SYNOPSIS

Name of Company: Nerviano Medical Sciences **Name of Finished Product:** Not applicable **Name of Active Ingredient:** Danusertib Hydrochloride (PHA-739358)	*(For National Authority Use only)*
Title of Study: A Phase II Study of PHA-739358 in Patients with Metastatic Hormone Refractory Prostate Cancer	
Protocol Number: AURA-6202-007	
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Study Centers: The study was conducted in 13 centers in Netherlands (1 center), in France (2 centers), in USA (2 centers) and in Italy (8 centers): 1) Erasmus University Medical Center, Daniel den Hoed Cancer Center, s-Gravendijkwal 230, Rotterdam, 3075 EA, Netherlands 2) Centre de Lutte Contre le Cancer Val d'Aurelle – Paul Lamarque, 208 rue des Apothicaires, Parc Euromédicine, 34298 Montpellier Cedex 5, France 3) Azienda Ospedaliera San Camillo Forlanini, Circonvallazione Gianicolense 87, 00152- Roma, Italy 4) Weill Cornell Medical College, University, 525 E, 68th Street, ST-359, 10021 New York, USA 5) Ospedale Civile, Viale Alfieri 36, 57128, Livorno, Italy 6) Azienda Ospedaliero-Universitaria Ospedali Riuniti "Umberto I G. M. Lancisi G. Salesi", Via Conca 71, 60126 Ancona, Italy 7) Ospedale "R. Silvestrini", Struttura Complessa di Oncologia Medica, Via Dottori 1, Località Sant'Andrea delle Fratte, Perugia, Italy 8) Azienda Ospedaliera San Luigi Gonzaga di Orbassano, SCDU Oncologia Medica, Regione Gonzole n.10, 10043 Orbassano (TO) , Italy 9) University of Washington, Seattle Cancer Care Alliance, 825 Eastlake Avenue East, Mailstop, G4-830 Seattle, Washington 98109, USA 10) Hôpital Beaujon, Service Inter Hospitalier de Cancerologie Bichat-Beaujon, 100 Boulevard du Général Leclerc, 92118 Clichy Cedex, France 11) Istituto Clinico Humanitas, Dipartimento di Oncologia Medical ed Ematologia, Via Manzoni 56, Rozzano (MI), Italy 12) Fondazione Centro S. Raffaele del Monte Tabor, Via Olgettina 60, 20132 Milano, Italy 13) Ospedale "Misericordia e Dolce", Unita' di Oncologia Medica, Dipartimento di Oncologia, Via Dolce de' Mazzamuti 7, 59100 Prato, 59100 Prato, Italy The Seattle Cancer Care Alliance (USA) received the IRB approval, but did not enroll any patient.	
Publication Reference: Bleuse J. P., Meulenbeld H. J., Vinci E. M., Raymond E., Vitali G., Santoro A., Dogliotti L., Berardi R., Cappuzzo F., Tagawa S. T., Sternberg C. N., Jannuzzo M. G., Mariani M., Petroccione A., De Wit R.. Randomized phase II study of danusertib (D) in second-line metastatic castration-resistant prostate cancer (CRPC). Proceeding of Annual Meeting Am. Soc. Clin. Oncol., 2011, J Clin Oncol 29: 15s, 2011. Abstr. 4628.	

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Studied Period (Years): Date of First Subject Enrolled: 31 October 2007 Date of Last Subject Completed: 09 March 2011	**Phase of Development:** Phase II

Objectives:

Primary:

To assess the antitumor activity of PHA-739358 administered as IV infusion according to two different dose schedules in metastatic HRPC patients progressing on standard, docetaxel-based, 1st-line chemotherapy for HRPC based on PSA response rate and to select the best dose schedule for further investigation.

Secondary:

To further assess the antitumor activity of PHA-739358 based on objective tumor response, PSA reduction, PSA velocity, and time related end-points (duration of PSA response, progression-free survival).

To assess PHA-739358 palliative effects on tumor pain.

To assess the safety and tolerability of the two PHA-739358 schedules tested in the target population.

Methodology: This was a Phase II, multi-center, non comparative, open-label, randomized study of PHA-739358 in adult patients with metastatic HRPC progressing on/after 1st line docetaxel based chemotherapy for HRPC. As PSA response to 1st line chemotherapy had shown to be predictive of PSA response to 2nd line chemotherapy, randomization was stratified according to PSA response to 1st line docetaxel based therapy (50% decrease or more vs less than 50%). The study consisted of two stages.

