# SYNOPSIS

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| **Name of Company:** Nerviano Medical Sciences<br>**Name of Finished Product:** Not applicable<br>**Name of Active Ingredient:**<br>Danusertib Hydrochloride ( PHA-739358) | *(For National Authority Use only)* |
| **Title of Study: Phase II study of PHA-739358 administered by 24-hour IV infusion every 14 days in advanced/metastatic breast, ovarian, colorectal, pancreatic, small cell lung and non small cell lung cancers** | |
| **Protocol Number:** AURA-6202-006 | |
| **Investigator(s):** Twenty-two Investigators enrolled patients at twenty-two sites in Belgium, Germany, Italy, France, Netherlands, Switzerland and United Kingdom. | |
| **Study Centers:**<br>- Università Cattolica del Sacro Cuore - Policlinico Universitario "A. Gemelli", Roma, Italy (Principal Investigator Prof. Carlo Barone, MD)<br>- Centro di Ricerca ad Alta Tecnologia -Scienze Biomediche, Campobasso, Italy (Principal Investigator Prof. Giovanni Scambia, MD)<br>- Istituto Clinico Humanitas IRCCS, Rozzano, Italy (Principal Investigator Prof. Armando Santoro, MD)<br>- Azienda Ospedaliera S. Camillo Forlanini, Roma, Italy (Principal Investigator Prof. Cora Sternberg, MD)<br>- Istituto Nazionale per lo studio e la cura dei Tumori, Milano, Italy (Principal Investigator Dott. Luigi Celio, MD)<br>- Istituto Dermopatico dell'Immacolata IDI-IRCCS, Roma, Italy (Principal Investigator Prof. Paolo Marchetti, MD)<br>- Azienda Ospedaliero-Universitaria Policlinico di Modena, Modena, Italy (Principal Investigator Prof. Pierfranco Conte, MD)<br>- Ospedale Sacro Cuore - Don Calabria, Negrar, Italy (Principal Investigator Dr. Maurizio Nicodemo, MD)<br>- Azienda Sanitaria Ospedaliera San Luigi Gonzaga, Orbassano, Italy (Principal Investigator Prof. Giorgio Vittorio Scagliotti, MD)<br>- General Hospital AZ Sint-Augustinus, Antwerpen-Vilrijk, Belgium (Principal Investigator Prof. Luc Dirix, MD)<br>- University Hospital Dept. of Oncology, UZ Gasthuisberg, Leuven, Belgium (Principal Investigator Prof. Patrick Schoeffski, MD)<br>- Institut Jules Bordet , Medical Oncology Clinic, Brussels, Belgium (Principal Investigator Prof. Ahmad Awada, MD)<br>- University Hospital Leuven, Dept of Obstetrics and Gynaecological , Leuven, Belgium (Principal Investigator Prof. Ignace Vergote, MD)<br>- Erasmus University Medical Center, Daniel den Hoed Cancer Center, Rotterdam, Netherlands (Principal Investigator Prof. Maja De Jonge, MD)<br>- VU Medisch Centrum, Medische Oncologie, Amsterdam, Netherlands (Principal Investigator Prof. Epie Boven, MD)<br>- Istituto Oncologico della Svizzera Italiana, Ospedale Regionale Bellinzona e Valli, Bellinzona, Switzerland (Principal Investigator Prof. Cristiana Sessa, MD)<br>- Institut Gustave-Roussy, Villejuif Cedex, France (Principal Investigator Prof. Fabrice Andrè, MD)<br>- University Hospital, Department of Médical Oncology, Lyon, France (Principal Investigator Prof. Veronique Trillet-Lenoir, MD)<br>- Institut Claudius Regaud, Toulouse, France (Principal Investigator Prof. Jean-Pierre Delord, MD) | |

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- Universitatslkinikum - Internal Medicine, Essen, Germany (Principal Investigator Prof. Wilfried Eberhardt, MD)
- Klinik und Poliklinik fur Innere Medizin I- Klinikum der Universitaet Regensburg , Regensburg, Germany (Principal Investigator Prof. Esther Endlicher, MD)
- Sir Bobby Robson, Cancer Trials Research Centre, Northern Centre for Cancer Care, Freeman Hospital, Newcastle upon Tyne, United Kingdom (Principal Investigator Prof. Elisabeth Ruth Plummer, MD)

**Publication Reference:**

E. Gallerani, J.P. Delord, P. Schöffski, I. Vergote, V. Trillet-Lenoir, M. Maur, M.G. Jannuzzo, A. Petroccione, G. Locatelli, D. Lorusso. Phase II study of Danusertib (D) in advanced/metastatic breast and ovarian cancers (BC, OC). J Clin Oncol 28:15s, 2010 (suppl; abstr. 5014)

B. Laffranchi, M.J. De Jonge, E. Bajetta, A. Hendlisz, R. Giuliani, C. Barone, E. Endlicher, M.G.Jannuzzo, R. Spinelli, A. Santoro. Phase II study of Danusertib (D) in advanced/metastatic colorectal and pancreatic cancers (CRC, PC). Proceeding of Annual Meeting Am. Soc. Clin. Oncol. 2010, abstr. ID e13558

| **Studied Period (Years):** | | **Phase of Development:** |
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| Date of First Subject Enrolled:: | 07 March 2007 | Phase II |
| Date of Last Subject Completed: | 13 July 2011 | |
| Date of Last Follow-up: | 25 August 2012 | |

**Objectives:**

**Primary:**
- To determine if PHA-739358 has antitumor activity against breast, ovarian, pancreatic, colorectal, small and non-small cell lung cancers.

**Secondary:**
- To evaluate the antitumor activity of PHA-739358 in comparison to the last prior therapy
- To evaluate the safety profile of PHA-739358.
- To monitor the PK of PHA-739358 in plasma
- To analyze the gene expression profile in tumor biopsies before and after treatment with PHA-739358 and to investigate any possible correlation with clinical/radiological assessment in consenting patients suffering from metastatic breast cancer (modified, as per Amendement No. 1, by extending the gene expression profile analysis to all tumor types, and later on deleted as per Amendement No. 3).
- To analyze genes/proteins which might predict responsiveness to Aurora kinase inhibitors in tumor biopsies collected at diagnosis and/or thereafter from ovarian cancer patients (added as per Amendement No. 2).
- To analyze genes/proteins which might predict responsiveness to PHA-739358 in paraffin embedded tumor biopsies collected at diagnosis and/or thereafter, in any case before the enrollment in the study, from NSCLC patients with squamous cell histology (added as per Amendement No. 3).

