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.
CLINICAL STUDY REPORT C14007 SYNOPSIS

Study Title: A Phase 1 Dose Escalation Study of MLN8237, an Aurora A Kinase Inhibitor, in Adult Patients With Nonhematological Malignancies, Followed by a Phase 2 of MLN8237 in Lung, Breast, Head and Neck, or Gastroesophageal Malignancies

Study Center(s): Phase 1: United States (US) (2 centers); Phase 2: Czech Republic (7 centers); France (5 centers); Poland (4 centers); and US (24 centers).


Phase: 1/2

Initiation Date (first patient enrolled): 16 February 2010

Completion Date (last patient completed): 03 May 2013

Study Objectives:

Phase 1

The primary objective of the phase 1 portion of the study was to assess the safety and tolerability of alisertib, formulated as an enteric-coated tablet (ECT), on a 7-day dosing schedule for determining the recommended dose and schedule of alisertib to be used in phase 2.

The secondary objectives of the phase 1 portion of the study were:

- To characterize the pharmacokinetics (PK) of alisertib, formulated as the ECT, administered on a 7-day dosing schedule.
Alisertib
Clinical Study Report C14007 Synopsis

- To describe any antitumor activity that may be observed with alisertib treatment in patients with advanced nonhematological malignancies.
- To determine the recommended phase 2 dose – pancreatic cancer (RP2D-P) in a subset of patients who met eligibility criteria for the pancreatic cancer patient cohort.

The exploratory objectives of the phase 1 portion of the study were:

- To assess biomarkers in relation to clinical response in banked tumor specimens including, but not limited to, Aurora A kinase protein expression, Aurora A kinase gene amplification, proteins related to Aurora A kinase signaling, and markers relevant to tumor type such as epidermal growth factor receptor (EGFR), KRAS, human epidermal growth factor receptor 2 (HER2), and human papilloma virus (HPV), and the status of transcriptional factors such as Myc family genes and proteins.
- To genotype peripheral blood samples for candidate biomarkers that may predict response to alisertib such as Aurora A polymorphisms Phe31Ile and Val57Ile that may influence tumor aneuploidy, breast cancer susceptibility gene 1 (BRCA1) and gene 2 (BRCA2) mutation polymorphisms in breast cancer, and polymorphisms in genes encoding enzymes that may contribute to alisertib metabolism/disposition (eg, uridine diphosphate glucuronosyltransferase [UGT] 1A1).
- To assess candidate markers of response to treatment in serum, such as but not limited to, markers of tumor cell death including full-length and caspase-cleaved cytokeratin 18 (CK18) fragments (M30/M65), and carbohydrate antigen 19-9 (CA19-9) in pancreatic cancer patients.
- To evaluate urinary excretion and renal clearance of alisertib.

Phase 2

The primary objective of the phase 2 portion of the study was to estimate the antitumor activity of alisertib as measured by overall response rate (ORR) in patients with advanced, unresectable nonhematological malignancies (non-small cell lung cancer [NSCLC], small cell lung cancer [SCLC], adenocarcinoma of the breast, head and neck squamous cell carcinoma [HNSCC], or adenocarcinoma of the esophagus/gastroesophageal junction or stomach).

The secondary objectives of the phase 2 portion of the study were:

- To assess the relationship between clinical response and molecular markers of response.
- To assess additional measures of antitumor activity, including time to progression (TTP), progression-free survival (PFS), and duration of response (DOR).
- To characterize the safety profile associated with alisertib.

The exploratory objectives of the phase 2 portion of the study were:

- To assess biomarkers in relation to clinical response in banked tumor specimens, including but not limited to, protein expression levels of Aurora A kinase and proteins related to Aurora A kinase signaling, and Aurora A kinase gene amplification, and markers relevant to tumor type such as EGFR, KRAS, estrogen receptor (ER), progesterone receptor, HER2, BRCA1, BRCA2, and HPV, and the status of transcriptional factors such as Myc family genes and proteins.
- To genotype peripheral blood samples for candidate biomarkers that may predict response to alisertib such as Aurora A polymorphisms Phe31Ile and Val57Ile that may influence tumor aneuploidy, BRCA1 and BRCA2 polymorphisms in breast cancer, and polymorphisms in
genes encoding enzymes that may contribute to alisertib metabolism/disposition (eg, UGT1A1).

- To assess candidate markers of response to treatment in serum, such as but not limited to, markers of tumor cell death including full-length and caspase-cleaved CK18 fragments (M30/M65).
- To contribute to evaluation of population PK using a limited sampling strategy.
- To assess safety and evidence for disease control in a subset of patients with HNSCC using retrospective analysis of a subset with tonsillar or base of tongue carcinoma with a high frequency of HPV-associated disease.

METHODS

**Design:** This was an open-label, multicenter study with a phase 1 dose escalation portion and a 2-stage, phase 2 portion, investigating alisertib in patients with relapsed or refractory advanced nonhematological malignancies. Throughout the conduct of this study, alisertib was administered orally (PO) as an ECT formulation.

