# CLINICAL STUDY PROTOCOL 13-033

## ALISERTIB (MLN8237)

***A Phase II, Multicenter, Randomized, Parallel Group Study to Compare Alisertib in Combination with Paclitaxel vs. Paclitaxel Alone in Patients with Metastatic or Locally Recurrent Breast Cancer***

**Protocol Number:** 13-033

**Indication:** Breast Cancer
**Phase:** II
**Sponsor:** Delta Clinical Research, LLC
**Therapeutic Area:** Oncology

**Protocol History**
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**CONFIDENTIAL**

# PROTOCOL SUMMARY

**Study Title:** A Phase II, Multicenter, Randomized, Parallel Group Study to Compare Alisertib in Combination with Paclitaxel vs. Paclitaxel Alone in Patients with Metastatic or Locally Recurrent Breast Cancer

**Phase:** 2

**Objectives**

The primary objective of this study is:

- To demonstrate the superiority of alisertib plus paclitaxel compared with paclitaxel alone in progression-free survival (PFS) in two cohorts of patients with metastatic or locally recurrent breast cancer, one with Estrogen Receptor-positive (ER+), Human Epidermal Growth Factor Receptor 2-negative (HER2-) disease and the other with triple-negative (TN) disease

The secondary objectives of this study are:

- To assess the safety of alisertib combined with paclitaxel
- To compare the objective response rates (ORR; complete response [CR] plus partial response [PR]) between the two treatment arms in each of the two cohorts
- To compare the clinical benefit rate (CBR; CR + PR + stable disease [SD] ≥6 months) between the two treatment arms in each of the two cohorts
- To assess overall survival (OS) in each of the treatment arms in each of the two cohorts
- To perform genomic profiling of patients' archived primary breast cancer tissue to identify potential predictive markers for benefit from alisertib plus paclitaxel

**Patient Population**

Women (≥18 years) with ER+/HER2- (Ki67 ≥15%) or with poorly differentiated and/or Grade 3 triple-negative (TN) locally advanced or metastatic breast cancer previously treated with 0-1 chemotherapy regimens for advanced disease. An Eastern Cooperative Group (ECOG) Performance Status of 0-1 and adequate organ function are required. Eligible patients must have measurable disease by Response Evaluation Criteria in Solid Tumors (RECIST v1.1) criteria, or lytic or mixed blastic/lytic bone-only disease. Patients with untreated or progressing brain metastases, or those that require corticosteroids, are not eligible. Additional inclusion and exclusion criteria are detailed in section 3.2 and section 3.2.3, respectively.

**Number of Patients**

252

**Study Design and Methodology**

Randomized parallel group study; 2 patient cohorts

**Duration of Study**

An accrual rate of 12-15 patients per month is anticipated with a similar distribution between cohorts; thus the accrual phase will be approximately 24 months. The last patient will be followed for approximately 12 months after enrollment, until disease progression or treatment-limiting toxicity occurs. Therefore the anticipated total length of the study is approximately 36 months.

**Treatments Administered**

Patients will be randomized to receive either Paclitaxel 60 mg/m$^2$ intravenously (IV) on days 1, 8 and 15 plus Alisertib 40 mg BID on days 1-3, 8-10, and 15-17 of a 28-day cycle or single-agent Paclitaxel 90 mg/m$^2$ IV on days 1, 8 and 15 of a 28-day cycle.

**Efficacy Data Collected**

The following evaluations will be conducted to assess the efficacy of alisertib plus paclitaxel:

- Tumor response will be assessed locally according to RECIST Version 1.1. The local investigator's assessment will be used for all endpoint analyses and for treatment decision making.
- The following imaging assessments will be performed:
    - Computed tomography (CT) of chest, abdomen, and pelvis at screening. Chest and abdominal CT imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment. Pelvic imaging will be continued at subsequent tumor assessments only if pelvic metastases are identified at screening.
    - A whole body Tc-99 bone scan at screening for bone lesions. If bone lesions are present at screening, bone scans will be repeated every 12 weeks after initiation of treatment for the first 32 weeks of treatment and every 16 weeks thereafter for the duration of the treatment period, using the same methodology used at screening. An End of Treatment bone scan is required only if the patient has bone metastases present at screening, or has developed progressive disease in the bone during study treatment. Patients whose first follow-up bone scan is read as progressive disease may stay on study therapy if the treating physician does not think the patient's disease has progressed clinically, i.e., no new bone pain or deterioration in performance status and no progression of disease in other sites. Subsequent bone scans that are read as demonstrating progressive disease will lead to termination of study therapy.
    - A baseline brain MRI at screening is only required for patients with a documented history of treated brain metastases (CT is allowed if MRI is contraindicated). A baseline brain MRI or CT scan is not required if

patients do not have a documented history of brain metastases. Brain MRI or CT will be obtained at each tumor assessment for patients with previously treated brain metastases. Imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. An End of Treatment Brain MRI or CT is required only for patients with historically treated brain metastases present at screening, or have developed brain metastases as part of their progressive disease during study treatment.

- Skin lesions, if present, will be documented at screening using a digital camera (color photography). Skin photographs will be continued at subsequent tumor assessments for any lesions that were photographed at screening. Skin lesions assessments should be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. An End of Treatment Skin lesion assessments is required only for patients with a documented history of skin lesions, or for patients who developed skin lesions as part of the progressive disease during study treatment.

**Correlative Studies**

The following studies will be conducted to assess molecular biomarkers potentially associated with benefit from alisertib plus paclitaxel:

- FFPE tissue from study patients' primary breast cancers will be retrospectively analyzed for potential biomarkers including, but not limited to expression of FOXM1 and AURKA, p53 mutation status, and degree of genomic instability.