PHA-739358 was to be administered intravenously, in the 1st stage of the study, according two dose schedules: Arm A, 330 mg/m^2 administered as 6-h IV infusion on Days 1, 8, and 15 of a 28-day cycle and Arm B, 500 mg/m^2 administered as 24-h IV infusion on Days 1 and 15 of a 28-day cycle. At completion of the 1st stage the best PHA-739358 schedule was to be selected for proceeding to the 2nd stage based on the observation of the number of PSA responses required to proceed (at least 3 out of 29 patients per arm) and taking into consideration treatment effect on other efficacy and safety secondary end-points.

Safety assessments (vital signs, hematology, blood chemistry, and urinalysis) were to be performed at baseline and repeatedly at different time points during the treatment period, depending on the parameter, and at the end of treatment. To monitor cardiac events, a 12-lead electrocardiogram (ECG) was to be performed at baseline visit and on treatment if clinically indicated. A Trans Thoracic Echocardiogram (TTE) was scheduled at pre-treatment visit to document left ventricular ejection fraction (LVEF). Patients showing LVEF value < 35% had to undergo a confirmatory multi gated acquisition (MUGA) scan. 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 an alternative anticancer therapy was started.

Efficacy assessments were to be based on PSA evaluation, tumor imaging assessments (bone scan, X-ray, CT scan, MRI), tumor pain, analgesic consumption and ECOG performance status (PS) assessment. Variations of tumor pain, analgesic, and PS scores during treatment were considered for the evaluation of the clinical benefit.

During the course of the trial two amendments were submitted to the ECs/IRBs of the investigational sites and implemented. The main purposes were the following:

Amendment No.1 (05 October 2007) was issued to include additional LVEF assessment in the 2nd stage of the study for patients randomized to received mitoxantrone plus prednisone. LVEF measurement were to be done, before each new mitoxantrone administration, in all patients who had already received a total cumulative dose

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of at least 100 mg/m^2.

Amendment No. 2 (10 April 2008) was implemented:
- to modify the definition of progression by including among the events indicative of clinical progression the need of radiotherapy for bone pain palliation;
- to recommend that in patients randomized to the 24-h infusion schedule, PHA-739358 was administered through a central line due to several reactions at site of injection (phlebitis) using peripheral lines;
- to take into consideration the new recommendation of the Prostate Cancer Clinical Trials Working Group (J Clin Oncol. 2008; 26:1148-1159) as follows: the definition of PSA progression had to be considered as an increase by 25 % or more (instead of 50 % increase); PSA increase had to represent at least 2 ng/mL (instead of 5 ng/mL) above the nadir value;and the treatment had to be continued for at least 12 week (in the absence of any other evidence of disease progression); bone scan and other tumor imaging assessments (e.g. CT, MRI, X-Ray, etc.) were to be performed every 12 weeks (instead of every 8 weeks).

Number of Subjects (Planned and Analyzed): At first stage 29 evaluable patients were required for each randomized schedule, for a total of 58 evaluable patients. If 3 or more responses had been observed out of 29 patients, the schedule had to be considered sufficiently active to enter the second stage of evaluation. At the second stage, further 27 evaluable patients were required for a total of 56 patients treated with the selected PHA-739358 schedule. At the end of the trial if 9 or more responses had been observed with the selected PHA-739358 dose/schedule out of 56 patients, the compound would have been considered sufficiently active to warrant further investigation. Considering, in the second stage of the study, a randomization 1:1 of patients to either the PHA-739358 dose/schedule selected or the control arm, the number of patients in the control group was estimated to be 27. Based on the above, the maximum number of evaluable patients required was 112. Considering a 5% rate of non evaluability, the sample size was extended to 118 subjects.