In the phase 1 portion of the study, patients with advanced nonhematological malignancies were enrolled. The starting dose of alisertib in the initial cohort was 10 mg twice daily (BID) \times 7 days. One patient was enrolled in the initial cohort. If toxicity \geq Grade 2 (per National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] criteria, version 4.0) was not observed in the patient in the first cycle, the next cohort (20 mg BID \times 7 days) opened to enroll 1 patient. If a toxicity of \geq Grade 2 was observed in the first 2 cohorts (10 or 20 mg BID), 2 more patients were to be added and the cohort was to revert to a 3 + 3 scheme. If 1 dose-limiting toxicity (DLT) was observed in any cohort, future escalations were 33% (adjusted to accommodate pill size). After the 40-mg BID cohort, dose escalations converted to 33%, adjusted to accommodate pill size. Dose escalation proceeded with a 7-day dosing/14-day rest cycle until the maximum tolerated dose (MTD) was reached, determined as the highest dose that resulted in \geq 2 DLTs in a cohort of up to 6 patients. The 7-day MTD cohort or a lower dose level, if the MTD was not considered tolerable for multiple cycles of therapy, was to be further investigated in a primary expansion cohort of 12 patients to further evaluate PK and safety.

In the phase 2 portion, patients were enrolled in 1 of 5 diagnosis groups: NSCLC, SCLC, adenocarcinoma of the esophagus/gastroesophageal junction or stomach, HNSCC, or adenocarcinoma of the breast. During the lead-in phase 1 portion of the study, the MTD and recommended phase 2 dose (RP2D) of alisertib ECT administered PO BID for 7 consecutive days followed by a minimum 14-day rest period was identified, and the PK profile was characterized in eligible patients. The MTD cohort or a lower dose level, if the MTD was not considered tolerable for multiple cycles of therapy, was to be expanded to 12 patients to further evaluate PK and safety. Additionally, a cohort of at least 12 patients with pancreatic cancer was to be enrolled at the RP2D-P (enrollment in this cohort was terminated because of slow enrollment; only 1 patient was enrolled).

In phase 2, alisertib ECT was administered PO at the MTD (or RP2D, if lower than the MTD) determined in the phase 1 portion of the study for 7 consecutive days, followed by a minimum 14-day rest period; the cycle length was 21 days. The final decision of dose and schedule to be used for the phase 2 portion of the study was made in consultation with the phase 1 investigators, sponsor, and Safety Management Team (SMT) following a review of the available safety, PK, and efficacy data.

The phase 2 portion of the study followed a 2-stage design. An interim analysis for futility stopping was to be conducted when 20 response-evaluable patients in each tumor indication were enrolled and had the opportunity to complete a minimum of 4 cycles of therapy or had discontinued therapy due...
to progressive disease (PD). The critical value for evaluation of each tumor type to proceed to the second stage was 2 (10%) responses in 20 patients, also supported by acceptable safety and tolerability reviewed throughout the conduct of the study by the SMT. For the second stage of phase 2 enrollment to proceed for a disease group, at least 2 responses were to be observed within the first 20 response-evaluable patients enrolled in that disease group. In the second stage, ORR was further evaluated in the disease groups that continued beyond the first stage.

In both the phase 1 and phase 2 portions of the study, patients received repeated cycles of alisertib treatment (see Duration of Treatment below). Patients enrolled in the phase 1 portion of the study were not to be enrolled in the phase 2 portion. A patient who discontinued treatment before occurrence of PD was followed off-treatment until PD was documented, the patient withdrew consent for further follow-up, or another anticancer therapy was started.

**Number of Patients (planned and analyzed):**

Approximately 270 patients (45 in phase 1 and 225 in phase 2) were planned for enrollment in the study. A total of 273 patients were enrolled and received at least 1 dose of study drug either in phase 1 or phase 2. In phase 1, all 24 patients were included in the Safety, DLT-Evaluable, and PK-Evaluable populations; 16 patients were included in the Response-Evaluable population. In phase 2, all 249 patients were included in the Safety population, 117 patients were included in the PK-Evaluable population, and 212 patients were included in the Response-Evaluable population.

**Diagnosis and Main Criteria for Inclusion:** Patients must have had a diagnosis of an advanced, unresectable, nonhematological malignancy for which standard curative or life-prolonging treatment did not exist or was no longer effective or tolerable. Enrollment in the phase 1 portion was not restricted by tumor histology; however, an expansion cohort included patients with adenocarcinoma of the pancreas. Enrollment in the phase 2 portion required 1 of the following histologic types: NSCLC, SCLC, invasive adenocarcinoma of the breast, HNSCC, or adenocarcinoma of the esophagus, gastroesophageal junction, or stomach.

**Test Product, Dose and Mode of Administration, Batch Number:** Alisertib ECT: 10 mg and 50 mg; PO administration; lot numbers summarized below:

**Alisertib Lot Numbers Shipped to Investigative Sites**

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Strength</th>
<th>Lot numbers</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECT</td>
<td>10 mg</td>
<td>100878, 18D069B, 1C017TA07</td>
</tr>
<tr>
<td></td>
<td></td>
<td>101115, 101116, 102548, 102646, 18D070B</td>
</tr>
<tr>
<td>ECT</td>
<td>50 mg</td>
<td>IC018TA04</td>
</tr>
</tbody>
</table>

Abbreviation: ECT = enteric-coated tablet.