**Safety Data Collected**

The following evaluations will be conducted to assess the safety of alisertib plus paclitaxel:

- Monitoring and recording of all adverse events and serious adverse events; regular monitoring of hematology, blood chemistry, regular measurement of vital signs, physical examination (including weight); and performance status.

- All patients who receive at least one dose of study drug will be evaluated for safety. Toxicities will be graded and reported according to the NCI CTCAE Version 4.03. Incidence and type of adverse events will be tabulated and summarized using descriptive statistics.

**Statistical Procedures**

Using a 2-stage sequential design, assuming that the addition of alisertib to paclitaxel will increase the median PFS time from 3.5 to 5.8 months and from 6 to 10 months in TN and in ER+/HER2- patients, respectively, 112 TN and 140 ER+/HER2- patients will be randomized to alisertib/paclitaxel or paclitaxel alone arms to detect a hazard ratio (HR) of

0.6.

PFS and OS will be analyzed using the Kaplan-Meier method and the stratified logrank test. A Cox proportional hazard model will be performed to assess the potential prognostic factors. ORR and clinical benefit rate (CBR) will be examined using univariate and multivariate approaches with the Fisher's exact tests and the logistic regression models. Toxicity will be reported using the NCI CTCAE Version 4.03 and tabulated by numbers and frequencies for all study related adverse events. Dose modifications will also be tabulated in the same way.

An interim analysis will be performed when the event number reaches 34 for the TN cohort. For the ER+/HER2- cohort, an independent interim analysis will be performed when there have been 23 events.

A Bayesian continuous interim monitoring rule will be applied to evaluate the probability of a 30% toxicity rate in the experimental arm and accrual will be halted if there is high probability of more than a 30% toxicity rate, where toxicity is defined as two or more delays and/or reductions due to toxicity in the first two cycles. The monitoring rule will be applied continuously after the first five patients are randomized to this arm. The statistical considerations section contains more details including the operating characteristics and stopping boundaries.

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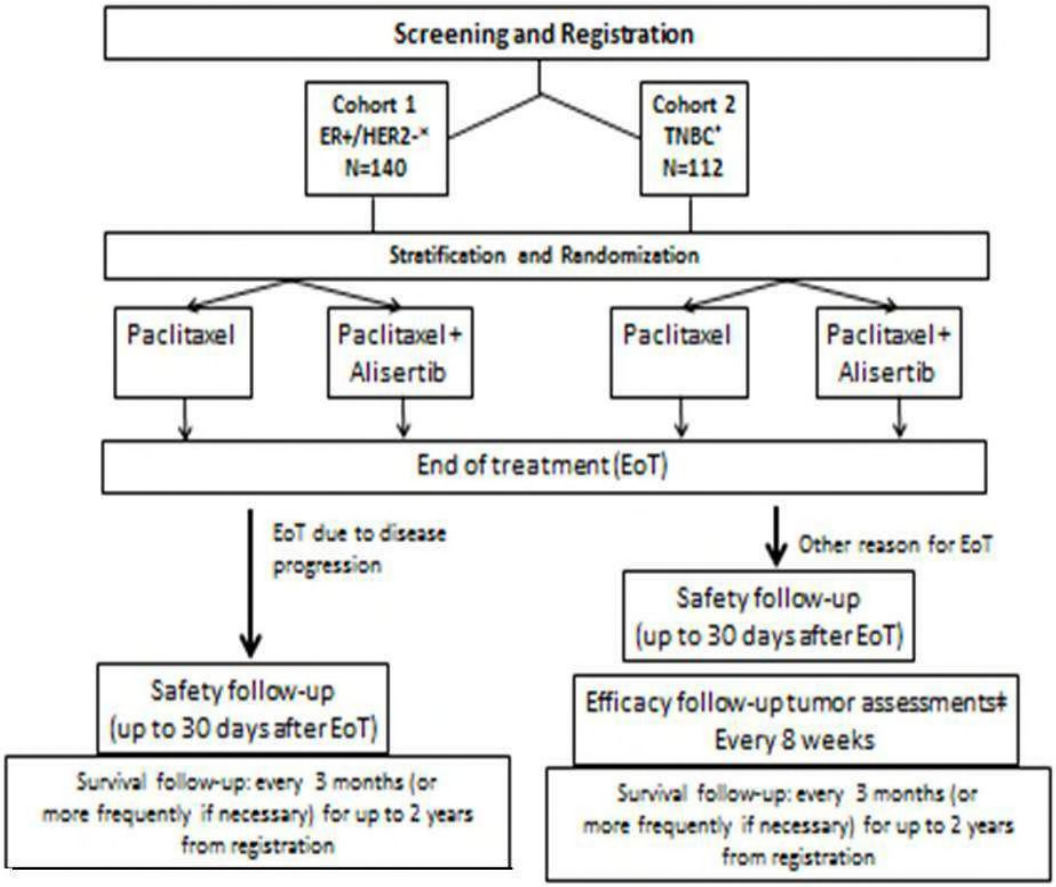
## LIST OF IN-TEXT TABLES

# Study Flow Diagram




*Invasive locally advanced or metastatic breast cancer; ≤1 prior chemotherapy regimen for advanced disease.
+Locally advanced or metastatic breast cancer; ≤1 prior chemotherapy regimen for advanced disease.
‡Efficacy follow-up tumor assessment will be performed on all patients except patients who progress.