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**Methodology:** This was a Phase II non-randomized, multicenter, multinational prospective study to explore the antitumor activity and safety of the intravenous Aurora-A and Aurora-B inhibitor PHA-739358 in breast, ovarian, colorectal, pancreatic, small cell lung and non small cell lung cancers.
Adult patients, with histologically or cytologically confirmed diagnosis of progressive advanced/metastatic breast, ovarian, colorectal, pancreatic, small cell lung or non small cell lung cancers, had to receive PHA-739358 by a 24-hour IV infusion every 14 days at the dose of 500 mg/m$^2$.
The choice for the dose was based on the RP2D obtained from the phase I study AURA-6202-002.
For each tumor type, a Simon's two-stage design was applied, allowing early termination at the first stage in case of low activity of PHA-739358 in a specific tumor type.
The primary endpoint of the study was the Progression Free (PFR) Rate at 4 months since treatment start, i.e. the proportion of patients who were still alive and had not progressed after 4 months from treatment start. The Progression Free was mandatorily to be assessed in the week following the completion of 4 calendar months since the first administration of PHA-739358, except for patients with an earlier documented progression.
During follow up period, survival status was to be monitored every 3 months for 15 months.
**Safety** assessments (vital signs, hematology, blood chemistry, and urinalysis) were to be performed at baseline and at different time points during the treatment period, depending on the parameter, and at the end of treatment. Additional hematology and blood chemistry laboratory assessments were to be done under the Investigator's judgment. Pregnancy test was to be done at baseline or within 7 days before treatment start (blood or urine) only for potential reproductive women.
A 12-lead electrocardiogram (ECG) was to be performed at baseline visit, at the end of infusion during Cycle 1, at the end of treatment visit and was to be repeated, if clinically indicated, to monitor cardiac events. As per Amendment No. 3, ECG monitoring was to be enhaced as follows: at baseline visit, on Day 1 (before and at the end of infusion) and on Day 8 at Cycles 1 and 2, and at the end of treatment visit. Repeated assessments to monitor cardiac events were under the Investigator's judgment. In addition QT/QTc length had to be measured every time an ECG was performed.
A Trans Thoracic Echocardiogram (TTE) or multigated acquisition scan (MUGA) was to be scheduled at pre-treatment visit and at the end of treatment visit to document left ventricular ejection fraction (LVEF). Patients were to be followed for adverse events (AE) from the signature of the Informed Consent form up to 28 days after the last dose of study treatment or until all drug-related toxicities had resolved or a new anticancer therapy was started.
**Efficacy** assessments were to be based on imaging assessments (X-Ray, CT scan, MRI). PET could be used (if available) in case of dubious or negative lesions. A clinical examination with photography (if applicable) to monitor superficial lesions and palpable organs (spleen, liver) was to be done at least once per cycle in parallel to the scheduled disease assessments. Tumor imaging was to be performed at baseline (within 21 days before the initial infusion treatment) and every 2 calendar months. Additional tumor imaging was to be done under Investigator's judgment. At the end of treatment visit, if more than 1 month had passed from last tumor imaging, another tumor assessment had to be performed.
As per Amendment No. 3, for all NSCLC patients with squamous histology, a confirmatory analysis of all CT scans, including the ones performed before the baseline documenting the tumor progression at the study entry, was to be done by a peer-review committee.
For **pharmacokinetic** purpose, two blood samples were to be collected from all patient few minutes before start of infusion and just before (5-10 minutes) the end of infusion, on Day 1 at Cycles 1, 2, 4 and 8. In case of serious adverse events, additional blood sample had to be collected, pending on the Investigator's judgment. PHA-739358 and its N-oxide metabolite PHA-816359 were to be assessed in plasma using a validated LC-MS/MS method.

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**Tumor marker** assessment was to be done to follow the evolution of the disease on treatment. The following markers were to be evaluated: CA-125 (ovarian cancer), CEA (colorectal cancer), CEA/CA19-9/CA-125 (pancreatic cancer). Tumor markers were to be evaluated at baseline (within 14 days before the initial infusion treatment), and at least every 4 cycles (every 2 months) within 5 days before Day 14. At the end of treatment, if more than 1 month had passed from last tumor marker assessment, another marker assessment had to be performed.

Changes in **gene expression** in pre- and post- treatment tumor biopsies of patients treated with PHA-739358 could be suggestive of target modulation and response to compound treatment. As per the original protocol, changes in gene expression were to be evaluated only in tumor biopsies obtained from voluntary patients with metastatic breast cancer treated with PHA-739358. Biopsies were to be done at baseline (within 14 days the initial infusion treatment) and on Day 1, Cycle 2 (within the last hour of the infusion). Any potential correlation of the expression profile and gene expression changes with clinical/radiological assessment was to be investigated. This secondary objective of the study was subsequently modified with protocol amendments as follows.

As per Amendment No.1, the analysis of gene expression profile in tumor biopsies, obtained before and after treatment, was to be performed in all consenting patients with accessible tumor lesions, and not only in voluntary patients with metastatic breast cancer.

As per Amendment No. 2 it was added, in patients suffering from ovarian cancer only, an explorative analysis on genes/proteins, which might predict responsiveness to PHA 739358. The analysis was to be done on tumor samples collected at diagnosis and /or thereafter in order to try to identify predictive markers of the outcome.

Finally, as per Amendment No. 3, the gene expression analysis planned in all consenting patients with accessible tumor lesions was deleted, and, in the subset of NSCLC patients with squamous cell histology only, it was added the explorative analysis of genes/proteins which might predict responsiveness to PHA 739358. Any potential correlation of basal tumor molecular features with clinical/radiological assessment was to be investigated to identify potential biomarkers predicting treatment efficacy. The analysis was to be done on paraffin embedded tumor biopsy obtained from the patients at the time of primary diagnosis and/or thereafter, in any case before the enrollment in the study.