**Duration of Treatment:** The maximum duration of therapy was 24 months unless, after discussion between the investigator and sponsor, it was determined that the patient would derive benefit from continued therapy beyond 24 months.

**Reference Therapy, Dose and Mode of Administration, Batch Number:** Not applicable

**Pharmacokinetic Assessments:** Pharmacokinetic blood samples to determine plasma concentrations of alisertib were obtained at scheduled times during Cycle 1 in phase 1 and phase 2. A single blood sample was obtained for determination of plasma concentrations of alisertib on Cycle 2, Day 8 in phase 1 and on Day 8 in Cycles 2 and 3 in phase 2.

Urine PK samples were obtained in Cycle 1 only to measure the amount of alisertib excreted in the urine starting as early as Cohort 3 (40 mg BID × 7 days) in phase 1.
Pharmacogenetic Assessments: Polymorphisms in genes encoding enzymes that may contribute to alisertib metabolism/disposition (eg, UGT1A1) were examined. One blood sample was obtained at Cycle 1, Day 1 before the first dose of alisertib to evaluate germline polymorphisms in the Aurora A kinase gene, and other genes specific to certain tumor types, such as BRCA1 and BRCA2 in breast cancer, that may play a role in the patient’s response to alisertib.

Assessments for Tumor Markers and Biomarkers of Response: A blood sample for measurement of tumor markers (eg, CA15-3) was obtained at protocol-specified time points if these had been followed in individual patients to reflect disease burden.

Banked tumor tissue (submitted slides or a paraffin-embedded block), if available, obtained as part of the patient’s standard care before Cycle 1, Day 1 and, if available, earlier periods dating from the patient’s original diagnosis, were collected for evaluation of Aurora A kinase protein expression and gene amplification and additional candidate biomarkers of response to alisertib and Aurora A pathway or Aurora pathway-related signaling.

Blood samples for assessment of potential serum biomarkers of response were obtained during phase 1 on Cycle 1, Day 1 before the first dose of alisertib and on Day 8 of Cycles 1 and 2. In phase 2, blood samples were obtained on Cycle 1, Day 1 before the first dose of alisertib; on Cycle 1, Day 8; and on Cycle 2, Day 8.

Efficacy Assessments: Extent of disease by diagnostic category was evaluated according to standard Response Evaluation Criteria in Solid Tumors (RECIST) guidelines, version 1.1. All patients underwent an evaluation of their disease at protocol-specified intervals with standard clinical examinations (eg, computed tomography [CT]/magnetic resonance imaging [MRI]). All patients with SCLC and NSCLC were to undergo an MRI scan with intravenous (IV) contrast (preferred) or CT with IV contrast of the brain irrespective of symptoms.

Safety Assessments: Safety measurements included assessment of adverse events (AEs) and clinically significant changes or abnormalities in physical examination findings, vital signs, and clinical laboratory results.

Statistical Methods

Pharmacokinetic Analysis: Plasma PK parameters were summarized across dose cohorts using descriptive statistics in phase 1. Plots of individual and mean plasma concentration-time profiles were presented by day. Urine PK data obtained in the phase 1 portion of the study were also summarized by dose cohort with descriptive statistics.

Pharmacogenetic Analysis: The results of genotyping for polymorphisms in UGT1A1 were summarized.

Efficacy Analysis: For phase 1, statistical analyses were descriptive and graphical in nature, and no formal hypothesis testing was performed. However, a by-patient listing of RECIST version 1.1 response and listings for PFS, TTP, and DOR were included.

For phase 2, the null hypothesis of the study was that each of the 5 arms had an ORR ≤ 5%. The alternative hypothesis was that an ORR ≥ 13% would be observed in any treatment arm. The primary efficacy analysis was based on the Response-Evaluable population. The number and percentage of patients in each response category (complete response [CR], partial response [PR], PD, and stable disease [SD]) were tabulated and the estimated ORR with 2-sided 95% exact binomial confidence intervals (CIs) was presented for each of the disease subtypes and for the study overall.

For the secondary efficacy endpoints in phase 2, PFS and TTP were analyzed based on the Safety population and Response-Evaluable population using the Kaplan-Meier method, by tumor type and
overall. Duration of response was analyzed for all responders using the Kaplan-Meier method for each tumor type and overall.

**Safety analysis:** Safety evaluations were based on the incidence, intensity, and type of AEs and clinically significant changes or abnormalities in the patient’s physical examination, vital sign measurements, and clinical laboratory results. Treatment-emergent AEs were tabulated by System Organ Class (SOC), High Level Term, Preferred Term, and treatment group. These analyses were performed using the Safety population for combined phase 1 and phase 2; phase 1 by dose level within the phase 1 dose escalation; phase 1 pancreatic patient; and phase 1 total groups for selected outputs.

**RESULTS**

**Demographic Results:** A total of 273 patients were enrolled and received treatment either in phase 1 (24 patients) or phase 2 (249 patients) of the study.