# Key Study Definitions

| ***Term*** | ***Definition*** |
|---|---|
| Baseline assessment | The assessment performed at the closest time before initiation of study drug administration. |
| Study drug | The term study drug is used in this protocol to represent alisertib (MLN8237). |
| Progression-free survival | Time from randomization to the date of first documented disease progression by RECIST (v1.1), or death from any cause, or last contact date. |
| Overall survival | Time from randomization to death from any cause. |

Abbreviations: RECIST = Response Evaluation Criteria In Solid Tumors

# Schedule of Events

| Evaluation and Visit Schedule | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening phase | Treatment phase[j] 28-Day Cycle (Day 22 begins rest week) | | | | | | | | | Post-treatment follow up phase | Survival phase |
| Cycle[a] | | Cycle 1[k] | | | Cycle 2[k] | | | Subsequent Cycles[k] | | | EOT | Endpoint (safety and efficacy) follow up | Survival follow up (every 3 months)[b] |
| Days | -28 to -1 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |
| Obtain study Informed Consent and HIPPA | X | | | | | | | | | | | | |
| Demography | X | | | | | | | | | | | | |
| Inclusion/ exclusion criteria | X | | | | | | | | | | | | |
| Pregnancy Test[c] | X | As clinically indicated | | | | | | | | | | | |
| ER, PgR and HER2 status | X | | | | | | | | | | | | |
| Ki67 status[d] | X | | | | | | | | | | | | |
| Complete medical history/current medical conditions | X | | | | | | | | | | | | |
| Diagnosis and extent of cancer | X | | | | | | | | | | | | |
| Prior antineoplastic therapy (surgery, medication, radiotherapy) | X | | | | | | | | | | | | |
| Physical examination | X[i/h] | X[i/h] | | | X[i/h] | | | X[i/h] | | | X[l] | | |

| Evaluation and Visit Schedule | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening phase | Treatment phase[j] 28-Day Cycle (Day 22 begins rest week) | | | | | | | | | | Post-treatment follow up phase | Survival phase |
| Cycle[a] | | Cycle 1[k] | | | Cycle 2[k] | | | Subsequent Cycles[k] | | | EOT | Endpoint (safety and efficacy) follow up | Survival follow up (every 3 months)[b] |
| Days | -28 to -1 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |
| Brief medical history | | X | | | X | | | X | | | | | |
| Performance status (ECOG) | X | X[i] | | | X[i] | | | X[h] | | | X[l] | | |
| Height | X | | | | | | | | | | | | |
| Weight | X | X | | | X | | | X | | | X[l] | | |
| Vital signs | X | X | | | X | | | X | | | X[l] | | |
| Hematology (CBC) | X | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X[e] | X | | |
| Serum chemistry (CMP) | X | X[f] | | | X[f] | | | X[f] | | | X | | |
| CT (Chest, Abdomen, Pelvis) | X[n] | X[n] Performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. | | | | | | | | | X[n] | X[n] | |
| Brain MRI | X[g] | X[g] Performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. | | | | | | | | | X[g] | X[g] | |
| Whole body Tc-99 bone scan | X[o] | X[o] Performed every 12 weeks after initiation of treatment for the first 32 weeks of treatment and every 16 weeks thereafter for the duration of the treatment period. | | | | | | | | | X[o] | X[o] | |

| Evaluation and Visit Schedule | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Screening phase | Treatment phase[j] 28-Day Cycle (Day 22 begins rest week) | | | | | | | | | | Post-treatment follow up phase | Survival phase |
| Cycle[a] | | Cycle 1[k] | | | Cycle 2[k] | | | Subsequent Cycles[k] | | | EOT | Endpoint (safety and efficacy) follow up | Survival follow up (every 3 months)[b] |
| Days | -28 to -1 | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |
| Skin Lesions | X[p] | X[p] Performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. | | | | | | | | | X[p] | | |
| RECIST Version 1.1 | X[q] | X[q] Performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment. | | | | | | | | | X[q] | X[q] | |
| Antineoplastic therapies since discontinuation of study treatment | | | | | | | | | | | | X | X |
| Alisertib administration | | Days 1-3, 8-10, and 15-17 of each 28-day cycle | | | | | | | | | | | |
| Paclitaxel administration | | X | X | X | X | X | X | X | X | X | | | |
| Prior/ Concomitant medications | X | X | X | X | X | X | X | X | X | X | X | X (Up to 30 days after last dose of treatment) | |
| Adverse events[m] | X | X | X | X | X | X | X | X | X | X | X | X (Up to 30 days after | |

**Evaluation and Visit Schedule**

| | Screening phase | Treatment phase[j] 28-Day Cycle (Day 22 begins rest week) | | | | | | | | | Post-treatment follow up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle[a]** | | **Cycle 1[k]** | | | **Cycle 2[k]** | | | **Subsequent Cycles[k]** | | | **EOT** | **Endpoint (safety and efficacy) follow up** | **Survival follow up (every 3 months)[b]** |
| **Days** | **-28 to -1** | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |
| | | | | | | | | | | | | **last dose of treatment)** | |
| **Patient pill diary** | | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | **X** | | | |
| **Archival tissue block** | **X** | Collect and send tumor biopsy (archival FFPE blocks or slides). **One formalin fixed paraffin embedded tumor block (or 20 unstained slides if tumor block is not available)** from the primary breast cancer. | | | | | | | | | | | |
| **Survival follow up** | | | | | | | | | | | | | **X** |

Abbreviations: CT = Computed Tomography; ECOG = Eastern Cooperative Group; EOT = End of Treatment; ER = Estrogen Receptor; FFPE = Formalin-Fixed Paraffin-Embedded; MRI = Magnetic Resonance Imaging; PgR = Progesterone Receptor; WOCBP = Women of Child-bearing Potential;

[a] A complete cycle is defined as 28 days.

[b] Additional survival assessments may be performed more frequently if required. Survival follow-up will continue for up to 2 years from date of registration. There is a +/- 7 business day window for follow up visit assessments. Any delay within this window is NOT a deviation.