During the course of the trial three protocol amendments implemented:

- Amendment No. 1 (dated 22 January 2007). The main purposes of this amendment were the following: to allow to perform tumor biopsies (and gene expression analyses) in all consenting patients with accessible tumor lesions and not only in metastatic breast cancer patient, as planned in the original study protocol; to give the definition of platinum resistant/refractory ovarian cancer patient; to exclude patients with an active second malignancy other than non melanoma skin cancer, within the previous 5 years. Moreover, based on a compatibility study results, it was specified that PVC and PE tubes/bags could be used and that, at the concentrations of PHA-739358 planned in the study, the 500 ml bags were recommended (but the 250 ml ones could also be used).
- Amendment No. 2 (dated 10 July 2008). The main purposes of this amendment were: to use tumor samples collected at diagnosis and/or thereafter from patients suffering from ovarian cancer, who participated in the clinical trial, to perform analysis on genes/proteins which could predict responsiveness to Aurora Kinase inhibitor (such as p53 levels and Aurora kinases protein expression) with the aim of comparing the results of responder patients to those who progressed; to investigate if these markers could help in identifying patients who had benefit from the treatment.
- Amendment No. 3 (dated 9 September 2009). This amendment moved from the observation that the patients with squamous NSCLC treated by PHA-739358 showed a better Progression Free Survival (PFS). As only a limited number of patients (7 patients with squamous cell histology out of 24 unselected NSCLC patients)

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contributed to the latter finding it required a confirmation in additional patients. The main purposes of this amendment were the following: to expand the investigation of PHA-739358 activity in the sole subgroup of squamous NSCLC patients, in keeping the original primary endpoint (PFS at 4 months) and hypotheses ($p_0 \leq 0.20$; $p_1 \geq 0.40$); to characterize some basal squamous cell carcinoma molecular features related to the mechanism of action of PHA-739358 on paraffin embedded tumor biopsies obtained at the time of diagnosis or thereafter, in any case before the enrollment in the study, and to identify potential biomarkers predicting treatment efficacy; to add a peer-review of all CT scans for all squamous NSCLC patients, including the CT scans performed immediately before baseline documenting the tumor progression at study entry. In addition, upon FDA suggestion, a further purpose of this protocol amendment was to enhance ECG monitoring, as "clinically significant QT prolongation with other aurora kinase inhibitors" had been reported, and to add dedicated exclusion criteria (as per ICH E14 Guidance). ECG tracing was to be performed at baseline visit, on Day 1 (before and at the end of infusion) and on Day 8 at Cycle 1 and 2, and at the end of treatment visit; QT/QTc length had to be measured every time an ECG was performed.
- Amendment No. 4 (dated 25 November 2009). This protocol amendment was presented upon specific requests from the French Competent Authority "AFSSAPS". The protocol was modified to incorporate the actions to be taken in case of QT/QTc prolongations occurred and two additional exclusion criteria specifying that patients with personal or familial history of syncope or unexplained loss of consciousness and patients with familial history of unexplained sudden death were not to be enrolled.

**Number of Subjects (Planned and Analyzed):**
A set of Simon's two stage designs was used to determine if PHA-739358 had sufficient activity to warrant to further development in any of the tumor types studied.
The two steps procedure allowed for early termination in case of low activity of PHA-739358 in a specific tumor category.

This design was based on testing a null hypotesis, H0: $p \leq p0$, that the true Progression Free Rate (PFR) at 4 months was less than or equal to some uninteresting level p0, against an alternative one that the true PFR achieved at least some desiderable target level p1. At first stage Simon's design aimed at stopping the trial if the alternative hypothesis, H1: $p \geq p1$, could be rejected.

In this trial $\alpha$ and $\beta$ were taken both equal to 0.1 and the following table presents, for each tumor type, the parameters p0 and p1 (tumor type distinctive) used in the set of hypotheses, the required number of evaluable patients to be recruited at each stage, and the critical number of responses to proceed to second stage and to reject null hypothesisat second and final stage.
As per Amendment No. 3, NSCLC patients with squamous cell histology were considered as a separate tumor category, with the same $p_0$, $p_1$ and required number of patients as for of the (unselected) NSCLC category. Patients with squamous cell histology already recruited under the unselected NSCLC tumor category were accounted for the squamous cell carcinoma distinct category.

For each tumor type, the median Progression Free Rate (PFR) retrieved from literature was used to approximate the PFR at 4 months under the null hypotesis. The computation was done assuming an exponential distribution of the survival function (i.e., constant hazard rate over time).

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**Table: Simon's Two Stage Design**

| $\alpha$=0.1 $\beta$=0.1 | Tumor Type | | | | | |
|---|---|---|---|---|---|---|
| | Breast | Ovarian | Pancreatic | CRC | SCLC | NSCLC |
| | 3rd line | 3rd line (Pt Res/Ref) | 2nd line | 3rd line | 2nd line | 2nd line |
| Median time of PFS for $p_0$ (months) | 1.7 | 2.8 | 2.3 | 2.0 | 1.7 | 1.7 |
| PFR at 4 months according to $p_0$ (%) | 20 | 37 | 30 | 25 | 20 | 20 |
| PFR at 4 months according to $p_1$ (%) | 40 | 57 | 50 | 44 | 40 | 40 |
| Median time of PFS for $p_1$ (months) | 3.0 | 5.0 | 4.0 | 3.4 | 3.0 | 3.0 |
| $n_1$ | **19** | **24** | **28** | **22** | **19** | **19** |
| $r_1$ | 3 | 9 | 7 | 5 | 3 | 3 |
| n | **36** | **42** | **39** | **43** | **36** | **36** |
| r | 10 | 19 | 15 | 14 | 10 | 10 |
| (r+1)/n (%) | 30.5 | 47.6 | 41.0 | 34.9 | 30.5 | 30.5 |

*PFS=Progression Free Survival; PFR=Progression Free Rate; $p_0$=uninteresting level of activity; $p_1$= interesting level of activity; $n_1$=first stage sample size of evaluable patients; $r_1$= upper limit for 1st stage rejection of drug; n=maximum sample size of evaluable patients; r= upper limit for 2nd stage rejection of drug; (r+1)/n = lowest percentage of progression free patients at 4 months by which $p_0$ is rejected at the end of 2nd stage.Pt Res/Ref = Platinum resistant/refractory*

Overall, in this study, the numbers of patient treated/evaluable for each tumor type were the following: 42/38 patients for breast cancer, 34/33 for ovarian cancer, 33/28 for CRC, 36/30 for pancreatic cancer, 18/12 for SCLC and 56/48 for NSCLC.