Diagnosis and Main Criteria for Inclusion:
Adult (age ≥ 18 years) male patients with histologically confirmed diagnosis of adenocarcinoma of the prostate classified as metastatic (stage D3 according to Jewett Staging System) and hormone-refractory disease, progressing after 1st line docetaxel-based chemotherapy. For patients with measurable disease, progression was to be defined by RECIST criteria. For patients without any measurable disease, appearance of new bone lesions at bone scan and PSA progression, according to recommendation from Prostate-Specific Antigen Working Group, was to be required. Other main selection criteria included: patients receiving corticosteroids requested for concomitant disease other than HRPC had to continue treatment at the same dose; patients receiving bisphosphonates therapy had to be on stable doses for at least 4 weeks with stable symptoms prior to enrollment (modified, as per Amendment No. 2, as follows: Patients receiving bisphosphonates therapy had to be on stable doses for at least 4 weeks); patients who had not undergone surgical castration had to continue on primary androgen deprivation with LHRH analogue, if any, and testosterone had to be < 50 ng/dL; prior radiotherapy was allowed provided that no more than 25% of bone marrow reserve had been irradiated and a minimum of 4 weeks had elapsed between the end of prior radiotherapy and the entry into the trial; ECOG-PS score: 0-2; life expectancy of at least 3 months; resolution of all acute toxic effects (excluding alopecia) of any prior surgery, radiotherapy, radio-surgery or chemotherapy to NCI CTC (Version 3.0) Grade ≤ 1; adeguate baseline laboratory data (Absolute Neutrophils Count, platelets , hemoglobin, serum creatinine, serum albumin, total serum bilirubin, AST/ALT, ALP); signed and dated informed consent; willingness and ability to comply with scheduled visits, treatment plan, laboratory tests and other study indications or procedures.
Patients with any the following were to be excluded: current enrollment in another therapeutic clinical trial,

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use of other investigational drugs within 30 days prior to treatment, more than one prior chemotherapy line, known brain or leptomeningeal disease, other prior malignancy (except for adequately treated basal or squamous cell skin cancer or superficial bladder cancer), any other cancer from which the patient had been disease-free for 5 years or greater, prior treatment with radiopharmaceuticals (e.g. Strontium-89, Samarium-153) within 8 weeks prior to enrollment, major surgery (within 4 weeks or not fully recovered prior to Day 1), refusal to avoid fathering a child during the study and in the following 3 months after the end of the treatment, uncontrolled hypertension with blood pressure exceeding 160/100 mmHg (Stage 2 hypertension according to the JNC 7/ NIH USA 2003 guideline), significant cardiovascular diseases including cardiac dysrhythmias (Grade ≥ 2) or major thrombolic event occurred in the last 6 months, known active infections, including HIV positive, history of allergic reactions to a similar structural compound, biological agent, or formulation, other severe acute or chronic medical or psychiatric condition or laboratory abnormality that might have increased the risk associated with study participation or study drug administration or might have interfered with the interpretation of study results.

Test Product, Dose and Mode of Administration, Batch Number: PHA-739358 was dosed based on the patient's body surface area. In Arm A, PHA-739358 was administered at the dose 330 mg/m^2 as a 6-h IV infusion on Days 1, 8 and 15 of a 28-day cycle. In Arm B, the compound was administered at the dose of 500 mg/m^2 as a 24-h IV infusion on Days 1 and 15 of a 28-day cycle.
PHA-739358 batch numbers used in the study were: N0700368, N0700421, N0700493, N0800163, N0800407, N0800662, N0800884, N0900674, N0900094, N0901024, N0901424, N1000069, N1000657, N1001453 and N1001851.

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

Duration of Treatment: Each patient could remain on treatment until study completion, disease progression, withdrawal of consent, patient refusal, non compliance by the patient with protocol requirements, patient was patient loss to follow-up, compromise patient's safety due to continuation of therapy or occurrence of unacceptable toxicity. For patients in disease progression, in presence of clinical benefit, further treatment was to be administered at the discretion of the treating physician and notified to the Sponsor. Patients who had discontinued the treatment in absence of disease progression were to be followed up until documentation of disease progression or start of another anticancer therapy. For the purpose of the study, the end of the trial was defined as the time when all the protocol specified numbers of patients were fully evaluable for the primary endpoint.

Endpoints and Criteria for Evaluation:

Efficacy:

Primary endpoint was:

- evaluation of the *PSA response rate* within the first three months of treatment, defined according to the recommendations from the Prostate-Specific Antigen Working Group (J Clin Oncol 1999;17:3461-346), i.e. proportion of patients achieving at least a 50% PSA decline from baseline confirmed by a second PSA value, 4 or more weeks later.