**Phase 1**

Patient disposition for phase 1 is summarized in the table below. Enrollment in the pancreatic cancer cohort was stopped because of the slow pace of patient accrual; only 1 patient was enrolled in this cohort.

**Phase 1 Patient Disposition**

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Pancreatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg BID (N = 1)</td>
<td>50 mg BID (N = 1)</td>
</tr>
<tr>
<td>20 mg BID (N = 3)</td>
<td>50 mg BID (N = 3)</td>
</tr>
<tr>
<td>40 mg BID (N = 4)</td>
<td>50 mg BID (N = 3)</td>
</tr>
<tr>
<td>50 mg BID (N = 3)</td>
<td></td>
</tr>
<tr>
<td>60 mg BID (N = 3)</td>
<td></td>
</tr>
<tr>
<td>Total (N = 24) n (%)</td>
<td></td>
</tr>
</tbody>
</table>

| Safety population<sup>a</sup> | 1 3 4 12 3 1 24 (100) |
| DLT-Evaluable population<sup>b</sup> | 1 3 4 12 3 1 24 (100) |
| PK-Evaluable population<sup>c</sup> | 1 3 4 12 3 1 24 (100) |
| Response-Evaluable population<sup>d</sup> | 1 3 3 7 2 0 16 (67) |

Source: C14007 CSR Table 14.1.1.1B.

Abbreviations: BID = twice daily; CSR = clinical study report; DLT = dose-limiting toxicity; MTD = maximum tolerated dose; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors.

Percentages were based on the total number of patients in the Safety population.

The expansion of MTD 50 mg BID patients was included under the Dose Escalation 50 mg BID column.

<sup>a</sup> Safety population was defined as all patients who received any amount of alisertib.
<sup>b</sup> The DLT-Evaluable population was defined as all patients in the phase 1 portion of the study who either experienced a DLT during Cycle 1 or completed at least 85% of the planned doses of alisertib and had sufficient follow-up data to determine whether a DLT occurred.
<sup>c</sup> PK-Evaluable population included all patients who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters.
<sup>d</sup> The Response-Evaluable population was defined as all patients who had measurable neoplastic disease according to the RECIST criteria at baseline, received at least 1 dose of alisertib, and had at least 1 postbaseline response assessment.

Most of the patients in phase 1 were male (15 patients, 63%) and white (18 patients, 75%). The median age was 57.0 years (range: 34-81 years). Per the inclusion criteria, all patients had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. The most common
primary diagnosis overall was sarcoma (4 patients, 17%), followed by colorectal cancer (3 patients, 13%), and liver cancer, ovarian cancer, and pancreatic cancer (2 patients, 8% each). (Note: only 1 of the 2 patients with pancreatic cancer was enrolled in the pancreatic cancer cohort). All other diagnoses were reported in 1 patient. The category of Other included 1 patient with metastatic neuroendocrine cancer and 2 patients each with chondrosarcoma and intrahepatic cholangiocarcinoma.

Phase 2

Patient disposition for phase 2 overall is summarized in the table below.

### Phase 2 Disposition

<table>
<thead>
<tr>
<th></th>
<th>Breast (N = 53)</th>
<th>Gastric (N = 55)</th>
<th>HNSCC (N = 55)</th>
<th>NSCLC (N = 26)</th>
<th>SCLC (N = 60)</th>
<th>Total (N = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Safety population</td>
<td>53 (51)</td>
<td>55 (58)</td>
<td>55 (82)</td>
<td>26 (88)</td>
<td>60 (40)</td>
<td>249 (47)</td>
</tr>
<tr>
<td>PK-Evaluable population</td>
<td>27 (51)</td>
<td>32 (58)</td>
<td>20 (36)</td>
<td>14 (54)</td>
<td>24 (40)</td>
<td>117 (47)</td>
</tr>
<tr>
<td>Response-Evaluable population</td>
<td>49 (92)</td>
<td>47 (85)</td>
<td>45 (82)</td>
<td>23 (88)</td>
<td>48 (80)</td>
<td>212 (85)</td>
</tr>
<tr>
<td>Patients ongoing</td>
<td>3 (6)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>1 (2)</td>
<td>5 (2)</td>
</tr>
</tbody>
</table>

Source: C14007 CSR Table 14.1.1.1A.

Abbreviations: CSR = clinical study report; HNSCC = head and neck squamous cell carcinoma; NSCLC = non-small cell lung cancer; PK = pharmacokinetic(s); RECIST = Response Evaluation Criteria in Solid Tumors; SCLC = small cell lung cancer.

Percentages were based on the total number of patients in the Safety population in each column. The diagnosis of HNSCC was not confirmed for Patient 58734-750. The patient is presented under the HNSCC column for any outputs pertaining to the Safety population but is not considered part of the Response-Evaluable population.

- **a** Safety population was defined as all patients who received any amount of alisertib.
- **b** PK-Evaluable population included all patients who had sufficient dosing data and alisertib concentration-time data to permit calculation of alisertib PK parameters.
- **c** The Response-Evaluable population was defined as all patients who had measurable neoplastic disease according to the RECIST criteria at baseline, received at least 1 dose of alisertib, and had at least 1 postbaseline response assessment.