**Diagnosis and Main Criteria for Inclusion:**

Patients with histologically or cytologically documented progressive advance/metastatic disease in one of the following solid tumors: breast cancer (3rd line of chemotherapy), ovarian cancer (3rd line, platinum resistant/refractory), colorectal cancer (3rd line), pancreatic cancer (2nd line), small cell lung cancer (2nd line), non small cell lung cancer (2nd line), and (added as per Amendment No. 3) squamous non small cell lung cancer (2nd line). To be included into the study, prior chemotherapy could be completed 2 weeks before study entry. Patients had to have available information about the first day of administration of the previous chemotherapy and the precise date when progression had been assessed and prior radiotherapy was allowed provided that a minimum of 2 weeks has elapsed between the end of prior radiotherapy and the entry into the trial. Other main selection criteria included: age 18 years or older, ECOG performance status 0 – 1; life expectancy of at least 3 months; adeguate hematological and biochemical baseline laboratory data: bilirubin ≤1.5 UNL, AST/ALT ≤ 2.5 UNL (≤ 5 UNL in case of liver metastases), ALP ≤ 2.5 UNL (≤ 5 UNL in case of liver and/or bone metastases), creatinine within normal limits (if out of range then performed the creatinine clearance evaluation ≥ 50 ml/min), ANC ≥ 1,500 cells/$mm^3$ , platelets count ≥ 75,000 cells/$mm^3$ , hemoglobin ≥ 10 g/dl ; resolution of all acute toxic effects (excluding alopecia) of any prior therapy to NCI CTCAE version 3.0 Grade ≤ 1; personally signed and dated IEC/IRB-approved informed consent form and willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study procedures. The presence of any of the following had to exclude a subject from study enrollment: previous high-dose chemotherapy requiring bone marrow rescue; concurrent enrollment in another investigational drug trial within the last 4 weeks; known brain or leptomeningeal disease (baseline computerized tomography [CT] or MRI scan of the brain required only in case of clinical suspicion of central nervous system metastases); uncontrolled hypertension with blood pressure exceeding 160/100 mmHg; pregnancy or breast-feeding; abnormal LVEF by Echocardiography(< 40%) or MUGA (< 45%); any of the following in the past 6 months:

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myocardial infarction, unstable angina, coronary/peripheral artery bypass graft, symptomatic congestive heart failure, cerebrovascular accident or transient ischemic attack, pulmonary embolism, deep vein thrombosis or other significant thromboembolic event; ongoing cardiac dysrhythmias Grade ≥ 2 according to NCI CTCAE version 3.0; known active infections including known human immunodeficiency virus (HIV) positivity; other severe acute or chronic medical or psychiatric condition or laboratory abnormality that may increase the risk associated with study participation or study drug administration or may interfere with the interpretation of study results and, in the judgment of the Investigator, would make the patient inappropriate for entry into this study; history of previous cancer, except skin basal-cell carcinoma or in situ carcinoma of the cervix, within the previous 5 years (added as per Amendment No. 1). As per Amendment No. 3, the following exclusion criteria were added: marked baseline prolongation of QT/QTc interval (e.g., repeated demonstration of a QTc interval > 450 milliseconds [ms]); a history of additional risk factors for torsade de pointes (e.g., heart failure, hypokalemia, family history of Long QT Syndrome); use of concomitant medications that prolong the QT/QTc interval. Two additional exclusion criteria (i.e., personal or familial history of syncope or unexplained loss of consciousness and familial history of unexplained sudden death) were implemented in France only, as per Amendment No. 4.

**Test Product, Dose and Mode of Administration, Batch Number:**

The dose of PHA-739358 was calculated on individual patient's body surface area. The dose regimen of 500 $mg/m^2$ in a 24-hour IV infusion every 14 days was selected in agreement with the recommended dose from Phase I studies. A dose escalation to 580 $mg/m^2$ was allowed, from the second cycle, in case of good tolerance; dose reduction up to 375 $mg/m^2$ was allowed on the basis of potential safety.
PHA-739358 batch numbers used in the study were:
N0700063, N0700160, N0700184, N0700189, N0700204, N0700205, N0700221, N0700246, N0700293, N0700295, N0700321, N0700328, N0700365, N0700368, N0700374, N0700410, N0700519, N0700644, N0700645, N0700646, N0700770, N0700810, N0700817, N0700818, N0700819, N0700820, N0700821, N0700822, N0700831, N0700832, N0800406, N0800597, N0900126, N0900939, N0901278, N0901707, N0902018, N1000336, N1000462, N1000595, N1000596, N1000937, N1000938, N1001755, N1001756.

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

**Duration of Treatment:**

Patient were to continue PHA-739358 treatment up to 20 cycles (study completion) or until disease progression, patient refusal, unacceptable toxicity or any of the other criteria for withdrawal such as changing in medical status of the patient (including pregnancy), patient's safety compromised in the Investigator's opinion or non compliance by the patient with protocol requirements or patient lost to follow up. Additional cycles were administered under Investigator's judgment.

**Endpoints and Criteria for Evaluation:**

**Efficacy:**

Primary endpoint was:
- Progression Free Rate at 4 months of treatment.

The secondary endpoints were:
- Response Rate (CR / PR) according to the RECIST Criteria.

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- Overall Survival.
- Duration of stabilization and duration of response.
- Ratio between the PHA-739358 TTP and the TTP observed in the immediately previous chemotherapy line.

**Safety:**

- Overall Safety profile of PHA-739358 characterized by type, frequency, severity (graded using the National Cancer Institute Common Terminology Criteria for Adverse Events [NCI CTCAE] Version 3.0), timing and relationship to study therapy of adverse events and laboratory abnormalities.

**Other:**

- Concentration of PHA-739358 in plasma at two different times: one a few minutes before start of infusion and one a few minutes before end of infusion. These two samples (taken at Cycles 1, 2, 4 and 8) were allowed to monitor the pre and post plasma drug concentration.
- Gene expression profile in tumor biopsies before and after treatment (deleted as per Amendment No. 3).
- Genes/proteins which might predict responsiveness to PHA-739358 in tumor biopsies from ovarian cancer patients (added as per Amendment No. 2).
- Genes/proteins which might predict responsiveness to PHA-739358 in tumor biopsies from NSCLC patients with squamous cell histology (added as per Amendment No. 3).

**Statistical Methods:**

The primary endpoint was Progression Free Rate (PFR) at 4 months, i.e. the proportion of patients who were still alive and did not have progress after 4 months from treatment start.

A set of Simon's two stage design was used for this trial.

The analysis of the primary endpoint was carried out in the subset of evaluable patients. A patient was deemed as evaluable if s/he had received at least one dose of PHA-739358, had baseline tumor assessment and one assessment falling 4 months after treatment start unless s/he had died or progressed earlier. A patient who had experienced clinical progression or death before the first on-treatment tumor assessment was considered as evaluable unless progression or death had occurred within 4 weeks from treatment start (early progression or death) in which case the drug was considered not to have had the chance to exert its effect. Conversely a patient not fulfilling the first inclusion criteria that qualify for the disease under study was not be considered as evaluable.