[c] Serum or urine pregnancy test (β-HCG) is required for all women of child-bearing potential at screening, within 3 business days prior to the first dose of paclitaxel alone or paclitaxel plus alisertib.

[d] Ki67 status should be obtained anytime before randomization. Ki67 should be documented in the eCRF for patients with ER+, HER2- MBC if testing was previously performed.

[e] CBC with differential and platelet count. CBC is to be done within 3 business days prior to scheduled dosing on Day 1 of each Cycle for both treatment arms; CBCs also need to be done on Days 8 and 15 of each cycle. Results must be known prior to dosing the patient on days when these assessments are done.

[f] Serum chemistry includes the following parameters: K+, Na+, Ca++, ALT, AST, total bilirubin, BUN, creatinine, alkaline phosphatase, bicarbonate, glucose, albumin, total protein, and creatinine clearance. CMP is to be done within 3 business days prior to scheduled dosing on Day 1 of each Cycle for both treatment arms. Results must be known prior to dosing the patient on days when these assessments are done. Calculation of creatinine clearance based on the creatinine values obtained from the CMP.

[g] A baseline brain MRI at screening is only required for patients with a documented history of treated brain metastases (CT is allowed if MRI is contraindicated). A

**Evaluation and Visit Schedule**

| | Screening phase | Treatment phase[j] 28-Day Cycle (Day 22 begins rest week) | | | | | | | | | | Post-treatment follow up phase | Survival phase |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **Cycle[a]** | | **Cycle 1[k]** | | | **Cycle 2[k]** | | | **Subsequent Cycles[k]** | | | **EOT** | **Endpoint (safety and efficacy) follow up** | **Survival follow up (every 3 months)[b]** |
| **Days** | **-28 to -1** | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |

baseline brain MRI or CT scan is not required if patients do not have a documented history of brain metastases. Brain MRI or CT will be obtained at each tumor assessment for patients with previously treated brain metastases. Imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. An End of Treatment Brain MRI or CT is required only for patients with historically treated brain metastases present at screening, or have developed brain metastases as part of their progressive disease during study treatment.

[h] Complete physical examination (including vital signs, height, oxygen saturation, performance status and body weight) must be obtained within 4 weeks prior to registration. Patients randomized to the paclitaxel and alisertib arm will be seen for Cycle 1 on days 1, 8 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only); for Cycle 2 on days 1 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only); and for Cycle 3 and subsequent cycles, patients will have a brief physical exam, review of AEs, concomitant medications, and vitals, weight, and performance status on day 1 of each cycle. Additional unscheduled visits may occur as required, such as in the case of an adverse event requiring medical attention. Patients receiving paclitaxel alone will be seen day 1 of each cycle to have a brief physical exam, review of AEs, concomitant medications, vitals, weight, and performance status.

[i] Patients receiving paclitaxel alone will have CBCs on days 1, 8 and 15 and will be seen by their oncology care provider every 28 days.

[j] Treatment must begin within 5 business days after patient registration on study, not including weekends or holidays.

[k] Cycle 1 only, the baseline values for those assessments that are done prior to cycle 1 may be used for Cycle 1 assessments as long as they are completed within 3 business days prior to the patient receiving their first dose of study drug. If more than 3 business days have elapsed since the baseline assessment, the assessment must be repeated. There is a window (up to 3 days prior to the scheduled time) for assessments during the study. Cycle 2 and subsequent cycles, there is a window of +3 days for treatment administration during the study.

[i] Up to 7 business days to complete “end of treatment” assessments following the last treatment.

[m] AEs will be collected within 4 weeks of patient starting study treatment, to include assessment of peripheral neuropathy. AEs will need to be entered into the EDC within 5 days.

[n] Computed tomography (CT) of chest, abdomen, and pelvis at screening. Chest and abdominal CT imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment. Pelvic imaging will be continued at subsequent tumor assessments only if pelvic metastases are identified at screening.

[o] If bone lesions are present at screening, bone scans will be repeated every 12 weeks after initiation of treatment for the first 32 weeks of treatment and every 16 weeks thereafter for the duration of the treatment period, using the same methodology used at screening. An End of Treatment bone scan is required only if the patient has bone metastases present at screening, or has developed progressive disease in the bone during study treatment.

| Evaluation and Visit Schedule | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | **Screening phase** | **Treatment phase[j] 28-Day Cycle (Day 22 begins rest week)** | | | | | | | | | **Post-treatment follow up phase** | **Survival phase** |
| **Cycle[a]** | | **Cycle 1[k]** | | | **Cycle 2[k]** | | | **Subsequent Cycles[k]** | | | **EOT** | **Endpoint (safety and efficacy) follow up** | **Survival follow up (every 3 months)[b]** |
| **Days** | **-28 to -1** | 1 | 8 | 15 | 1 | 8 | 15 | 1 | 8 | 15 | | | |

[p] If present, will be documented at screening using a digital camera (color photography). Skin photographs will be continued at subsequent tumor assessments for any lesions that were photographed at screening. Skin lesions assessments should be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. An End of Treatment Skin lesion assessments is required only for patients with a documented history of skin lesions, or for patients who developed skin lesions as part of the progressive disease during study treatment.