In the Safety population, slightly more than one-half of patients (141 patients) in phase 2 overall were male. Per the protocol, all patients with breast cancer were female. Most patients were white (231 patients, 93%). The median age was 61.0 years (range: 30-88 years) and was similar among cohorts. Per the inclusion criteria, all patients in phase 2 had an ECOG performance status of 0 or 1. Most patients (182, 73%) had Stage IV disease at study entry, and most (244, 98%) had received prior antineoplastic therapy. One hundred thirty-four (54%) patients had undergone prior surgical therapy, and 176 (71%) had received prior radiation therapy.

The most common histological classification of the SCLC Safety population was small cell carcinoma, not otherwise specified (NOS) (45 patients, 94%). Most (39 patients, 65%) patients with SCLC were former smokers and 30% (18 patients) were current smokers. The median number of cigarette pack-years was 42 (range: 6-120).

The most common histological classification of the NSCLC Safety population was adenocarcinoma, NOS (11 patients, 42%) followed by squamous cell carcinoma, NOS (5 patients, 19%). Most
(16 patients, 62%) patients with NSCLC were former smokers and 19% (5 patients) were current smokers. The median number of cigarette pack-years was 38 (range: 3-125).

The most common histological classification of the breast cancer Safety population was infiltrating duct carcinoma, NOS (33 patients, 62%) followed by lobular carcinoma, NOS (6 patients, 11%), adenocarcinoma (3 patients, 6%), and invasive ductal carcinoma (2 patients, 4%). All other forms were reported in 1 (2%) patient each. Subtype of breast cancer was known for 32 patients: luminal A (15 patients), normal breast-like (9 patients), basal (5 patients), and luminal B (3 patients). Thirty-five (66%) patients were positive for the estrogen receptor, and 22 (42%) were positive for the progesterone receptor. Baseline HER2 status was assessed by both immunohistochemistry and fluorescence in situ hybridization (FISH). Of the 47 patients with results by immunohistochemistry, 9 had a positive result. Of the 21 patients with results by the FISH method, 5 had a positive result. Breast cancer susceptibility gene 1 mutation was reported positive in 1 patient. A negative result for BRCA1 and gene 2 mutation (BRCA2) was reported in 4 patients each. In the breast cancer Response-Evaluable population, 26 patients were assessed as hormone receptor (HR)-positive, 9 as HER2-positive, and 14 as triple negative.

The most common histological classification of the gastric cancer Safety Population was adenocarcinoma, NOS (33 patients, 60%), followed by adenocarcinoma intestinal type (5 patients, 9%); 13% (7 patients) had a classification of Other. All other histological subtypes were reported in 1 or 2 patients. Of the 13 patients with HER2 results by the FISH method, HER2 was amplified in 3 patients. Of the 54 patients with results for Helicobacter pylori, 3 patients had a positive result.

The most common histological classification of the HNSCC Safety population was squamous cell carcinoma, NOS (38 patients, 69%) followed by basaloid squamous cell carcinoma (4 patients, 7%), and carcinoma, NOS (3 patients, 5%); histological subtypes was classified as Other in 6 (11%) patients. Most (36 patients, 65%) patients were former smokers, and 7 (13%) patients were current smokers. The median number of cigarette pack-years was 30 (range: < 1-113). Of 7 patients with known results for HPV at study entry, 6 tested positive.

**Pharmacokinetic Results:** Alisertib PK was evaluated in 24 patients in the phase 1 portion of the study over the dose range of 10 to 60 mg BID. Alisertib steady-state trough concentrations on Cycle 1, Day 8 were obtained from 117 patients at the MTD/RP2D of 50 mg BID in the phase 2 portion of the study. The clinical PK results indicated that alisertib absorption is fast, with the peak plasma concentration of alisertib achieved at approximately 3 hours postdose. The overall mean steady-state terminal half-life following multiple-dose administration of alisertib was 21 hours. The steady-state exposure of alisertib increased with increasing dose over the dose range of 10 to 60 mg BID. Urinary excretion of alisertib was negligible. At the RP2D of 50 mg BID, the geometric mean alisertib steady-state trough concentration was consistent with that previously reported for alisertib. Trough concentrations of alisertib were generally comparable across cancer types (breast, gastric, HNSCC, NSCLC, and SCLC) in the phase 2 portion of the study.

**Pharmacogenetic Results:** Genotyping for polymorphisms in UGT1A1 was conducted in 24 patients during the phase 1 portion of the study. UGT1A1 genotype data will be formally evaluated as a potential covariate in the final cross-study population PK analysis to confirm understanding of the contribution of UGT1A1 genotype to the variability in alisertib PK. The results of the population PK analysis will be reported separately.

