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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>
<thead>
<tr>
<th>NAME OF COMPANY</th>
<th>ARIAD Pharmaceuticals, Inc. (a wholly-owned subsidiary of Takeda Pharmaceutical Ltd.co.)</th>
</tr>
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<tr>
<td>NAME OF FINISHED PRODUCT</td>
<td>Ponatinib (Iclusig&lt;sup&gt;®&lt;/sup&gt;) tablets</td>
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<tr>
<td>NAME OF ACTIVE INGREDIENT</td>
<td>Ponatinib (Iclusig&lt;sup&gt;®&lt;/sup&gt;)</td>
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**TITLE OF STUDY:** Phase 2 Trial of Ponatinib in Patients with Metastatic and/or Unresectable Gastrointestinal Stromal Tumor Following Failure of Prior Tyrosine Kinase Inhibitor Therapy

**INVESTIGATORS:**

There were a total of four investigators/sites for this study in the United States (US).

**STUDY CENTER(S):**

**PUBLICATIONS BASED ON THIS STUDY:**

The publications based on this study included:


These abstracts are included in Appendix 16.1.11.

**STUDIED PERIOD:**

- Study start date: 05 June 2013.
- First patient in: 19 June 2013.
- This study was completed.
- Enrollment completed: 1 October 2014.
- Data are presented from study initiation (05 June 2013) to 01 August 2016 (database cut-off date).

**PHASE OF DEVELOPMENT:**

- Phase 2
Analysis was performed on a data extraction date of 01 August 2016.

**OBJECTIVES:**
The primary objective was:
- To assess clinical benefit in patients with c-KIT (KIT) Exon 11-mutant GIST (Cohort A) defined as clinical benefit rate (CBR), which is the composite of complete response (CR), partial response (PR) and stable disease (SD) lasting $\geq 16$ weeks per modified response evaluation criteria in solid tumors (RECIST 1.1 [Demetri et al. Lancet 2012;S0140-6736:61857-1]) as a measure of disease control.

The secondary objectives were:
- To assess clinical benefit in patients with GIST that lacks an activating KIT Exon 11 mutation (Cohort B) and in the total patient population
- To assess progression-free survival (PFS) in each cohort and in the total patient population
- To assess objective response rate (ORR) in each cohort and in the total patient population
- To assess overall survival (OS) in each cohort and in the total patient population
- To evaluate the safety and tolerability of ponatinib in the total patient population
- To assess limited elements of pharmacokinetics in the total patient population.

Note that the pharmacokinetic results and exploratory results are not presented in this abbreviated Clinical Study Report.

**METHODOLOGY:**
The initial version of the study was an open-label, single-arm, multicenter, phase 2 study of ponatinib in patients with metastatic and/or unresectable GIST previously treated with at least 1 TKI.

During a clinical hold that began on 08 October 2013, the US Food and Drug Administration required that patients who had not already responded to ponatinib and had not been previously treated with the 3 TKIs approved for the treatment of GIST (imatinib, sunitinib, and regorafenib) be immediately discontinued from the study. The study protocol was then modified to include patients who had experienced failure of imatinib, sunitinib, and regorafenib therapy.

Patients were assessed for the primary endpoint of clinical benefit at 16 weeks as defined as the composite endpoint of CR+PR+SD (modified RECIST 1.1). The analysis of the primary endpoint was in patients whose tumors had an activating mutation in Exon 11 of KIT (Cohort A). Patients with tumors with other activating mutations such as those mutations in KIT Exon 9 or in PDGFR-α or patients with native KIT were included in Cohort B. Secondary efficacy endpoints included CBR at 16 weeks in Cohort B and in the total patient population, and PFS, OS, and ORR, evaluated both separately in Cohort A and in Cohort B, and in the total patient population. The safety and tolerability of ponatinib was assessed as a secondary endpoint.

At screening, patients who met the inclusion/exclusion criteria and agreed to participate in the study signed the informed consent form. Screening tests were performed within 21 days prior to the first dose of ponatinib, with the
Patients were enrolled into one of two cohorts, Cohort A or Cohort B, based on the presence or absence of KIT Exon 11 mutations (see above). Patients were enrolled into the study prior to determination of the appropriate cohort (as long as both cohorts were open for enrollment).