The secondary endpoints were:

- *Duration of PSA response*, defined according to the recommendations from the Prostate-Specific Antigen Working Group, i.e. from date of first 50% PSA decline to the date of first PSA rise by 50% above the

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nadir, provided that the increase was of at least 5 ng/ml or back to the baseline and modified as per the new guidelines (J Clin Oncol. 2008; 26:1148-1159), i.e. from date of first 50% PSA decline to the date of first PSA rise by 25% above the nadir, provided that the increase was at least 2 ng/ml or back to the baseline;

- *30% PSA reduction*, defined as proportion of patient achieving at least a 30% PSA decline from baseline confirmed by a second PSA value, 4 or more weeks later;
  PSA velocity, defined as the rate of change in PSA levels during the first 3 months of treatment (J Natl Can Inst. 2006; 98:516-521);
- *Progression Free Survival (PFS)*, defined as the time from the date of randomization to the date of first documentation of progression, or of death due to any cause, whichever came first. Progression of disease was defined as any of the following:
  - For patients with measurable disease, progression was defined by RECIST criteria (J Natl Can Inst. 2000; 92:205-216);
  - For patients without any measurable disease, progression was defined by either appearance of one or more new lesion outside the bone or two or more new bone lesions at bone scan or one new lesion at bone scan associated to PSA progression according to recommendations from the Prostate-Specific Antigen Working Group;
  - In the absence of objective signs of progression (based on PSA and/or imaging as defined above) clinical progression had to be substantiated by at least one of the following:
    - 2-point increase of analgesic score measured on a 5-point analgesic scale (Oncology 2005; 68:2–9) compared to the lowest score attained (at baseline or on treatment) lasting 2 weeks or more;
    - 3-point increase of pain score on a 10-point pain numerical rating scale (National Comprehensive Cancer Network. Clinical Practice Guidelines in Oncology™. Adult Cancer Pain.V.1. 2006) compared to the lowest score attained (at baseline or on treatment), lasting 2 weeks or more;
    - 2-point worsening (increase) of ECOG Performance Status (PS) lasting 2 weeks or more compared to the lowest score attained (at baseline or on treatment), lasting 2 weeks or more;
    - occurrence of clinical events consistent with disease progression including spinal cord compression, pathologic fracture or (added as per Amendment No. 2) requirement of radiotherapy for bone pain palliation;
- *Objective tumor response rate*, defined as the proportion of patients with measurable disease at baseline achieving complete or partial overall best response according to RECIST criteria.
- *Clinical benefit rate*, defined as the proportion of patients with pain score ≥ 2 on a 10-point pain intensity scale and/or analgesic score ≥ 1 on a 5-point analgesic scale at baseline achieving a clinical benefit defined as:
  - a ≥ 2-point decrease of pain score during treatment accompanied by stable or reduced analgesic score as compared to baseline lasting at least 2 weeks

  or

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- a ≥ 1-point decrease of analgesic score accompanied by stable/ reduced pain score as compared to baseline lasting at least 2 weeks

and

- ECOG-PS score unchanged or decreased vs baseline.

Safety: 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.
The frequency of dose delays/reductions due to treatment related toxicities was to be used as an additional parameter to evaluate schedule tolerability.

Statistical Methods:
All randomized subjects who actually had received at least one treatment dose, with treatment assignment designated according to the actual treatment received were to be considered as "treated population". This population was to be analyzed for patient disposition, all baseline characteristics and for the analysis of treatment administration. Treated patients with documented PSA progression at study entry, without any major protocol violations, with a baseline and at least two post baseline PSA assessments, the first of them within 3 months from treatment start, were to be considered as **"**evaluable population" for the analyses of PSA primary and secondary endpoints. Treated patients with at least 1 on treatment safety assessment were to be considered as "safety population".
Consistently with the study design, no comparative analyses were to be performed to detect a statistical difference between arms. Each output display, summary statistic and analysis was to be performed broken down by schedule/treatment arm and overall where applicable.
Violation of eligibility criteria at study entry and major on study deviations were to be identified and documented. Reasons for non evaluability were also to be displayed. Frequency distribution of treated patients according to treatment duration and reasons for stopping treatment was to be provided by treatment arm.
Baseline characteristics were to be analyzed by frequency distributions for the categorical/categorized variables and summary statistics including mean, standard deviation, median, minimum and maximum for the quantitative variables. Individual data were to be presented in listings.
Treatment administration was to be summarized in terms of treatment duration, number of administered cycles, total administered dose, absolute and relative dose intensity, dose modifications and delays.
Descriptive statistics of dose intensity were to be calculated on a per-patient basis (i.e. considering the whole study treatment period of each patient). Delayed cycles, dose reductions and reasons for deviations were to be described.