**Efficacy Results:** The primary objective of the phase 2 portion of the study was to estimate the antitumor activity of alisertib as measured by ORR in patients with advanced, unresectable, nonhematological malignancies (NSCLC, SCLC, adenocarcinoma of the breast, HNSCC, or adenocarcinoma of the esophagus/gastroesophageal junction or stomach). The ORR was 13% (28 patients) in the total Response-Evaluable population, with patients in the breast cancer cohort (9 patients, 18%) and SCLC cohort (10 patients, 21%) showing the highest response rates. All
responders achieved PR; no patient achieved CR. Among breast cancer patients, the ORR was 23% (6/26 patients) for those who were HR-positive, 22% (2/9 patients) for those who were HER2-positive, and 7% (1/14 patients) for those who were triple negative. Among patients with SCLC, the ORR was 25% (3/12 patients) for those with relapsed resistant/refractory disease and 19% (7/36 patients) for those with relapsed sensitive disease. With only 1 (4%) responder in the NSCLC cohort, this indication did not proceed to phase 2.

A secondary objective in the phase 2 portion of the study was to assess additional measures of antitumor activity, including PFS, DOR, and TTP, which provided further evidence of the antitumor activity of alisertib. Results for the breast cancer and SCLC cohorts are summarized in the table below.

Secondary Efficacy Endpoints for Breast Cancer and SCLC Cohorts (Response-Evaluable Population)

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Breast (N = 49)</th>
<th>SCLC (N = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS (days), Median (95% CI)</td>
<td>164 (78, 239)</td>
<td>64 (43, 103)</td>
</tr>
<tr>
<td>DOR (days), Median (95% CI)</td>
<td>169 (85, 366)(^a)</td>
<td>125 (93, NE)(^b)</td>
</tr>
<tr>
<td>TTP (days), Median (95% CI)</td>
<td>164 (78, 239)</td>
<td>78 (42, 114)</td>
</tr>
</tbody>
</table>

Source: C14007 CSR Table 14.3.1.2B, Table 14.3.1.3B, and Table 14.3.1.4.
Abbreviations: CI = confidence interval; CSR = clinical study report; DOR = duration of response; NE = not estimable; PFS = progression-free survival; SCLC = small cell lung cancer; TTP = time to progression.
\(^a\) N = 9 (all responders).
\(^b\) N = 10 (all responders).

Safety Results

Phase 1

The primary objective of the phase 1 portion of the study was to assess the safety and tolerability of alisertib, formulated as an ECT, on a 7-day dosing schedule in a 21-day treatment cycle for determining the recommended dose and schedule of alisertib to be used in phase 2. In the 50-mg BID cohort, 1 of 6 patients experienced a Cycle 1 DLT (Grade 4 febrile neutropenia) during the dose escalation phase. Escalation to the next dose level of 60 mg BID was not tolerated because of Grades 3 and 4 hematological toxicities. This dose was the maximum administered dose and was considered to be above the MTD. Expansion of the 50-mg BID cohort occurred with the addition of 3 more patients treated at this dose level. As only 1 of the first 6 DLT-evaluable patients in the 50-mg BID cohort experienced DLT in Cycle 1, this dose level was defined as the MTD. Based on acceptable tolerability across multiple cycles, this dose also was determined to be the RP2D administered for 7 days of a 21-day treatment cycle.

An overall summary of incidence rates for treatment-emergent AEs is provided in the table below. All 24 patients who participated in this phase of the study experienced at least 1 treatment-emergent AE, and 20 (83%) patients experienced an event that was assessed by the investigator as drug related. The most commonly reported AEs by SOC were Gastrointestinal disorders (21 patients, 88%) followed by AEs in the SOCs of Metabolism and nutrition disorders (19 patients, 79%) and Blood and lymphatic system disorders (17 patients, 71%). The most commonly reported event was fatigue (14 patients, 58%) followed by nausea and decreased appetite (13 patients, 54% each), neutropenia (12 patients, 50%), diarrhea and vomiting (11 patients, 46% each), and stomatitis, leukopenia, and alopecia (10 patients, 42% each).
Overall Summary of Treatment-Emergent Adverse Events – Phase 1 (Safety Population)

<table>
<thead>
<tr>
<th>Dose Escalation</th>
<th>Pancreatic</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 mg BID (N = 1)</td>
<td>50 mg BID (N = 1)</td>
</tr>
<tr>
<td>20 mg BID (N = 3)</td>
<td>Total (N = 24)</td>
</tr>
<tr>
<td>40 mg BID (N = 4)</td>
<td>n</td>
</tr>
<tr>
<td>50 mg BID (N = 12)</td>
<td>n</td>
</tr>
<tr>
<td>60 mg BID (N = 3)</td>
<td>n</td>
</tr>
<tr>
<td>Any AE</td>
<td>1</td>
</tr>
<tr>
<td>≥ Grade 3 AE</td>
<td>1</td>
</tr>
<tr>
<td>Drug-Related AE</td>
<td>1</td>
</tr>
<tr>
<td>Drug-Related ≥ Grade 3 AE</td>
<td>0</td>
</tr>
<tr>
<td>SAE</td>
<td>1</td>
</tr>
<tr>
<td>AE Resulting in DC</td>
<td>0</td>
</tr>
<tr>
<td>On-Study Deaths</td>
<td>0</td>
</tr>
</tbody>
</table>

Source: C14007 CSR Table 14.4.1.1B.