All patients were started at a 45 mg once-daily oral ponatinib dose. For patients with SD or better at the end of Cycle 6, as determined by modified RECIST 1.1, the dose of ponatinib had to be reduced to 30 mg daily, if the dose had not already been reduced for other reasons. Patients who had progressive disease (PD) were either withdrawn from the study or those who were felt to have ongoing benefit despite RECIST-defined PD who remained on the study with the approval of the sponsor could have their dose re-escalated (up to a maximum of 45 mg/day) upon loss of response. Doses could also be reduced to manage drug-related adverse events (AEs) and in some cases could be re-escalated once the events resolved. Doses could also be reduced to account for drug-drug interactions and could be re-escalated once interacting drugs were withdrawn. No daily dose higher than 45 mg was permitted.

Efficacy assessments comprised response using modified RECIST 1.1 and long-term survival follow-up. Safety assessments included AEs, routine physical examination and vital sign assessments, laboratory evaluations, electrocardiography, and echocardiography; concomitant medication data were also collected.

End-of-Treatment/Withdrawal Visit procedures were conducted within 2 weeks following the patient’s last dose of ponatinib or the patient/investigator decision to end treatment, whichever was later.

All AEs ongoing or starting within 30 days after the End-of-Treatment had to be recorded on the electronic case report form. After this time, ongoing AEs thought to be at least possibly study-drug related and all ongoing serious treatment-emergent AEs (TEAEs) were to be followed at least every 4 weeks until they resolved to baseline (or National Cancer Institute [NCI] Common Terminology Criteria for AEs [CTCAE] Grade ≤1), stabilized, or were considered to be chronic or irreversible.

Survival data were collected every 6 months (±1 month) starting after the last dose of study drug or the investigator/patient decision to discontinue treatment, whichever occurred later, and continued for up to 24 months (as long as patients continued to receive benefit) from the time the last patient was enrolled. These data were obtained either during a visit or through phone contact.

**NUMBER OF PATIENTS (PLANNED AND ANALYZED):**

Planned: It was planned to enroll approximately 45 patients (approximately 30 patients in Cohort A and 15 patients in Cohort B) at approximately 3 centers.

Analyzed: A total of 45 patients (30 patients in Cohort A and 15 patients in Cohort B) were enrolled at 4 centers.

**DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION:**

All patients must have met all the following inclusion criteria for study entry:

1. Male or female patients ≥18 years old.
2. GIST with failure of prior TKI therapy defined as:
   a. Histologically confirmed metastatic and/or unresectable GIST after experiencing failure of prior treatment with imatinib, sunitinib, and regorafenib. If prior TKI treatment was neoadjuvant therapy, then relapse had to have occurred during the neoadjuvant therapy in order to consider it failed therapy.
   b. Patients in Cohort A had to have evidence of activation mutations of Exon 11 of KIT in their tumors. Demonstration of an Exon 11 mutation could be based on prior assessment or on evaluation of a tumor sample after enrollment in this study. Patients in Cohort B had to have GIST that lacked activating mutations in KIT Exon 11, but could have evidence of another activating mutation such as in KIT Exon 9 or PDGF-α. Patients could be enrolled in the study prior to determination of appropriate cohort (as long as both cohorts were open for enrollment).
3. Measurable disease per modified RECIST 1.1. A lesion in a previously irradiated area was eligible to be considered as measurable disease as long as there was objective evidence of progression of the lesion prior to study enrollment.
4. Eastern Cooperative Oncology Group (ECOG) performance status of 0, 1, or 2.
5. Adequate hepatic function as defined by the following criteria:
   a. Total serum bilirubin ≤1.5 x upper limit of normal (ULN), unless due to Gilbert’s syndrome
b. Alanine aminotransferase (ALT) ≤2.5 ULN or ≤5.0 x ULN if liver metastases were present
   c. Aspartate aminotransferase (AST) ≤2.5 ULN or ≤5.0 x ULN if liver metastases were present.

6. Adequate renal function as defined by the following criterion:
   a. Serum creatinine <1.5 x ULN.

7. Adequate pancreatic function as defined by the following criterion.
   a. Serum lipase and amylase ≤1.5 x ULN.

8. For patients of childbearing potential, a negative pregnancy test had to be documented prior to enrollment.
9. Female and male patients who were fertile had to agree to use an effective form of contraception with their
   sexual partners from signing of the informed consent form for this study through 4 months after the end of
   the treatment.
11. Willingness and ability to comply with scheduled visits and study procedures.
12. Fully recovered (≤Grade 1 or returned to baseline or deemed irreversible) from the acute effects of prior
    cancer therapy before initiation of study drug.