SUMMARY OF RESULTS:
The present study consisted of two subsequent stages. The results here below reported concern 81 patients treated in the 1st stage of the study, since the second stage was not activated.
Disposition of Subjects and Baseline Characteristics:
Eighty-eight patients were randomized and 81 treated, 43 according to the PHA-739358 6-h IV schedule (Arm A) and 38 according to the 24-h IV schedule (Arm B). Overall 7 patients were randomized but never treated, 2 in Arm A and 5 in Arm B. At the time of the database lock (09 March 2012), the trial was completed. At study entry all patients had metastatic disease, and the majority of them (60.5% of patients in Arm A and 52.6% in Arm B) presented lesions both in bone and in other organs (mainly lymph nodes). Liver metastasis were present in patients treated in Arm A only (18.6%). The majority of treated patients (81.4% in Arm A and

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84.3% in Arm B) showed a high Gleason score (≥7), indicating the high aggressiveness of tumor and consequently a worse patient prognosis. High level of serum PSA (>20 ng/mL) were detected in 90.7% of patients in Arm A and 100.0% in Arm B. The majority of patients at baseline required at least one analgesic therapy (60.5% of patients in Arm A and 53.5% in Arm B) and 32.6% of patients in Arm A and 39.5% in Arm B required daily narcotic analgesics and were classified with analgesic Score 4. At baseline corticosteroids and biphoshonates use was higher in Arm A than in Arm B: 53% of patients in Arm A and 42.1% in Arm B were on treatment with corticosteroids, while patients treated with biphosponates were 46.5% in Arm A and 31.6% in Arm B.

The most frequent reason for treatment discontinuation for both arms was disease progression (72.1% in Arm A and 78.9 % in Arm B). Treatment was discontinued due to AE in 18.6% of patients in Arm A and 7.9% in Arm B and as per Investigator's decision in 4.7% of patients in Arm A and 7.9% in Arm B.

The mean age at study entry was 68.3 years in Arm A and 67.9 in Arm B, being 76% of patient 65-year-old or above in both arms. All patients were of white race in Arm A; 92.1% and 2.6% were of white and black race, respectively, in Arm B; for 2 patients in Arm B race was not reported. In Arm A, ECOG-PS scored predominantly 1 (55.8%), while, in Arm B, an equal number of patients had ECOG-PS score 0 or 1 (47.4% each). Weight and height were within the limits of normality.

PHA-739358 was dosed based on the patient's body surface area. The intended dose intensity for the two schedules was equivalent, being 247.5 and 250.0 mg/m^2/week for Arm A and B, respectively. In Arm A, the 43 treated patients received a total of 113 cycles. The median number of cycles per patient was 2 (range 1-8). Twenty-five out of 43 (58.1%) patients received >1 cycle of treatment. The median treatment duration was 8.43 weeks (range 0.14-37.14). In Arm B, the 38 treated patients received a total of 164 cycles. The median number of cycles per patient was 3 (range 1-33). Twenty-eight out of 38 (73.7%) patients received >1 cycle of treatment. The median treatment duration was 9.93 weeks (range 0.14-132.14). Exposure was lower in Arm A than in Arm B, as evidenced by the recorded dose intensity corresponding to 74% and 86% of the as per protocol intended weekly dose, respectively. Treatment modifications, mainly dose delays and dose omissions were more frequent in Arm A (118 events in 37 patients) than in Arm B (66 events in 28 patients), involving a total of 84 out of 113 Cycles (74.3%) in Arm A, and a total of 60 Cycles out of 164 in Arm B (36%). Considering the occurrence of treatment delays, 92 in Arm A vs 58 in Arm B, the Arm B schedule seems to be better tolerated than the Arm A one. Treatment delays were mainly due to hematologic toxicity (50 cases in Arm A vs 19 cases in Arm B), being uncomplicated neutropenia the most frequent reason for delay in both tested arms.