Abbreviations: AE = adverse event; BID = twice daily; DC = discontinuation; MTD = maximum tolerated dose; SAE = serious adverse event.

Percentages are based on the total number of patients in the Safety population in the total column.

A treatment-emergent adverse event is defined as any AE that occurred after administration of the first dose of any study drug through 30 days after the last dose of any study drug, or until the start of subsequent antineoplastic therapy, whichever occurred first, any event that was considered by the investigator to be drug-related regardless of the start date of the event, or any event that was present at baseline but worsened in intensity or was subsequently considered by the investigator to be drug-related.

On-study deaths are defined as deaths that occurred between the first dose of study drug and 30 days of the last dose of study drug.

A patient counts once for each type of event.

The expansion of MTD 50-mg BID patients was included under the dose escalation 50 mg BID column.

Two patients died within 30 days after receiving the last dose of study drug. In both cases, the fatal AE (acute respiratory distress and disease progression) was considered by the investigator as not related to study drug treatment.

A total of 14 (58%) patients experienced at least 1 treatment-emergent serious adverse event (SAE); 7 (29%) patients had at least 1 SAE that was assessed by the investigator as drug related. Drug-related SAEs included febrile neutropenia, neutropenia, leukopenia, anemia, vomiting, nausea, diarrhea, abdominal pain, stomatitis, pyrexia, pneumonia, and failure to thrive.

Seven (29%) patients experienced at least 1 AE that resulted in discontinuation of alisertib treatment. Events that led to discontinuation included confusional state, urinary retention, spinal cord compression, febrile neutropenia, anemia, gastrointestinal hemorrhage, decreased white blood cell (WBC) count, decreased lymphocyte count, fatigue, hyperbilirubinemia, hyponatremia, hypophosphatemia, and pancreatic carcinoma. All the AEs that led to discontinuation of study drug treatment except 2 (confusional state and febrile neutropenia) were assessed by the investigator as not study drug related.

**Phase 2**

An overall summary of incidence rates for treatment-emergent AEs is provided in the table below. Of the 249 patients who participated in the phase 2 portion of the study, 241 (97%) patients...
experienced at least 1 treatment-emergent AE, and 229 (92%) patients experienced an event that was assessed by the investigator as drug related. The most commonly reported AEs by SOC were Gastrointestinal disorders (184 patients, 74%), followed by AEs in the SOCs of General disorders and administration site conditions (172 patients, 69%) and Blood and lymphatic system disorders (164 patients, 66%). The most commonly reported event was fatigue (124 patients, 50%), followed by neutropenia (117 patients, 47%), anemia (107 patients, 43%), and alopecia (98 patients, 39%).

Overall Summary of Treatment-Emergent Adverse Events – Phase 2 (Safety Population)

<table>
<thead>
<tr>
<th></th>
<th>Breast (N = 53)</th>
<th>Gastric (N = 55)</th>
<th>HNSCC (N = 55)</th>
<th>NSCLC (N = 26)</th>
<th>SCLC (N = 60)</th>
<th>Total (N = 249)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Any AE</td>
<td>52 (98)</td>
<td>52 (95)</td>
<td>54 (98)</td>
<td>26 (100)</td>
<td>57 (95)</td>
<td>241 (97)</td>
</tr>
<tr>
<td>≥ Grade 3 AE</td>
<td>44 (83)</td>
<td>42 (76)</td>
<td>37 (67)</td>
<td>18 (69)</td>
<td>43 (72)</td>
<td>184 (74)</td>
</tr>
<tr>
<td>Drug-Related AE</td>
<td>51 (96)</td>
<td>49 (89)</td>
<td>51 (93)</td>
<td>25 (96)</td>
<td>53 (88)</td>
<td>229 (92)</td>
</tr>
<tr>
<td>Drug-Related ≥ Grade 3 AE</td>
<td>38 (72)</td>
<td>28 (51)</td>
<td>30 (55)</td>
<td>17 (65)</td>
<td>32 (53)</td>
<td>145 (58)</td>
</tr>
<tr>
<td>SAE</td>
<td>23 (43)</td>
<td>30 (55)</td>
<td>19 (35)</td>
<td>8 (31)</td>
<td>28 (47)</td>
<td>108 (43)</td>
</tr>
<tr>
<td>AE Resulting in DC</td>
<td>2 (4)</td>
<td>6 (11)</td>
<td>4 (7)</td>
<td>1 (4)</td>
<td>13 (22)</td>
<td>26 (10)</td>
</tr>
<tr>
<td>On-Study Deaths</td>
<td>0 (0)</td>
<td>4 (7)</td>
<td>2 (4)</td>
<td>3 (12)</td>
<td>13 (22)</td>
<td>22 (9)</td>
</tr>
</tbody>
</table>

Source: C14007 CSR Table 14.4.1.1A.

Abbreviations: AE = adverse event; CSR = clinical study report; DC = discontinuation; HNSCC = head and neck squamous cell carcinoma; MTD = maximum tolerated dose; NSCLC = non-small cell lung cancer; SCLC = small cell lung cancer; SAE = serious adverse event.

Percentages are based on the total number of patients in the Safety population in each column.