Patients were not eligible for participation in the study if they met any of the following exclusion criteria:

1. Major surgery within 28 days prior to initiating therapy.
2. History of bleeding disorder.
3. History of acute pancreatitis within 1 year of study or history of chronic pancreatitis.
5. Uncontrolled hypertriglyceridemia (triglycerides >450 mg/dL).
6. Clinically significant, uncontrolled, or active cardiovascular disease, specifically including, but not
   restricted to:
   a. Any history of myocardial infarction
   b. Any history of unstable angina
   c. Congestive heart failure within 6 months prior to enrollment, or left ventricular ejection fraction
      less than lower limit of normal per local institutional standards within 6 months prior to
      enrollment
   d. History of clinically significant (as determined by the treating physician) atrial arrhythmia
   e. Any history of ventricular arrhythmia
   f. Any history of cerebrovascular accident or transient ischemic attack
   g. Any history of peripheral vascular infarction, including visceral infarction; or any
      revascularization procedure of any vasculature, including the placement of a stent
   h. Venous thromboembolism including deep venous thrombosis or pulmonary embolism within
      6 months prior to enrollment.
7. Uncontrolled hypertension (diastolic blood pressure >90 mm Hg; systolic >150 mm Hg). Patients with
   hypertension should have been under treatment on study entry to effect blood pressure control.
8. Taken medications with a known risk of Torsades de Pointes. These medications are listed in Appendix A
   of the protocol.
9. Taken any medications or herbal supplements that are known to be strong inhibitors of cytochrome P450
   3A4 within at least 14 days before the first dose of ponatinib. These medications are listed in Appendix B
   of the protocol.
10. Had ongoing or active infection. This included, but was not limited to, the requirement for intravenous
    antibiotics.
11. Known history of human immunodeficiency virus. Testing was not required in the absence of prior
    documentation or known history.
12. Pregnant or breastfeeding.
13. Malabsorption syndrome or other gastrointestinal illness that could affect oral absorption of study drugs.
14. Individuals with a history of a different malignancy, other than cervical cancer in situ, basal cell or
    squamous cell carcinoma of the skin, were ineligible, except if they had been disease-free for at least
    5 years, and were deemed by the investigator to be at low risk for recurrence of that malignancy OR if the
    other primary malignancy was neither currently clinically significant nor requiring active intervention.
15. Use of any approved TKIs or investigational agents within 2 weeks or 6 half-lives of the agent, whichever
    was longer, prior to receiving study drug.
16. Any condition or illness that, in the opinion of the investigator, compromised patient safety or interfered
with the evaluation of the drug.

**TEST PRODUCT, DOSE, AND MODE OF ADMINISTRATION; BATCH NUMBER:**
Ponatinib was provided as a 45 mg tablet, and was self-administered by each patient as a once-daily oral dose. Ponatinib was also provided as a 15 mg tablet for patients who received a dose reduction to 30 mg or 15 mg.

<table>
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<th>Study Product</th>
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<td>31 October 2016</td>
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**DURATION OF TREATMENT:**
The total estimated duration of the study was up to 3 years, including 12 months to accrue patients with up to 2 years for treatment and follow-up for the last patient.

Patients remained on treatment for as long as they continued to receive benefit from ponatinib or until disease progression, development of intolerance, patient withdrawal of consent, or decision by the investigator. The median duration of follow-up was 14.25 months (range: 0.4 months to 34.3 months).

**REFERENCE THERAPY, DOSE AND MODE OF ADMINISTRATION; BATCH NUMBER:**
No reference therapy was included in this study.

**CRITERIA FOR EVALUATION:**
The primary endpoint was:
- CBR consisting of CR+PR+SD by modified RECIST 1.1 at 16 weeks in patients with KIT Exon 11 mutant GIST (Cohort A)

The secondary endpoints were:
- CBR at 16 weeks in patients with GIST that lacks an activating KIT Exon 11 mutant (Cohort B) and in the total study population
- PFS in each cohort and in the total patient population
- ORR (CR+PR) in each cohort and the total patient population
- OS in each cohort and in the total patient population
- Safety and tolerability of ponatinib
- Steady-state plasma concentration of ponatinib (C_{ss}) at selected time points.