PFR was assessed at the end of each of the two steps of the trial. Point estimates were presented along with two-tail 95% confidence intervals.

All secondary efficacy endpoints (response rate, response duration and duration of stable disease, overall survival, ratio of patient's TTPs) were to be evaluated in the evaluable patients. For response rate, point estimate as well as two-tail 95% confidence intervals was reported. Summary descriptive statistics including range and median values were estimated according to the Kaplan-Meier method for response duration, TTP, stabilization of disease and overall survival.

Descriptive statistical analyses and individual data listings were produced for the analysis of patient's disposition, protocol deviations, baseline characteristics, and safety data in treated patients.

**SUMMARY OF RESULTS:**

**Disposition of Subjects and Baseline Characteristics:**

A total of 223 patients were enrolled and 219 patients were treated. Four patients, one with colorectal cancer, one with pancreatic cancer and 2 with NSCLC, were never treated.

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At the time of the database lock (19 March 2013), the trial was completed.
According to the inclusion criterion No.1, at the study entry 205 patients (93.6%) had metastatic disease and 14 (6.4%) patients presented locally advanced disease. The most frequent sites of metastases were lymph nodes and liver and the majority of patients had two disease recurrences/progressions before entering the study (38.8%). All patients had diagnosis confirmed either by histology (86.8%) or cytology (13.2%). At primary diagnosis tumor stage was III, IV or extensive-stage (SCLC) in for 71.2 % of patients. In breast cancer, HER2 was expressed in 11.9 % of patients, estrogen and progesterone receptors were positive in 78.6% and 61.9% of patients, respectively. Seven patients (16.7%) presented triple-negative disease (estrogen and progestine receptors were absent and HER2 was not overespressed). Patients suffering from ovarian carcinoma expressed estrogen and progestin receptors in 11.8% and 8.8% of cases, respectively. In the ovarian cancer setting, 26 patients (72.2%) were resistant and 10 (27.8%) refractory to prior platinum therapy.
Smoking history has been collected only for NSCLC patients with squamous histology. Fifteen out of 39 treated patients (38.5%) were current smoker, and 18 (46.1%) former smoker, most of them (28.2%) having quitted 10 years ago or less.Three patients had never smoked.
In all tumor categories, the most frequent reason for treatment discontinuation was disease progression (189 patients, 86%). Overall treatment was discontinued due to AE in 5.5% of patients, as for Investigator's decision in 3.7% of patients, refusal to continue treatment in 4.1% of patients and withdrew the consent in 0.5% of patients.
The mean age at study entry was 59.2 years, being 26.9% of patient 65-year-old or above, and 92.2% were of white race. Femal gender was predominatly (59.8%). An equal number of patients had ECOG-PS score 0 or 1 (47.9% and 51.1%, respectively), while 09% of patients had ECOG-PS score 2.

**Treatment exposure:**
PHA-739358 was dosed based on the patient's body surface area. The median dose intensity and median relative dose intensity of PHA-739358 were very similar for all tumor types, ranging from 211.4 to 249.1 mg/m²/week and from 84.6 % to 99.6 %, respectively. The maximum number of completed cycles per patient, was reported for each tumor type: the values ranged from 58 (SCLC) to 317 (NSCLC). The median number of cycles delivered per patient ranged from 3 to 4 with a minimum of 1 cycle and a maximum ranging from 5 to 40 cycles, depending of the tumor type. As regards treatment duration the total number of weeks ranged between 121.7 for SCLC and 712.4 for NSCLC (median from 7.6 to 10.0). Considering all tumor types treatment modifications consist mainly in dose delays and infusions not completed as per protocol. The most frequent reasons for dose delays were hematological toxicities (uncomplicated neutropenia) and logistic/technical reasons. The main reasons for infusions recorded "not completed as per protocol" were logistic/technical reasons mostly consisted in small deviations (± 1h) from the scheduled infusion duration not affecting the PHA-739358 total dose administered.
Moreover, as per protocol, 7 patients were treated (all but one starting from Cycle 2) with the increased dose of 580 mg/m$^2$, since no Grade≥ 3 hematological toxicity was observed during the previous cycle.

**Efficacy Results:**
PHA-739358 did not meet protocol criteria to conclude for activity in any of the tumor categories investigated in this trial. However, some indication of activity was obtained in breast, ovarian, pancreatic and NSCL cancer as described below.
For breast cancer patients (mostly in 3$^{rd}$ line of chemotherapy) the PFR at Month 4, observed at completion of the first stage of the study, met the protocol criteria to proceed with the second stage (i.e. at least 3 out of 19 evaluable patients free from progression at Month 4). At the end of the first stage, 5 out of 19 patients were free from progression at Month 4 assessment: the 2$^{nd}$ stage of the study was opened to accrual and completed

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with a total of 42 patients enrolled and treated. Overall 7 out of 38 evaluable patients (18.4%; 95% CI: 7.7% – 34.3%) were free from progression after 4 months of treatment, as compared to the 11 (or more) out of 36 required at the end of the second stage to reject the null hypotesis. Best tumor response was SD in 10 out of 38 evaluable patients (26.3%), with a median duration of 23.3 weeks.Overall survival ranged from 2.0 to 31.2+ months, with a median value of 12.0 months. As regards tumor marker assessment (CEA) available data are insufficient to draw any conclusion.

For ovarian cancer patients (mostly in 3rd line of chemotherapy) the PFR at Month 4, observed at completion of the first stage of the study, did not meet the protocol criteria to proceed with the second stage. The recruitment was definitely stopped at the end of the first stage with a total of 33 patients enrolled and treated. Overall 4 out of 33 evaluable patients were free from progression after 4 months of treatment, as compared to the 10 (or more) out of 24 required at the end of the first stage to not reject the alternative hypothesis and to proceed with the second stage. According to RECIST criteria, one PR was documented in one out of 33 evaluable patients (3.0%) lasting 3.97 months; SD was reported as best response in 10 patients (30.3%). CA-125 response was reported by 3 out of 33 patients (9.1%), all free from progression at Month 4, including the patient with documented PR. These patients had on treatment a clinically relevant decrease in serum levels of the tumor marker CA-125 (i.e., ≥50% with respect to baseline), indicating a partial response of the disease. Overall survival ranged from 2.9 to 24.1 months, with a median value of 9.8 months and was ≥ 9 months in 16 (48.5%) out of 33 evaluable patients, rising to 19 months or more in 6 patients (18.2%).