[q] Performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment. Tumor response will be assessed locally according to Response Evaluation Criteria in Solid Tumors (RECIST) Version 1.1

# LIST OF ABBREVIATIONS

| Abbreviation | Definition |
|---|---|
| °C | degrees Celsius |
| µM | micromolar |
| β-hCG | Beta human chorionic gonadotropin |
| 5-HT3 | 5-Hydroxytryptamine type 3 |
| AE | adverse event |
| ALT | alanine aminotransferase |
| ANC | absolute neutrophil count |
| ASCO | American Society of Clinical Oncology |
| AST | aspartate aminotransferase |
| AUC | area under the curve |
| AURKA | Aurora kinase A |
| BA | Bioavailability |
| BID | twice a day |
| BRCA | breast cancer gene |
| BSA | body surface area |
| BZD | benzodiazapine |
| CBR | clinical benefit rate |
| CGH | comparative genomic hybridization |
| CLIA | Clinical Laboratory Improvement Amendments |
| cm | centimeter |
| CNS | central nervous system |
| CR | complete response |
| CT | computed tomography |
| CTCAE | (NCI) Common Terminology Criteria for Adverse Events |
| CTEP | Cancer Therapy Evaluation Program |
| CTI | Clinical Trial Information |
| CTMS | Clinical Trial Management System |
| CYP | cytochrome P450 |
| DEHP | di(2-ethylhexyl)phthalate |
| dL | deciliter |
| DLBCL | diffuse large B cell lymphoma |
| DLT | dose-limiting toxicity |
| DNA | deoxyribonucleic acid |

| Abbreviation | Definition |
|---|---|
| DS&E | Drug Safety and Epidemiology |
| ECG | electrocardiogram |
| ECOG | Eastern Cooperative Group |
| eCRF | electronic case report form |
| ECT | enteric-coated tablet |
| ED | efficacious dose |
| EGFR | epidermal growth factor receptor |
| EOT | end of treatment |
| ER | estrogen receptor |
| FDA | Food and Drug Administration |
| FDG | fluorodeoxyglucose |
| FFPE | formalin fixed paraffin embedded |
| FISH | Fluorescence in-situ hybridization |
| FOXM1 | forkhead box protein M1 |
| GABAAα1 | gamma-amino butyric acid Aα1 |
| GAR | Global Alert and Response |
| GCP | Good Clinical Practice |
| GGT | gamma glutamyl transferase |
| GI | gastrointestinal |
| GLP | Good Laboratory Practice |
| H2 | histamine H2 receptor |
| HDL | high density lipoprotein |
| HDPE | high-density polyethylene |
| HER2 | human epidermal growth factor receptor 2 |
| hERG | Human Ether-à-go-go Related gene |
| HIPAA | Health Insurance Portability and Accountability Act |
| HIV | Human Immunodeficiency Virus |
| HR | Hazard Ratio |
| ht | height |
| IκB | I kappa B kinase; cytokine response kinase that activates transcription factor NF-kappa b at serine 32 and 36 |
| IB | Investigator's Brochure |
| ICAM-1 | intercellular adhesion molecule 1 |
| ICH | International Conference on Harmonisation |
| IEC | independent ethics committee |

| Abbreviation | Definition |
|---|---|
| IHC | Immunohistochemistry |
| IND | Investigational New Drug |
| IRB | institutional review board |
| IV | intravenous |
| kg | kilogram |
| Ki | inhibitory constant |
| lbs | pounds |
| LDL | low density lipoprotein |
| $m^2$ | square meters |
| MBC | metastatic breast cancer |
| mg | milligram |
| MI | mitotic index |
| min | minute |
| mL | milliliter |
| $mm^3$ | cubic millimeters |
| mmol | millimole |
| MRI | magnetic resonance imaging |
| MTD | maximum tolerated dose |
| mTOR | Mammalian Target of Rapamycin |
| NaF | sodium fluoride |
| NCI | National Cancer Institute |
| NF-κB | nuclear factor-κB |
| ng | nanogram |
| nM | nanomole |
| NYHA | New York Heart Association |
| ORR | objective response rate |
| OS | overall survival |
| p21 | p21 (ras) farnesyl-protein transferase |
| p27 | cyclin-dependent kinase inhibitor |
| p53 | tumor suppressor protein with molecular weight of 53 kDa |
| PARP | poly (ADP-Ribose) polymerase |
| PET | positron emission tomography |
| PFS | progression-free survival |
| Pgp | P-glycoprotein |

| Abbreviation | Definition |
|---|---|
| PgR | progesterone receptor |
| PIC | powder-in-capsule |
| PK | pharmacokinetic |
| PPI | proton pump inhibitor |
| PR | partial response |
| PVC | polyvinyl chloride |
| QD | once a day |
| Rb | retinoblastoma protein |
| RECIST | Response Evaluation Criteria in Solid Tumors |
| RP2D | recommended phase 2 dose |
| SAE | serious adverse event |
| SD | stable disease |
| SGOT | serum glutamic-oxaloacetic transaminase |
| SGPT | serum glutamic-pyruvic transaminase |
| TGI | tumor growth inhibition |
| Tmax | time to maximal plasma concentration |
| TN | triple negative |
| TNBC | triple negative breast cancer |
| TTP | time to progression |
| UGT | UDP-glucuronosyltransferase |
| UGT1A1 | UDP-glucuronosyltransferase 1A1 |
| ULN | upper limit of normal |
| UPN | Unique patient number |
| US | United States |
| USP | United States Pharmacopeia |
| VCAM-1 | vascular cell adhesion molecule 1 |
| w/w | weight-to-weight ratio |
| WHO | World Health Organization |
| wt | weight |
| WOCBP | women of childbearing potential |

# 1. INTRODUCTION AND STUDY RATIONALE

## 1.1 Overview of the Disease

Breast cancer is the most common malignancy in women worldwide, with incidence rates as high as 89.7 per 100,000 women.[1] Although there have been a number of important treatment advances in recent years, and overall mortality is declining due to earlier detection and more effective treatment of early stage disease, metastatic breast cancer (MBC) remains incurable and is the second leading cause of cancer deaths among women.[2]