The following efficacy and safety assessments were performed:

**Efficacy:**
Efficacy assessments comprised response using modified RECIST 1.1 and long-term survival follow-up. Tumor assessments were performed at baseline and every 2 cycles for the first 6 cycles, then every 3 cycles until treatment discontinuation. Response evaluation for target, non-target lesions, and new lesions were defined in the protocol according to RECIST 1.1. Survival data were collected approximately every 6 months (±1 month) starting after the last dose of study drug or the investigator/patient decision to discontinue treatment, whichever occurred later, and continued for up to 24 months from the time the last patient was enrolled.

**Safety:**
Safety assessments included routine physical examination and vital sign (temperature, pulse, respiratory rate, and
blood pressure) assessments, laboratory evaluations (including serum chemistry, fasting cholesterol/lipid, and hemoglobin A1c, C-reactive protein, and cardiac blood tests), electrocardiography, and echocardiography. Adverse events were recorded throughout the study (from the time of informed consent to 30 days after the End-of-Treatment) and the severity of AEs was graded according to the NCI-CTCAE Version 4.0.

**STATISTICAL METHODS:**

For all analyses, one month was defined as 28 days (the same length as a cycle of ponatinib treatment), unless otherwise specified. Summary data were presented in a tabular format for the 2 cohorts and for the total population. Categorical data were summarized by the number and percentage of patients in each category. Continuous variables were summarized by descriptive statistics including N, mean, standard deviation, median, and range. The baseline value for a protocol assessment was defined as the last non-missing value on or before the first dose date of study drug, unless otherwise specified.

**Analysis Populations:**

There were 2 analysis populations in the study:

- Intention to treat (ITT) population included all patients who received any dose of ponatinib in the study.
- Per-protocol population (PP) included all patients who received any dose of ponatinib, and had no major protocol violations that could be expected to impact response data, such as failure to satisfy one or more eligibility criteria, administration of other anti-cancer therapy concurrent with study drug.

The ITT population was the primary analysis population for analyses of efficacy and safety. The numbers of patients in the ITT and PP populations were tabulated.

**Patient Disposition:**

The numbers of patient still on study drug, the numbers of patients discontinued from study drug (including the numbers of patients who were not participating in follow-up, were currently in survival follow-up, had withdrawn consent, were lost to follow-up, or had died), and the primary reason for treatment discontinuation were summarized.

**Demographics and Baseline Characteristics:**

Demographic and baseline characteristics, including disease diagnosis history, tumor KIT/PDGFRA mutation status at baseline, prior exposure to TKIs, and target lesions at study entry, were summarized separately for each cohort.

**Prior and Concomitant Medications:**

Prior and concomitant medications were coded to the latest version of the World Health Organization drug dictionary prior to database lock.

**Efficacy**

**Timepoint Tumor Response**

Tumor responses were derived according to RECIST 1.1.

For target lesions, up to 2 lesions per organ and 5 lesions in total were selected at baseline and followed at post-baseline to assess the sum of the longest diameter (SLD) in mm of all lesions.

- CR: 100% decrease from baseline in SLD
- PR: ≥30% to <100% decrease from baseline in SLD
- SD: Not in the other categories
- PD: ≥20% increase from the smallest prior SLD and with ≥5 mm absolute increase, or appearance of a new lesion
- Not Evaluated (NE): Assessment not done at all or partially done and not PD.

Note that for the calculation of CR or PR for target lesions, the baseline SLD was to be used as reference; for calculation of PD, the smallest SLD on study among all prior visits including baseline was to be used as reference. Both percent change from baseline and percent change from the smallest prior SLD needed to be calculated. A response was determined in the order of PD, NE, CR, PR, and SD.

If all tumors identified at baseline were not assessed at all at a post-baseline visit, then the response was NE at that visit. If the tumors were partially assessed, evaluation of PD took place first (e.g., ≥20% increase); if no PD could be assigned, then NE was assigned.
Best Overall Response
The best overall response was the best response recorded from the start of the treatment until disease progression (taking as reference for PD the smallest measurements recorded on study). The patient’s best response assignment depended on the achievement of both measurement and confirmation criteria. The best overall response across all timepoints was derived based on the overall responses reported by the investigator. Progressive disease was based on RECIST radiological assessments. Clinical progression reported at treatment discontinuation was not considered documented or objective PD.