A treatment-emergent AE (is defined as any AE that occurred after administration of the first dose of any study drug through 30 days after the last dose of any study drug, or until the start of subsequent antineoplastic therapy, whichever occurred first, any event that was considered by the investigator to be drug-related regardless of the start date of the event, or any event that was present at baseline but worsened in intensity or was subsequently considered by the investigator to be drug-related.

On-study deaths are defined as deaths that occurred between the first dose of study drug and 30 days of the last dose of study drug.

A patient counts once for each type of event.

The diagnosis of HNSCC was not confirmed for Patient 58734-750. The patient is presented under the HNSCC column for any outputs pertaining to the Safety population but is not included in the Response-Evaluable population.

Twenty-two (9%) patients died within 30 days after receiving the last dose of study drug. In most cases (13 patients), the fatal event was disease progression. Other fatal events included arterial injury, pulmonary embolism, deterioration in general physical health (2 patients), dyspnea, secretion of inappropriate antidiuretic hormone, pneumonia, hyponatremia, and respiratory distress. In all cases, the fatal AE was assessed by the investigator as not related to study drug treatment.

A total of 108 (43%) patients experienced at least 1 treatment-emergent SAE; 45 (18%) patients had at least 1 SAE that was assessed by the investigator as drug related. Drug-related SAEs included febrile neutropenia, neutropenia, anemia, leukopenia, pancytopenia, thrombocytopenia, stomatitis, aphthous stomatitis, diarrhea, vomiting, nausea, colitis, abdominal pain, asthenia, fatigue, pyrexia, dehydration, failure to thrive, hypokalemia, decreased WBC count, decreased neutrophil count, decreased platelet count, decreased hemoglobin, sepsis, pneumonia, urinary tract infection, muscular...
Alisertib
Clinical Study Report C14007 Synopsis

weakness, somnolence, sedation, acute generalized exanthematous pustulosis, palmar-plantar erythrodysesthesia syndrome, hypotension, keratitis, and confusional state.

Twenty-six (10%) patients experienced at least 1 AE that resulted in discontinuation of alisertib treatment. These events included neutropenia, decreased neutrophil count, febrile neutropenia, sepsis, anemia, thrombosis, hepatic failure, pulmonary embolism, palmar-plantar erythrodysesthesia syndrome, gastroesophageal cancer, large intestine perforation, decreased appetite, nausea, vomiting, dysphagia, fatigue, hemoptysis, small cell lung cancer (stage unspecified), disease progression, dyspnea, inappropriate antidiuretic hormone secretion, ileus, empyema, pleural effusion, hyponatremia, thrombocytopenia, and acute generalized exanthematous pustulosis. Most of the AEs that led to discontinuation of study drug treatment were assessed by the investigator as not study drug related. Events that were assessed as related to study drug were neutropenia, sepsis, palmar-plantar erythrodysesthesia syndrome, acute generalized exanthematous pustulosis, febrile neutropenia, fatigue, and thrombocytopenia.

Clinical Laboratory Tests and Other Safety Measures: Phases 1 and 2

In both the phase 1 and phase 2 portions of the study, decreases from baseline in mean WBC count, hemoglobin, platelet count, absolute neutrophil count, and absolute lymphocyte count generally were observed starting at the Day-8 assessment, with a return toward baseline by Day 1 of the following treatment cycle. Mean changes from baseline in serum chemistry parameters generally were not clinically relevant. Clinically significant, treatment-emergent laboratory abnormalities were reported as AEs. The most frequently reported laboratory AEs were in the Blood and lymphatic system disorders SOC, including neutropenia (phase 1: 12 patients, 50%; phase 2: 117 patients, 47%); anemia (phase 1: 6 patients, 25%; phase 2: 107 patients, 43%); leukopenia (phase 1: 10 patients, 42%; phase 2: 51 patients, 20%); and thrombocytopenia (phase 1: 6 patients, 25%; phase 2: 51 patients, 20%). In addition, laboratory AEs of decreased WBC count, decreased neutrophil count, decreased platelet count, and decreased hemoglobin were reported in the SOC of Investigations.

In both the phase 1 and phase 2 portions of the study, mean changes from baseline in vital signs (blood pressure, heart rate, and temperature) were small and not clinically meaningful. Electrocardiogram data were obtained during the phase 1 portion of the study and, in general, most findings were not clinically meaningful.

CONCLUSIONS

Based on the results of this phase 1/2 study, the following conclusions can be made:

- Alisertib absorption was fast, the steady-state exposure of alisertib increased with increasing dose over the dose range studied (10–60 mg BID), urinary excretion of alisertib was negligible, and at the RP2D of 50 mg BID, the geometric mean alisertib steady-state trough concentration was consistent with that previously reported.

- Alisertib administered as single-agent therapy showed evidence of activity in the solid tumor types studied, with the highest activity observed in patients with breast cancer or SCLC.

- Alisertib 50 mg BID × 7 days of a 21-day treatment cycle had a manageable toxicity profile.

- These data support further clinical evaluation of alisertib in solid tumors, particularly breast cancer and SCLC.

Date of Report: 06 January 2014