It is now recognized that breast cancer is a heterogeneous disease, with distinct subtypes distinguished by expression of hormone receptors and human epidermal growth factor receptor 2 (HER2) as well as by characteristic gene expression profiles.[3,4] Breast cancers that express estrogen receptors (ER) or progesterone receptors (PgR) generally have the best prognosis out of all of the subtypes. They are typically sensitive to endocrine agents such as tamoxifen and aromatase inhibitors, and may respond to multiple lines of treatment with these agents in the metastatic setting; however, resistance ultimately develops and at this point, cytotoxic chemotherapy becomes the mainstay of treatment.[2]

Triple-negative breast cancer (TNBC) is defined by the absence of ER, PgR, and HER2 receptor expression. By hierarchical clustering of gene expression patterns, these cancers most often segregate with the 'basal-like' intrinsic subtype, although additional subtypes have been identified, including 'claudin-low', 'HER2-enriched with or without HER2 gene amplification', 'luminal B', 'luminal A' and 'molecular apocrine'.[5] Compared with other breast cancer subtypes, TNBC is associated with a worse prognosis, including a shorter time to recurrence in early-stage disease, and a shorter time between recurrence and death in the metastatic setting.[6] TNBC is insensitive to currently available targeted therapies (endocrine or HER2-directed agents), as would be expected by the absence of hormone or HER2 receptors, and thus, cytotoxic chemotherapy remains the foundation of treatment for patients with this subtype of breast cancer.[2] To date, although no clear molecular target has been identified and proven to have therapeutic value, a number of targeted agents have been evaluated with mixed results, including inhibitors of epidermal growth factor receptor (EGFR) and poly-(ADP-ribose) polymerase (PARP), and clinical trials are ongoing to evaluate the potential role of antiangiogenic agents and androgen receptor antagonists.[6]

For the first line cytotoxic treatment of HER2 negative (HER2-) patients with MBC, various chemotherapy agents can be used, including taxanes which are among the most active agents in BC. Single agent objective response rates (ORRs) range from 20 to 50%.[7] However,

eventually all patients will progress with a median time to progression (TTP) of 5 to 8 months. As an example of the single agent response rates, in the recent E2100[8] and AVADO[9] randomized Phase III trials in first-line HER2- MBC, the response rates were 22% and 46% and median progression-free survival (PFS) was 5.8 and 8.1 months, respectively for the paclitaxel and docetaxel control arms (single agent control arm data presented from the combination trials with bevacizumab).

Aurora Kinase A (AURKA) is a serine/threonine kinase that is important in regulating the transition from G2 in mitosis, and is itself regulated by the pro-proliferative cell cycle transcription factor FOXM1.[10,11] Genomic instability can be induced in several cancers, including breast cancer, due to increased levels of AURKA. In breast cancer, the Translational Genomics Research Institute (TGen) has performed whole genome and RNA sequencing on the metastatic cancer and normal tissue harvested from 14 patients with metastatic TNBC. Results demonstrated co-overexpression of FOXM1 and AURKA in 10 of the 14 metastatic TNBC patients, in association as well with other markers of rapid proliferation.[12] Overexpression of these genes has been validated at Caris Diagnostics using CLIA-certified array expression analysis of the patients' cancers. Another study of archival formalin-fixed paraffin-embedded (FFPE) TNBC tissue has also shown overexpression of FOXM1 and AURKA.[13] Two retrospective studies of patients with early-stage breast cancer have shown an association between AURKA expression and prognosis. In the first study, which included 122 patients with TNBC, high expression of AURKA was associated with shorter overall and recurrence-free survival compared with lower expression levels, particularly when Ki-67 expression was also high.[14] The second study found higher AURKA expression predicted for shorter metastasis-free survival in node-negative patients with ER+, HER2- breast cancer.[15]

Thus, there is a need for improved therapies for endocrine-resistant hormone receptor positive MBC as well as metastatic TNBC, and AURKA may be a therapeutic target in these patient populations.

## 1.2 Alisertib (MLN8237)

### 1.2.1 Aurora A Kinases and the Aurora A Kinase Inhibitor Alisertib (MLN8237)

Alisertib (International Proprietary Name, also known as MLN8237) is a selective small molecule inhibitor of Aurora A kinase that is being developed for the treatment of advanced malignancies. Aurora A kinase belongs to a highly conserved family of serine/threonine

protein kinases that also includes Aurora B and Aurora C. Aurora A and Aurora B are expressed in all actively dividing cells, while Aurora C expression is largely restricted to dividing germ cells.[16] Aurora A localizes to centrosomes and the proximal mitotic spindle during mitosis where it functions in a diverse set of mitotic processes.

The evidence supporting Aurora A kinase as a therapeutic target for the treatment of malignancies comes from several sources. First, the Aurora A kinase gene is amplified, overexpressed, or both in many tumors, including colon, breast, pancreatic, and bladder cancers, as well as certain lymphomas, leukemias, and myeloma.[17,18,19,20,21] Aurora A overexpression in human cancers has been correlated with increased aneuploidy and centrosome amplification.[22] Second, forced overexpression of Aurora A kinase in experimental models results in the transformation of normal cells, suggesting that Aurora A overexpression may be oncogenic.[17] Lastly, in a number of different experimental systems, Aurora A inhibition leads to mitotic delays and severe chromosome alignment and segregation defects, followed by cell death.[23,24,25,26] Overall, the essential role of Aurora A in mitotic progression and its dysregulation in certain cancers makes it an attractive therapeutic target.