Primary Analysis of the Primary Endpoint
The primary analysis of the primary endpoint was performed using modified RECIST 1.1 based on standard computed tomography or magnetic resonance imaging alone (Eisenhauer et al. Eur J Cancer 2009;45:228-47). The primary efficacy endpoint was the CBR in Cohort A, calculated based on investigator reported overall response using modified RECIST 1.1. The complete benefit rate was defined as the percentage of patients with a response defined as a CR, PR or SD at 16 weeks (with a 2-week window). The point estimate of CBR, and a 95% confidence interval (CI) based on the exact binomial distribution (Clopper-Pearson exact CI) were presented. The primary analysis of the primary endpoint was based on the ITT population. The analysis was repeated using the PP population.

Analysis of the Secondary Efficacy Endpoints
The analyses of secondary efficacy endpoints were performed using both ITT and PP populations. The secondary efficacy endpoints used RECIST PD reported by the investigator.

Clinical benefit rates in patients in Cohort B and in the total study population were analyzed in the same way as in Cohort A.

Objective response rate was defined as the percentage of patients having a best overall response of either CR or PR per RECIST 1.1 reported by the investigator. Estimates of ORR, including CR and PR in each cohort and in the total population and their 95% CIs based on the exact binomial distribution, were presented.

Progression-free survival was defined as the duration of time from the first dose of study drug to the first documented objective PD due to any cause, whichever came first. Death was considered as an event (1) if patients who did not have a post-baseline tumor assessment died within 16+2 weeks of the first dose date (e.g., after missing 2 consecutive tumor assessments) or (2) if patients who had at least 1 post-baseline tumor assessment died within the next 2 scheduled assessments (+2 weeks) after the last evaluable scan. The last evaluable/adequate tumor assessment without PD was the last time the patient’s response was known to be progression-free. Progression-free survival was analyzed using the Kaplan-Meier method. Median PFS and the 95% CI were provided. The probability of remaining progression-free at 6 and 12 months were presented.

Overall survival was defined as the time interval from the first dose of study drug to death due to any cause. Overall survival was censored at the last date the patient was known to be alive or lost to follow-up. Patients with no post-baseline data had OS censored on the date of the first dose of study drug. Overall survival was analyzed using the Kaplan-Meier method. Median survival time and the 95% CI were provided. The survival probability at 6 and 12 months were presented.

Subgroup analyses for the primary efficacy endpoint and selected secondary efficacy endpoints were performed by key baseline potential prognostic factors.

SAFETY

Analysis of Secondary Safety Endpoint
All safety analyses were performed on the ITT population, which included all patients who received at least one dose of study drug. The safety data from all cohorts were pooled.

Parameters pertaining to study drug exposure (duration of exposure, number of days dosed, dose intensity [mg/day], total cumulative dose) were summarized separately for each cohort.

Compliance was summarized, including relative dose intensity (calculated as dose intensity divided by 45 times 100, up to Cycle 6 for patients enrolled under protocol amendment 3). The numbers of patients who had a dose reduction and those who had a dose interruption of at least 3 days were provided.

Treatment-emergent AEs were summarized by preferred term (PT) only and by both PT and system organ class (SOC); all AEs were listed. All AEs with an onset date on or after the first dose date of study drug and no later than 30 days after the last dose date of study drug were considered treatment-emergent. Treatment-emergent AEs were
summarized by highest toxicity grades (severity), relatedness to study drug (in the opinion of the investigator), and by action taken with study drug (treatment discontinuations due to AEs). All AEs for which the relationship to study drug was classified as possibly related, probably related, or definitely related were considered treatment-related. Serious AEs, both overall and by relationship to study drug, were also summarized. Adverse events resulting in study drug discontinuation and the number of patients who died were described.

A listing of patients who developed vascular occlusive events was provided. Vascular occlusive events were categorized as arterial thrombotic events (cardiac ischemic/thrombotic events, cerebral ischemic/thrombotic events, peripheral ischemic/thrombotic events) or venous thrombotic events. Arterial occlusive and venous thrombotic events that met the broad search criteria (which excluded non-serious mild/CTCAE Grade 1 events) were included in the listing.

Hepatotoxic TEAEs were summarized by PT only and by both PT and SOC. Treatment-related hepatotoxic TEAEs and serious hepatotoxic events were summarized by highest toxicity grades.