Efficacy Results:
Overall 60 out of 81 treated patients were evaluable for the primary endpoint represented by PSA response (≥50% PSA decrease). Two patients only, one for each arm (1 out of 31 evaluable patients in Arm A and 1 out of 29 in Arm B), both responder to prior docetaxel therapy, achieved a confirmed PSA response, lasting 8.29 and 33.57 weeks, respectively. An additional patient randomized in Arm B had on treatment a confirmed PSA reduction ≥ 30%. The number of patients achieving a PSA response was insufficient to activate the second stage of the study in both schedule tested.

No objective tumor response was reported. Disease stabilization was the best overall response observed. Considering the treated patients with at least one on treatment tumor assessment, disease stabilization was reported by 8 out of 31 patients treated in Arm A (25.8%) and 13 out of 30 patients in Arm B (43%). Clinically relevant disease stabilizations (lasting ≥6 months) were reported in 4 out of 31 patients in Arm A

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(12.9%) and 7 out of 30 patients in Arm B (23.3%).

Is noteworthly that 3 patients treated in Arm B, all responder to prior docetaxel based therapy and with metastatic disease localized in the bone, showed a remarkable disease stabilization lasting more than 20 months. Two of them after PHA-739358 administration showed a PFS value considerably higher than the one obtained after the last docetaxel therapy (20.73 *vs* 12.02 months and 10.71 *vs* 30.69 months, respectively), and the third one showed a PFS value similar to that obtained after previous docetaxel therapy (i.e. 20.57 *vs* 21.65 months). Moreover one of these, who also achieved a confirmed PSA response, remained disease free more than 1 year after receiving the last treatment dose.

Four patients, 1 in Arm A and 3 in Arm B, all not responder to prior docetaxel based therapy, had a clinically relevant disease stabilization lasting more than 6 months.

In the treated patient population an interesting PFS (median value 12.0 weeks) was reported for both arms. In particular, PFS ranged from 1.43 to 40.00 weeks in Arm A and from 1.29 to 133.43 weeks in Arm B, with a median value of 12.14 weeks in Arm A (95% C.I. 10.86-15.14) and 12.00 weeks in Arm B (95% C.I. 10.29-17.00).

In the subset of patients evaluable for clinical benefit (overall 52 patients, 64.2%), 6 out of 28 (21.4%) in Arm A and 4 out of 24 (16.7%) in Arm B showed on treatment a confirmed improvement of pain and/or analgesic score, associated to stable or reduced ECOG-PS.

Safety Results:
All treated patients (43 in Arm A and 38 in Arm B) were evaluable for safety and all of them experienced at least 1 treatment emergent adverse event in the first or subsequent cycles.

Overall PHA-739358 safety profile, known from the previous clinical experience in solid tumors and hematological malignancies, is confirmed with both schedules tested and no new target organ toxicities emerged.

Mielotoxicity represented the main toxicity independent from the treatment schedule used and consisted in neutropenia (91.4%) leukopenia (58.0%), anemia (51.9%), lymphocytopenia (46.9%) and thrombocytopenia (12.3%). The incidence and severity of neutropenia was slightly higher in Arm A (95.3%, 55.8% Grade 3-4) than in Arm B (86.8%, 47.4% Grade 3-4). The incidence of anemia was higher in Arm B than in Arm A (60.5% vs 44.2%) being Grade 3-4 events more frequent in Arm A (11.6% vs 7.9%). Overall neutropenia complicated by fever was observed in 4 cases (2 per arm).
For both arms the percentage of Grade 3-4 anemia was slightly higher than the one reported in Phase I studies in patients with solid tumors treated with the same schedules also at higher dose intensity.

The most frequently reported non hematologic adverse events (i.e. occurring in ≥ 20% of patients) were nausea, fatigue/asthenia, diarrhoea, pyrexia, constipation, anorexia, vomiting, and tumor related pain. Nausea, diarrhoea, fatigue/asthenia and anorexia were reported as drug-related adverse events in ≥ 20% of patients. Mild to moderate in severity drug related nausea and diarrhoea were more frequently observed in patients treated in Arm B (as already reported in the phase I study in solid tumors with the same schedule) while anorexia was more frequent in Arm A. Fatigue/asthenia were observed with the same frequency in both treatment arms.
CTC Grade 3-4 drug-related events were more frequently reported in Arm A and consisted in fatigue/ asthenia (6 cases), febrile neutropenia (2 cases), anorexia, hypertension, dyspnoea, liver function tests abnormal (2 cases each), nausea, stomatitis, metabolic acidosis, night sweats and pneumonia (1 case each). In Arm B

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fatigue/asthenia and febrile neutropenia were observed in 2 cases each, and constipation, alanine aminotransferase increased and disseminated intravascular coagulation in one case each. No Grade 5 drug-related events were reported.