In pancreatic cancer setting, at least 8 successes out of 28 evaluable patients were required to proceed with the second stage. Indeed 3 out of 30 evaluable patients were free from progression at 4 months precluding passage to the second stage. In 2nd line treatment of pancreatic cancer patients, PHA-739358 showed limited activity in terms of disease stabilization: 6 patients out of 30 evaluable (20%) had stable disease as best response and 3 of them remained stable for more than 6 months. Overall survival ranged from 1.1 to 23.9+ months, with a median value of 4.0 months, and lasted more than 6 months in 10 out of 30 (33%) evaluable patients. Tumor marker CA 19-9 measurements were in agreement with the evolution of the disease only in few cases. Only one out of the 3 patients free from PD at Month 4 had on treatment a clinically significant fall in CA 19-9 levels (> 90% with respect to baseline); for the other 2 patients CA 19-9 either remained stable or increased. Six out of the 21 patients, showing clinical or documented PD as best overall response, had on treatment a rise in CA 19-9 levels ranging from 20 to 49%. CEA measurements were performed at baseline and on treatment in 16 out of 36 treated patients (44.4 %). A clinically significant decrease in CEA value (-71% from baseline), together with a significant fall in CA 19-9 levels, was recorded at Month 4 in one of the 3 patients that showed prolonged disease stabilization. On treatment rising CEA was associated to disease progression (clinical or documented) in 12 patients.

For NSCLC patients (in 2nd line of chemotherapy) the PFR at Month 4, observed at the completion of the first stage in unselected patients, did not meet the protocol criteria to proceed with the second stage. Anyway, based on preliminary signs of benefit observed only in patients with squamous cell histology (3 out of the 6 evaluable patients as per the original study protocol were free from progression at Month 4), the protocol was amended to expand the investigation of PHA-739358 in this subgroup of patients. In NSCLC patients with squamous cell histology, the PFR at Month 4, observed at completion of the first stage of the study, met the protocol criteria to proceed with the second stage (i.e. at least 3 out of 19 evaluable patients free from progression at Month 4). In the second stage, overall 5 out of 31 (16.1%) evaluable patients with squamous histology were free from progression after 4 months of treatment. The enrollment to the second stage was closed considering that the predefined threshold required at the end of the second stage to reject the null hypotesis and to call activity (i.e., 11 or more patients free from progression out of 36 evaluable) would have never been met. Considering squamous cell histology, one PR lasting 24.4 weeks was documented in 1 out of

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31 evaluable patients; prolonged SD (≥ 25 weeks) was reported as best response in 4 patients (12.9%) and SD in 13 patients (41.9%). Considering non-squamous histology, best response was SD in 8 out of 17 evaluable patients (47.1%). Median OS was 10.1 (95% CI 5.7-10.6) for squamous patients and 8.3 (95% CI 5.7-12.9) for patients with non-squamous histology. Tumor biopsies obtained from NSCLC patients with squamous cell histology were analyzed for evaluation of biomarker expression by IHC and by FISH. The protein expression analysis was performed by ICH on tumor biopsies from 27 patients and showed that proliferative markers such as Aurora-A, Aurora-B, TPX-2, and MDR proteins were expressed in a low percentage of tumoral cells (score 0–1%) while Scr and Survivin markers were hightly expressed in most patients (score 2 – 5 %). An unsupervised hierarchical cluser analysis performed on these results showed that the patients responder and not responder were randomly distributed. FGFR1 gene amplification and centromere 8 aneuploidy were evaluated by FISH in tumor biopsies from 18 patients. Two out of the 14 evaluable samples (one obtained from a responder and another one from a non responder patient) showed FGFR1 gene amplification; all biopsies but one showed polisomy of chromosome 8, and one biopsy showed also monosomy of chromosome 8.No correlation was noticed between protein expression, FGFR1 gene amplification/ CEN 8 aneuplody and response to treatment. However the limited number of sample analyzed (particularly by FISH) and the limited number of patients showing objective response after PHA-739358 treatment do not allow drawing any definite conclusion.

None of the SCLC evaluable patients (mostly in 2$^{nd}$ line of chemotherapy) was free from progression at Month 4 assessment. Recruitment in this trial was definitively closed after enrollment of 18 patients in the first stage of the study in order to avoid exposure of new patients to a treatment that was unlikely to achieve the targeted level of activity at the end of the 1st stage. Only 2 patients reported SD as best overall response at Month 2, one of them with shrinkage of tumor lesions of 29%. The patient went off treatment due to Investigator's decision after 4 cycles of PHA-739358.

In spite of preliminary signs of benefit observed in 2 CRC patients, treated in Phase I study AURA-6202-002 at 180 and 500 mg/m2 and showing long lasting disease stabilisation (23.9 and 52.3 weeks, respectively), in the present trial PHA-739358 was not active in 3$^{rd}$ line treatment for metastatic CRC. All the 28 treated patients evaluable for efficacy progressed before the end of the 4th month. Recruitment in this trial was definitively closed at the end of the first stage and the second stage never took place.

Based on the outcome of this study, it can be concluded that PHA-739358 monotherapy, although did not meet protocol criteria to conclude for activity in any of target populations evaluated, showed some signs of activity when administered in breast, ovarian, pancreatic and non small cell lung cancers, as second/third line treatment for advance/metastatic disease. These results warrant further development in these and/ or additional indications in combination with other anticancer therapies.

**Safety Results:**

Overall 219 patients were treated and were evaluable for safety. The median number of cycles delivered per patient ranged from 3 to 4 depending on tumor type with a minimum of 1 and a maximum of 40 cycles. Only 1 patient completed and exceeded the planned 20 treatment cycles (patient No. 0169 suffering from NSCLC received 40 cycles of treatment). As regards treatment duration the total number of weeks ranged between 121.7 for SCLC and 712.4 for NSCLC (median from 7.6 to 10.0). Median dose intensity and median relative dose intensity of PHA-739358 were very similar for all tumor types, ranging from 211.4 to 249.1 mg/m²/week and from 84.6 % to 99.6 %, respectively. Treatment modifications mostly consisted of delays in treatment administration whilst fewer occurrences of dose reductions were observed. Moreover, as per protocol, 7 patients were treated (all but one starting from Cycle 2) with the increased dose of 580 mg/m$^2$, since no ≥ Grade 3 hematological toxicity was observed during the previous cycle.