Cardiac failure events were listed.

Clinical laboratory data results were standardized and graded according to NCI-CTCAE Version 4.0 criteria, when applicable. The change from baseline to the worst on-study result was summarized for these standardized results. Listings of laboratory test results were also generated for all laboratory data collected.

Summaries of maximum post-baseline systolic and diastolic blood pressures and maximum shift from baseline were provided. Summaries of baseline echocardiogram results and change from baseline to the minimum post-baseline assessment were provided.

RESULTS

DISPOSITION OF PATIENTS

Of the 45 patients in the ITT population, 30 patients were in Cohort A and 15 patients were in Cohort B.

At the time of analysis (01 August 2016), all 45 patients included in the ITT population had discontinued ponatinib treatment. The most common primary reason for treatment discontinuation was documented PD (RECIST) (18 patients; 40%), followed by AEs (where the reason for discontinuation was not PD [8 patients; 17.8%]), and clinical PD (7 patients; 15.6%). The median duration of follow-up was 14.25 months (range: 0.4 months to 34.3 months). A total of 32 patients (71.1%) were known to have died on or before the database cutoff date. Two patients (4.4%) died due to TEAEs that were considered by the site investigators as possibly related to ponatinib (pneumonia in 1 patient and pulmonary embolism in another patient).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS

The mean (± SD) age of patients included in the ITT population was 57.5 (± 12.63) years. Over half of the patients were male (26 patients; 57.8%) and most patients were of white race (44 patients; 97.8%).

Almost all patients in the ITT population had an ECOG performance status of 0 (23 patients; 51.1) or 1 (21 patients; 46.7%) at study entry. The most common primary tumor sites most recently diagnosed were the stomach (15 patients; 33.3%), small intestine (14 patients; 31.1%), intra-abdominal area (extravisceral) (7 patients; 15.6%), and sites classified as “other” (6 patients; 13.3%). The mean (± SD) size of the most recently diagnosed tumors was 10.60 cm (± 4.867). Patients had received a mean (± SD) of 4.42 (± 1.840) prior cancer regimens. A total of 3 patients (6.7%) had previously received just 1 approved TKI; 16 patients (35.6%) had received 2 approved TKIs, and 26 patients (57.8%) had received imatinib, sunitinib and regorafenib. The majority of patients had resistance/intolerance to a prior imatinib (43 patients; 95.6%) or sunitinib (38 patients; 84.4%) containing regimen and approximately half of patients had resistance/intolerance to a prior regorafenib-containing regimen (25 patients; 55.6%).

At study entry, all 30 patients in Cohort A had GIST mutated in KIT Exon 11. In addition, a small number of patients in Cohort A had additional GIST mutations in KIT Exon 13 (2 patients; 6.7%), KIT Exon 17 (3 patients; 10.0%), or the PDGFR-α mutation H845Y (1 patient; 3.3%). As expected, no patients in Cohort B had KIT Exon 11 mutated KIT at study entry. In Cohort B, 7 patients (46.7%) had KIT Exon 9 mutation, 1 patient (6.7%) had KIT Exon 13 mutation, 2 patients (13.3%) had KIT Exon 17 mutation, and 6 patients (40.0%) had no identified mutations in KIT or PDGFR-α.

PRIOR AND CONCOMITANT MEDICATIONS

All patients in the ITT population had taken at least one prior anticancer therapy. The prior anticancer therapies most commonly reported were imatinib (45 patients; 100%), sunitinib (41 patients; 91.1%), regorafenib (27 patients;
60.0\%), sora\-fenib (14 patients; 31.1\%), and nilotinib (7 patients; 15.6\%).

All patients in the ITT population continued to take at least one concomitant medication after the first dose of ponatinib. The concomitant medications most commonly reported were Anatomical Therapeutic Chemical (ATC) 2 upper terms of analgesics (37 patients; 82.2\%), drugs for constipation (29 patients; 64.4\%), antiemetics and antinauseants (25 patients; 55.6\%), anti-inflammatory and antirheumatic products (23 patients; 51.1\%), and mineral supplements (23 patients; 51.1\%). The most commonly reported concomitant medications (preferred name terms under an individual ATC 2 upper term) were oxycodone (22 patients; 48.9\%), ibuprofen (18 patients; 40.0\%), prochlorperazine (17 patients; 37.8\%), macrogol 3350, ondansetron, and sodium docusate (16 patients; 35.6\% each), acetylsalicylic acid and lisinopril (15 patients; 33.3\% each), paracetamol (14 patients; 31.1\%), sennoside A+B (13 patients; 28.9\%), omeprazole, triamcinolone, and vitamins (not otherwise specified) (12 patients; 26.7\% each), furosemide and lorazepam (11 patients; 24.4\% each), and hydrochlorothiazide, metoprolol, and potassium chloride (9 patients; 20\% each).

