital signs or ECG assessments.

A total of 2 patients achieved CR and 2 patients achieved PR, all of whom had 1 prior line of therapy. PFS of at least 6 months was demonstrated in 8 patients (11.9%), 7 of these among those with only 1 prior line of therapy. The clinical benefit rate (CR+PR+stable disease [SD]>6mos) was 16.0% for the patients with 1 prior treatment regimen (8 of 50 patients), and 5.9% for the patients with 2 prior treatment regimens (1 of 17 patients). Estimated median PFS (from Kaplan-Meier method) was 2.1 months (90% CI: 1.9-3.6mo).

Date of report: 06-Feb-2014