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Two hundred and sixteen out of 219 treated patients (98.6%) experienced at least 1 AE in the first or subsequent cycles.Overall the most frequent AEs (frequency of ≥ 10%) were fatigue/asthenia (73.5%, 62.1% drug-related), nausea (44.7%, 42.0% drug-related), diarrhea (37.9%, 35.2% drug-related), constipation (31.5%, 18.3% drug-related), anorexia (29.7%, 23.3% drug-related), pyrexia and vomiting (26.5% each, 10.0% and 21.5% drug-related, respectively), dyspnea (24.2%, 2.3% drug-related), abdominal pain (22.4%, 4.6% drug-related), alopecia (20.5%, all drug related), anemia (18.7%, 16.9% drug-related), cough (16.0%, 1.8% drug-related), back pain (13.2%, 0.9% drug-related), chest pain (12.8%, 2.7% drug-related), weight decrease (12.3%, 4.6% drug-related), headache (11.0%, 5.9% drug-related), oedema peripheral (10.5%, 1.8% drug-related), abdominal pain upper and hypertension (10.0% each, 5.5% and 7.3% drug-related, respectively).
Drug related Grade 3-4 events occurred in 80 patients (36.5%) and included fatigue/asthenia (28 cases each, 12.8%), febrile neutropenia (17 cases, 7.8%), neutropenia, anaemia (9 cases, 4.1%), diarrhea (8 cases, 3.7%), leukopenia (5 cases, 2.3%), neutropenic sepsis (3 cases, 1.4%), chest pain, pyrexia, abdominal pain, urinary tract infection,anorexia, hypertension and transaminases increased (2 cases each, 0.9%), febrile bone marrow aplasia, extravasation, letargy, mucosal inflammation, abdominal pain upper, dysphagia, vomiting, infection, hypophosphatemia, jugular vein thrombosis, thrombosis, venous thrombosis of the limb, hepatic disorder and function abnormal, headache, pruritus and rash erythematous (1 case each, 0.5%).No Grade 5 drug-related events were reported.
No relevant differences in hematological toxicity were observed among tumor types. Overall neutropenia was the most frequent hematological toxicity (94.4%) as well as the most frequent cause of Grade 3-4 toxicities (82.9%) followed by anemia, mostly of Grade 1-2 in severity, reported in 64.1% of patients. Febrile neutropenia and neutropenic sepsis were reported respectively in 17 (7.8%) and 3 (1.4%) out of the 219 treated patients.
Non-hematological laboratory abnormalities were less frequent than the hematological ones and mainly related to mild to moderate elevations of liver enzymes. AST and ALT increased in 28.4% and 31.6% of patients respectively, being of Grade 3-4 in severity in only 3.3% and 3.7% of cases, respectively. ALP increase was reported in 38.1% of patients (2.8%, Grade 3-4). Hyperbilirubinemia was observed in 11.2% of cases (2.3% Grade 3-4).
Hypertension (transient, asymptomatic, reversible, mostly of Grade 1-2 in severity) was reported as drug related adverse events in 14 patients (6.6%). Grade 3 occurred in 2 of them: one patient (pancreatic cancer), who had a single hypertensive episode at Cycle 1 (8 h after start infusion), recovered with no action taken and continued study treatment for other 3 cycles; another patient (CRC), who reported an hypertensive episode at Cycle 1 Day 7 leading to dose reduction, continued treatment with no other action taken for other 3 cycles.

During treatment no clinically relevant abnormalities in ECG tracing were observed in all tumor categories. However 10 patients had ECG tracing alteration reported as clinical adverse event being only two of them (namely, Grade 1 sinus tachycardia in a patient with non squamous-NSCLC, and 2 episodes of Grade 2 atrial flutter in a squamous-NSCLC patient, reporting other ECG alterations at baseline and on treatment) considered as related to study medication.
As per FDA recommendation, with Amendment No. 3 additional ECG recordings were included in the study, with QTc evaluation every time an ECG was performed. Only one out of 32 patients (treated after amendment implementation) presented QTc interval prolongation recorded as Grade 1 clinical AE related to study drug (to note that the patient was also receiving metamizol and nebilet, both reported as drugs that might lead to QTc prolongation).Previous to Amendment No. 3, only one patient presented a treatment emergent QTc prolongation, recorded as AE, not related to study drug.
No on treatment alterations of LVEF were reported in all treated patients with the exception of 2 patients that

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showed LVEF decreases ≥ 10% with respect to baseline. None of the observed alterations was considered clinically relevant and none was associated to drug related adverse events.
In the clinical database 167 SAEs have been recorded in 99 treated patients and 61 (36.5%) of them, occurred in 43 patients, were considered as related to the study treatment.
Overall, 21 deaths on study (i.e., occurring from patient's consent up to 28 days after last treatment dose) were reported. All patients' deaths and events with fatal outcome were assessed by the Investigators as unrelated to the study drug except for two patients who died due to bacterial sepsis and septic shock, both unlikely related to the study drug. Almost all patients died due to progression of the underlying cancer or due to events related to their cancer.

**Pharmacokinetic Results:**
Plasma concentrations data were available for 195 out 219 treated patients. After each cycle of treatment $C_{endinf}$ values of PHA-739358 were comparable among patients with different tumor types while through concentrations of PHA-739358 were highly variable due to the closeness of the concentrations to the LLOQ value. After repeated cycles of treatment, accumulation ratio of PHA-739358 $C_{endinf}$ was in the range 0.830 - 0.917 in breast cancer, 1.00 - 1.42 in ovarian cancer, 0.824 - 1.17 in pancreatic cancer, 0.496 - 1.07 in CRC, 0.796 - 1.75 in SCLC and 0.871 - 1.82 in NSCLC patients. Throughout the cycles of treatment, metabolite to parent $C_{endinf}$ ratios were, on average, 0.509 (excluding $C_4$ and $C_8$ pre-dose ratios), 0.791, 0.460, 0.630, 0.325 and 0.305 in breast, ovarian, pancreatic, colorectal, SCLC and NSCLC patients, respectively. No difference on end infusion concentration of PHA-739358 was apparent among patients with different tumor types. Apart the higher PHA-739358 $C_{endinf}$ terms of the accumulation ratio range in SCLC (1.75) and NSCLC (1.82) patients, metabolite to parent ratio was similar among patients and approximately equal to 1, indicating, overall, no relevant accumulation of the maximal concentrations of the compound after repeated cycles of treatment. Throughout cycles of treatment, as overall mean, the levels of the metabolite accounted for 50 % than those of the parent compound. Cycle 1 concentrations at end infusion of PHA-739358 were similar to that one (mean ± SD: 3.20 ±1.29 μM) obtained in a previous pharmacokinetic study.