**EFFICACY RESULTS:**

**Primary Endpoint**

The CBR, comprising the proportion of patients with a CR, PR, or SD by modified RECIST 1.1 at 16 weeks in patients with KIT Exon 11-mutant GIST (Cohort A), was 35.7\% (95\% CI: 18.6, 55.9). A total of 10 of the 28 patients in Cohort A included in the analysis derived clinical benefit from ponatinib; 1 patient (3.6\%) had a PR and 9 patients (32.1\%) had SD at 16 weeks. No CR at 16 weeks was observed in the study.

**Secondary Endpoints**

The CBR at 16 weeks was 30.2\% (95\% CI: 17.2, 46.1) in the ITT population overall and 20.0\% (95\% CI: 4.3, 48.1) in Cohort B. The CBR at 16 weeks in the PP population overall and by cohort were generally similar to the rates in the ITT population. The CBR at 16 weeks for Cohort A appeared to be greater than that in Cohort B for both the ITT (35.7\% [95\% CI: 18.6, 55.9] and 20.0\% [95\% CI: 4.3, 48.1], respectively) and PP (41.7\% [95\% CI: 22.1, 63.4] and 23.1\% [95\% CI: 5.0, 53.8], respectively) populations, but the differences between the cohorts were not statistically significant due to the limited sample size of the study.

The ORR among patients with at least 1 post-baseline scan or discontinued without a scan was 4.7\% (95\% CI: 0.6, 15.8) in the ITT population overall, 7.1\% (95\% CI: 0.9, 23.5) in Cohort A, and 0\% (95\% CI: 0.0, 21.8) in Cohort B.

The median duration of PFS was 110.0 days (95\% CI: 57.0, 252.0) in the ITT population overall, 112.0 days (95\% CI: 57.0, 252.0) in Cohort A, and 57.0 days (95\% CI: 55.0, 502.0) in Cohort B.

The median duration of OS was 402.0 days (95\% CI: 267.0, 738.0) in the ITT population overall, 411.0 days (95\% CI: 234.0, 836.0) in Cohort A, and 399.0 days (95\% CI: 90.0, -) in Cohort B.

**SAFETY RESULTS:**

**Exposure**

The mean dose intensity (daily dose) of ponatinib was 39.24±6.283 mg/day. The mean number of days from the first to the last dose of ponatinib was 201.1±254.03 days and the mean number of days dosed was 189.3±245.44 days. On average (mean), patients took ponatinib on 94\% (SD±7.9) of the expected dosing days and patients received a mean of 87.21\% of the expected total dose. Almost half (44.4\%) of patients in the ITT population had any dose of ponatinib reduced; and almost half (48.9\%) had a dose interruption of at least three days.

**Treatment-emergent Adverse Events**

Treatment-emergent AEs were reported in all 45 patients of the ITT population. The most commonly reported TEAEs (with an incidence of >30\% of patients overall, in decreasing order of frequency) were rash, fatigue, abdominal pain, headache, constipation, myalgia, hypertension, peripheral edema, decreased appetite, and dry skin.

Treatment-related TEAEs were reported in all 45 patients of the ITT population. The most commonly reported TEAEs (with an incidence of >30\% of patients overall, in decreasing order of frequency) were rash, fatigue, myalgia, constipation, headache, and dry skin.

The maximum severity of treatment-related TEAEs per patient was most commonly Grade 2 (moderate; 33.3\% patients) or Grade 3 (severe; 42.2\% patients) TEAEs.

**Serious Treatment-emergent Adverse Events**

Serious TEAEs were reported in 26 patients (57.8\%). The most commonly reported serious TEAEs (with an incidence of \(\geq 5\%\) of patients, in decreasing order of frequency) each occurred in <10\% of patients and were abdominal pain, small intestine obstruction, pneumonia, and neoplasm progression.
Treatment-related serious TEAEs were reported in 9 patients (20.0%). The most commonly reported treatment-related serious TEAE was pulmonary embolism (2 patients; 4.4%).