Blood chemistry abnormalities were mostly of Grade≤ 2 except for elevations in ALP, creatinine and γGT, and sporadic cases of alterations in blood electrolytes. The alterations were mainly due to worsening of underlying disease. Liver function abnormality (2 cases, Arm A, already present at baseline as Grade 1-2), and ALT increase (one case, Arm B) were reported as Grade 3-4 drug-related AEs.

As far as BP is concerned, all the recorded hypertensive episodes were classified as mild to moderate in severity except for three Grade 3 events, probably related to study drug. These events were observed in 2 patients in Arm A, confirming that sporadic hypertensive episodes may occur with treatment schedules characterized by short time of infusion.

During treatment no clinically relevant abnormalies in ECG tracing were observed in both arms. However 3 patients in Arm A and 4 in Arm B had ECG tracing alterations reported as clinical adverse events, being only one of them (namely Grade 1 bradycardia) considered as related to study drug.

No on treatment alterations of LVEF were observed in the treated patients with the exception of 4 patients, 2 per arm, who showed LVEF values slightly below LLN. None of the reported alterations was considered clinically relevant, and none was associated to drug-related AEs.

The Company Pharmacovigilance was notified of the occurrence of 58 SAEs in 32 out of the 81 (39.5 %) treated patients. Twenty-one SAEs (out of 58) were consided drug-related by the investigator and occurred in 15 patients. Among them, an unexpected event reported as probably drug related by the Investigator, was one episode of DIC occurred in one patient (Arm B) who died due to pneumonia later on, during the recovery period of the episode of DIC. It is known from the literature that DIC may occur secondary to prostate adenocarcinoma, representing the most frequent coagulation disorder in this setting, and may develop as a manifestation of advanced disease. To note that this patient had a remarkable PSA increase during the screening period (from 600 to 1164 ng/mL) associated to heavy lymph node involvement suggesting a worse prognosis.
An additional patient (Arm A) who had during Cycle 1 a SAE possibly related to study drug (namely renal failure, metabolic acidosis, liver function test increase and dispnea), actually presented at study entry an advanced stage of the disease with metastasis involving bone, lung and lymph nodes and a PSA value of 190.6 ng/mL, that increased to 334.8 ng/mL during Cycle 1.

Overall one death on study (i.e. occurring from patient's consent up to 28 days after the last treatment dose) was reported: one patient (71 years, randomized to Arm B) died due to pneumonia, unlikely related to study drug, 12 days after receiving the first Cycle 1 dose of PHA-739358.

CONCLUSIONS:
In conclusion, the safety profile observed is consistent with the previous experience with the drug in patients with other malignancies. No new toxicities were observed with the only exception of one episode of DIC in one patient who went on to develop febrile neutropenia and later pneumonia during the recovery period of the episode of DIC. In this study there was a higher incidence of neutropenia in patients treated in Arm A and the schedule administered to Arm B appeared to be better tolerated. Nevertheless, it cannot be ruled out that the patients in Arm A were at higher risk due to the presence of liver metastasis (absent among patients in Arm B), and the concomitant use of therapy with glucocorticoids and bisphophonates compared to patients in Arm

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B. Mild to moderate in severity drug related gastrointestinal toxicities, were more frequently observed in patients treated in Arm B, as already observed in the phase I study in solid tumors with the same schedule. In spite of the poor response in term of PSA decrease, the interesting PFS and the number of long lasting disease stabilizations (some of which lasted longer than on previous docetaxel and others observed in patients who had not responded to previous docetaxel treatment) may warrant further investigation in this patient's population. Development of specific biomarkers predictive for response may enable selecting patients who could potentially benefit of PHA-739358 treatment.. Development of specific biomarkers predictive for response may enable selecting patients who could potentially benefit of PHA-739358 treatment.	
Date of the Report: 30 March 2012	