Given the obligatory role of mitosis in tumor proliferation, an Aurora A inhibitor would be expected to have potential applications across a broad range of human tumors. Indeed, alisertib has demonstrated activity against a variety of nonclinical solid tumor and hematologic malignancy models grown in vitro and in vivo, as described below. Alisertib is also expected to be toxic to proliferating normal tissues, such as the bone marrow, gastrointestinal (GI) epithelium, and hair follicles because any cell that is in mitosis, where Aurora A is expressed and active, should be susceptible to the effects of an Aurora A kinase inhibitor.

## 1.3 Preclinical Experience with Alisertib

### 1.3.1 In Vitro Studies

Alisertib (MLN8237) is an ATP-competitive and reversible inhibitor of Aurora A kinase in vitro with an inhibition constant (Ki) of 0.43 nM. The data from both enzymatic and cell-based assays demonstrated that alisertib is a selective and potent inhibitor of Aurora A kinase. Alisertib inhibited proliferation of a wide variety of tumor cell lines grown in culture. Moreover, treatment of tumor cell lines with alisertib induced phenotypes consistent with Aurora A kinase inhibition, including mitotic spindle defects, mitotic delay, and apoptosis.[26, ,27,28,29] For further details, refer to the Investigators' Brochure (IB).

### 1.3.2 In Vivo Studies

Alisertib (MLN8237) demonstrated antitumor activity when administered orally on a daily basis for approximately 21 days (maximal tumor growth inhibition [TGI] > 90%) in several experimental human solid and hematologic tumor models grown as xenografts in immunocompromised mice. The maximally efficacious dose (ED) for each model varied: between 10 and 30 mg/kg if given once daily (QD) and 20 mg/kg if given twice daily (BID). Studies in the HCT-116 colon tumor model showed that less frequent dosing (eg, 5 days on followed by 5 days off) was also efficacious, demonstrating that continuous dosing is not necessary for antitumor activity. A single oral dose of alisertib given to nude mice bearing subcutaneous HCT-116 human colon tumors resulted in inhibition of activated Aurora A kinase and an increase in mitotic cells. Therefore, mitotic index (MI) can be used as a pharmacodynamic marker of alisertib in some in vivo settings. The relationship between pharmacokinetics (PK), pharmacodynamics, and efficacy was further studied in HCT-116 xenografts using oral dosing and subcutaneous osmotic mini-pumps. Both a pharmacodynamic response and efficacy (antitumor activity) were achieved using either route of administration. The data from these studies suggest that the maximum pharmacodynamic effect (mitotic accumulation) and efficacy are achieved at steady state plasma concentrations of 1 μM. Moreover, the maximally efficacious oral doses of alisertib in the HCT-116 model (30 mg/kg QD) resulted in plasma concentrations of 1 μM for 8 to 12 hours post-dose. Plasma concentrations of alisertib associated with saturating levels of pharmacodynamic and antitumor activity (1 μM) were exceeded at the recommended phase 2 dose (RP2D) of alisertib in patients (50 mg BID).

To determine whether alisertib would enhance the antitumor effects of standard of care agents in solid and hematologic malignancies, nonclinical combination studies were performed. Combination therapy with alisertib and docetaxel resulted in additive or synergistic effects during the dosing period, with prolonged tumor growth delay in multiple solid tumor xenograft models after terminating treatment. These effects were also observed in alternative intermittent dosing schedules. Combination treatment with paclitaxel in 2 xenograft models of breast cancer generally resulted in additive or synergistic antitumor activity, with tumor growth delay observed. In diffuse large B cell lymphoma (DLBCL) xenograft models, combination therapy with alisertib and rituximab resulted in synergistic, additive, or subadditive effects depending on the dose and model; however, prolonged tumor growth delays were observed in every case after terminating treatment, and in some cases complete cures were maintained.

### 1.3.3 Safety Pharmacology, Toxicology, and Drug Metabolism

Safety pharmacology studies with alisertib (MLN8237) did not identify significant adverse effects in nonclinical studies, including in the central nervous system (CNS) and cardiovascular systems. No alisertib-related effects on clinical signs or physical examination findings indicative of impaired respiratory function (i.e., labored or shallow breathing), or microscopic changes in the lungs of animals that survived until scheduled termination, were noted at tolerated doses in Good Laboratory Practice (GLP)-compliant, repeat-dose, toxicology studies. Alisertib exhibited minimal activity against the rapidly activating component of $I_{Kr}$, which is encoded by hERG ($IC_{50}$ and Ki > 100 μM). Alisertib had in vitro activity against the GABAAα1 benzodiazepine binding site (Ki = 290 nM).

The dose-limiting toxicities (DLTs) for alisertib in both rats and dogs after repeat daily oral dosing for 2 cycles (each cycle consisted of 7 consecutive days separated by a 14-day dose holiday) or for 6 cycles (each cycle consisted of 21 consecutive days of dosing separated by a 7-day dose holiday) were consistent with inhibition of Aurora A kinase by alisertib. Principal findings in toxicology studies in rats and dogs included GI signs, panleukopenia, decreased reticulocyte counts, and increased mitotic figures and apoptosis (single-cell necrosis) in tissues with a high basal cellular replication rate. These findings are indicative of toxicity to rapidly replicating cell populations and are consistent with the outcomes associated with Aurora A kinase inhibition. No off-target effects were seen in the GLP-compliant toxicology studies. Alisertib was negative in the bacterial reverse mutation assay (Ames assay) both in the absence and presence of Aroclor™ 1254-induced rat liver S9 fractions. In a rat bone marrow micronucleus assay, alisertib was considered to be equivocal for clastogenicity.