Deaths
Grade 5 (fatal) TEAEs/serious TEAEs within 30 days of the last ponatinib administration were reported in 5 patients (neoplasm progression in 2 patients; and pneumonia, hepatic failure, and respiratory failure in 1 patient each). Treatment-related Grade 5 serious TEAEs were reported in 2 patients, pneumonia, which led to the death of 1 patient within 30 days of the last dose of ponatinib, and pulmonary embolism, which led to the death of another patient more than 30 days after the last ponatinib dose.

TEAEs Leading to Discontinuation
TEAEs led to discontinuation of study drug in 8 patients (17.8%) (where the reason for discontinuation was not PD), including treatment-related TEAEs (fatigue, diplopia, pneumonia, right ventricular dysfunction, peripheral artery stenosis, and acute respiratory failure) in 6 patients. Two patients had TEAEs leading to discontinuation, which were considered not related or probably not related to ponatinib treatment (abdominal pain and hepatic failure).

Adverse Events of Special Interest
Arterial occlusive and venous thrombotic TEAEs that met the broad search criteria (which excluded non-serious mild/CTCAE Grade 1 events) were reported in 5 patients (11.1%) (a total of 8 TEAEs) and comprised serious TEAEs of pulmonary embolism (2 patients [4.4%]) and myocardial ischemia, cerebrovascular accident, peripheral artery stenosis, and deep vein thrombosis (1 patient [2.2%] each), and non-serious TEAEs of cerebrovascular accident and peripheral artery stenosis (1 patient [2.2%] each).

Hepatotoxic Treatment-emergent Adverse Events
Hepatotoxic TEAEs were reported in 17 patients (37.8%), including 14 patients (31.1%) with at least 1 treatment-related hepatotoxic TEAE. The most commonly reported treatment-related hepatotoxic TEAEs (with an incidence of ≥5% of patients, in decreasing order of frequency) each occurred in <25% of patients and were increased blood alkaline phosphatase, increased AST, and increased ALT. The majority of the hepatotoxic TEAEs resolved.

Cardiac Failure Treatment-emergent Adverse Events
Cardiac failure TEAEs were reported in 5 patients (11.1%), including serious TEAEs of congestive cardiac failure and right ventricular dysfunction (1 patient [2.2%] each) and non-serious TEAEs of decreased ejection fraction (3 patients [6.7%]) and pulmonary edema (1 patient [2.2%]). The cardiac failure TEAEs were all considered possibly related to ponatinib treatment, except for the TEAE of pulmonary edema, which was considered probably not related to ponatinib.

Laboratory Evaluations
Shifts in laboratory parameters from baseline (values of less than CTCAE Grade 3) to the worst value post-baseline of CTCAE Grade 3 or CTCAE Grade 4 were reported in ≤3 patients (6.7%) for any particular laboratory assessment, with the exception of increased lipase (8 patients [17.8%]) and decreased hemoglobin (5 patients [11.1%]).

Vital Signs and Physical Examinations
Vital signs and physical examination TEAEs reported in ≥10% of patients included hypertension (17 patients [37.8%]), pyrexia (10 patients [22.2%]), and decreased weight (7 patients [15.6%]).

Electrocardiograms and Echocardiograms
Electrocardiogram and cardiac findings included TEAEs of decreased ejection fraction and atrial fibrillation (3 patients [6.7%] each), sinus tachycardia (2 patients [4.4%]), and congestive cardiac failure, myocardial ischemia, pericardial effusion, right ventricular dysfunction, and sinus bradycardia (1 patient [2.2%] each).

CONCLUSION:
In conclusion, ponatinib treatment resulted in a CBR of 35.7% (95% CI: 18.6, 55.9) in patients with activating KIT Exon 11-mutant GIST, with a PR in 1 patient (3.6%) and a best response of SD in 9 patients (32.1%) at 16 weeks. The safety and tolerability profile of ponatinib in this population of patients with metastatic and/or unresectable GIST was generally consistent with the results of ponatinib clinical studies conducted in other indications; there were no new safety signals or patterns of events indicative of a new safety concern.

DATE OF THE REPORT: 03 November 2017