**CONCLUSIONS:**
The safety profile observed is consistent with the previous experience with the drug in patients with solid tumors. No new toxicities were reported and the main target organ was the hematopoietic system in all tumor categories. Neutropenia was the most frequent toxicity (94.4%) as well as the most frequent cause of Grade 3-4 toxicities (82.9%). Anaemia and thrombocytopenia mostly of Grade 1-2 were only occasionally reported.
Fatigue/asthenia, mainly Grade1-2 in severity, was the most frequent drug related AE in all tumor types, reaching the highest frequency in breast and ovarian cancer patients (76.2% and 73.5%, respectively), followed by NSCLC and SCLC (67.9% and 61.1 %), and pancreatic cancer and CRC patients (38.9 % and 33.3%). As far as Grade 3-4 events, frequency of fatigue/asthenia was considerably lower in all tumor types ranging from 8.8% (ovarian cancer) to 16.7% (SCLC).
Mild to moderate in severity drug related gastrointestinal toxicities, were more frequently observed in ovarian cancer (94.1%) and in breast cancer patients (73.8%), ranging from 51.1% to 63.9% in the other tumor categories tested.
PHA-739358 monotherapy did not meet protocol criteria to conclude for activity in any of the tumor categories investigated, since the number of evaluable patients free from progression at Month 4 remained below the threshold required in the protocol. However, some indication of activity was observed in advanced/ metastatic NSCLC, ovarian, pancreatic and breast cancer, as described below.
In NSCLC (in 2$^{nd}$ line of chemotherapy) the PFR at Month 4 did not meet the protocol criteria to proceed with the second stage, but there were signs of benefit in the subgroup of patients with squamous cell histology (3

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out of the 6 evaluable patients were free from progression at Month 4); so the protocol was amended to expand the investigation of PHA-739358 in this subgroup. In this expansion the study could proceed to the second stage but the overall number of patients reaching the endpoint (5 out of 31) was insufficient to rule out the null hypothesis. Nevertheless it is important to note that one patient with squamous cell histology achieved a confirmed PR lasting 24.4 weeks and SD was achieved in 13 patients (41.9%). Among patients with non-squamous histology, best response was SD in 8 patients (47.1%). Median OS was 10.1 (95% CI 5.7-10.6) for squamous patients and 8.3 (95% CI 5.7-12.9) for patients with non-squamous histology. The presence of a durable partial response in a second line population suggests that PHA-739358 could have a role in a subset of patients. Tumor biopsies obtained from NSCLC patients with squamous cell histology were analyzed for evaluation of expression of biomarkers such as Aurora-A, Aurora-B, TPX-2, and MDR, Scr and Survivin by IHC. An unsupervised hierarchical cluser analysis performed on these results showed that the patients responder and not responder were randomly distributed. Evaluation of FGFR1 gene amplification and centromere 8 aneuploidy by FISH was also performed on the tumor samples. No correlation was noticed between FGFR1 gene amplification/CEN 8 aneuplody and response to treatment. However the limited number of sample analyzed (particularly by FISH) and the limited number of patients showing objective response after PHA-739358 treatment do not allow drawing any definite conclusion.

After this protocol was prepared it has become clear that NSCLC, as other tumors, includes several diseases which, although arising in the same organ and classified in the same histologic type, represent a group of separate entities with specific molecular and genetic profiles that have prognostic and therapeutic implications. This new molecular subgroups can be a small part of the overall population (such as the translocation EML4/ALK, which is observed in 4-7% of the general NSCLC population) and therefore the observed benefit rate will be very low in an unselected population even if treated with the appropriate agent. Thus it cannot be ruled out that PHA-739358 might have a role in a specific subset of patients that needs to be characterized.

Similarly in ovarian cancer (mostly in 3$^{rd}$ line of chemotherapy), although only 4 evaluable patients were free from progression after 4 months of treatment in stage 1 (as compared to the ≥10 required by the protocol), it is important to note that one PR (lasting 3.97 months) and 10 SD were reported according to RECIST (33.3% overall), with 3 of these patients showing a CA-125 response. In recent trials in 2$^{nd}$ line therapy in the refractory/resistant population, the observed OS is approximately 10 months. To note that in the present study, in 3$^{rd}$ line chemotherapy, the observed overall survival was ≥ 9 months in 16 (48.5%) evaluable patients, 7 of them refractory and 9 resistant to prior platinum based therapy. This finding suggests that, although only one PR was reported and the number of events required by the protocol was not fulfilled, therapy provided benefit to some patients.

In pancreatic cancer, 3 out of 30 evaluable patients (mostly in 2$^{nd}$ line of chemotherapy) were free from progression at 4 months, precluding passage to the second stage (at least 8 successes out of 28 evaluable patients required). Best tumor response was SD in 6 patients (20%). The median OS was 4.0 months (range from 1.1 to 23.9+ months), and lasted more than 6 months in 10 (33%) patients, suggesting that, even if the primary endpoint of the study was not met, some patients did benefit from the therapy with PHA-739358.

In breast cancer 7 out of 38 evaluable patients (18.4%; 95% CI: 7.7% – 34.3%) were free from progression at Month 4 at the end of the second stage. Best tumor response was SD in 10 patients (26.3%), with a median duration of 23.3 weeks. Overall survival ranged from 2.0 to 31.2+ months, with a median value of 12.0 months.

In spite of preliminary signs of benefit observed in AURA-6202-002 Phase I study (where one SCLC patient achieved a confirmed PR and two CRC patients showed SD lasting 23.9 and 52.3 weeks) in the present trial PHA-739358 was not active in advanced/metastatic SCLC and CRC when administered as 2$^{nd}$ line and 3$^{rd}$ line treatment, respectively.

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| Based on the outcome of this study, it can be concluded that PHA-739358 monotherapy, although did not meet protocol criteria to conclude for activity in any of target populations evaluated, showed some signs of activity when administered in breast, ovarian, pancreatic and non small cell lung cancers, as second/third line treatment for advance/metastatic disease. These results warrant further development in these and/ or additional indications in combination with other anticancer therapies. | |
| **Date of the Report:**<br>13 May 2013 | |