Alisertib is metabolized by multiple phase I (cytochrome P450 [CYP]3A4, CYP2C9, CYP2C19, and CYP1A2) and phase II (uridine diphosphate glucuronosyltransferase [UGT] 1A1, 1A3, and 1A8) enzymes. Using human liver microsomes with the appropriate cofactors, the percent contribution of CYP and UGT was calculated to be 13.1% and 86.9%, respectively, showing that CYP isozymes play a minor role in the metabolism of MLN8237. MLN8237 is unlikely to inhibit the 5 major CYP enzymes, 1A2, 2C9, 2C19, 2D6, and 3A4/5 ($IC_{50}$ > 100 μM) when administered at the projected human efficacious dose. MLN8237 is not a mechanism-based inhibitor of CYP3A4/5. Alisertib inhibited the P-glycoprotein (Pgp)-mediated efflux of paclitaxel (Taxol®) in Caco 2 cells with an $IC_{50}$ of 4.0 μM.

Detailed information regarding the nonclinical pharmacology and toxicology of alisertib may be found in the IB.

## 1.4 Clinical Experience

As of 29 March 2015, the following company-sponsored alisertib studies were in progress or completed: 10 single-agent phase 1 studies (C14001, C14002, C14003, C14010, C14013, C14014, C14017, C14019, TB-MA010030, and TB-MA010033); 2 single-agent, phase 1, DDI studies (C14015 and C14020); 3 single-agent, phase 2 studies (C14004, C14005, and C14006); 1 single-agent, phase 1/2 study (C14007); 1 single–agent, phase 3 study (C14012); and 5 combination studies (C14008 [phase 1/2] with paclitaxel, C14009 [phase 1] with docetaxel, C14011 [phase1] with either rituximab, or rituximab + vincristine, C14018 with paclitaxel [phase 2], and C14022 with paclitaxel [phase 1]).Three dosage forms of alisertib have been developed for clinical studies: powder in capsule (PIC), enteric-coated tablet (ECT), and oral solution. The initial phase 1 (C14001 through C14003) and phase 2 (C14004 through C14006) studies employed the PIC formulation. Studies C14001 and C14003 were amended to evaluate the ECT formulation; C14001 evaluated the relative bioavailability (BA) of the PIC and ECT formulations in solid tumor patients, and C14003 evaluated the clinical safety and pharmacokinetic (PK) of the ECT formulation in patients with hematologic malignancies. Relative BA of the PIC, ECT, and oral solution has also been investigated in Study C14010. The ECT formulation is being used in more recent studies (C14007 through C14009, C14011 through C14015, C14017, TB-MA010030 and TB-MA010033) and will be used in future studies.The dose-escalation, phase 1 study, C14007, evaluated multiple dose levels from 10 to 60 mg BID for 7 days in repeat, 21-day cycles and 50 mg BID has been determined to be the MTD. The recommended phase 2 dose (RP2D) was established in Studies C14001 and C14002 at 50 mg BID for the 7-day schedule followed by a 2-week, treatment-free period. Study C14007 confirmed the RP2D and schedule for the ECT formulation.

Alisertib has also been evaluated as a single agent in a phase 1/2 study in adults with solid tumors; phase 2 data from the breast cancer cohort were recently presented.[30] Fifty-three patients with relapsed/refractory breast cancer, previously treated with ≤4 prior cytotoxic regimens for metastatic or recurrent disease, received alisertib 50 mg BID for 7 days followed by 14 days rest in 21-day cycles. Forty-nine patients were evaluable for response, with an ORR of 18% for all patients. The ORR was 23% in the ER+/HER2- cohort (n=26) and 7% in the triple-negative cohort (n=14), with a median PFS of 7.9 months and 1.5 months respectively. Patients with HER2+ disease (n=7) had an ORR of 22% and a median

PFS of 4.1 months. Some responses in the ER+/HER2- and HER2+ cohorts have been maintained for > 1 year. Grade ≥3 drug-related AEs were reported in 72% of patients. Grade ≥3 neutropenia occurred in 49% of patients, with 4% of patients experiencing febrile neutropenia. Treatment emergent SAEs occurred in 21% of patients; the most common events were aphthous stomatitis (n=3), anemia, febrile neutropenia, and neutropenia (each n=2), and 57% of patients required alisertib dose reductions. No on-study deaths were reported.

Alisertib is structurally related to the benzodiazepines (BZD) (eg, diazepam, lorazepam) and also has activity against the GABAAα1 BZD receptor. BZD-like effects (eg, somnolence, confusion, memory loss) have been observed to be associated with the onset of maximal plasma concentration (e.g., $T_{max}$ [time to maximum plasma concentration]). CNS effects associated with peak plasma levels have been generally managed by administration of divided doses (e.g., BID administration), although dose reductions have sometimes been required. While CNS effects attributed to alisertib were also generally reversible and manageable by dose delay or reduction, the causal relationship, and thus optimal approach to management, were sometimes confounded by diverse causes including, but not limited to, concomitant medications (e.g., narcotic analgesics, antianxiety medications), comorbidities (e.g., infection, anemia, electrolyte abnormalities), or progressive malignancy (e.g., brain metastases).

The clinical experience with alisertib includes treatment with multiple doses and schedules and is summarized in the IB.

## 1.5 Pharmacokinetics

Following oral administration of alisertib as an ECT formulation, peak concentrations of alisertib were generally achieved by 3 hours post-dose. The overall median $T_{max}$ was 3 hours following 7 days of BID multiple oral dose administration. The overall peak-to-trough ratio was 2.2 and accumulation ratio was 2.4. The terminal half-life was approximately 21 hours following 7 days of multiple dosing. Steady-state plasma exposures of alisertib increased in an approximately dose-proportional manner over the range of 5 to 200 mg/day in patients with advanced solid tumors. Pharmacokinetic steady-state conditions were approximately achieved by Day 7 following daily oral administration. The predominant route of elimination for alisertib is fecal, consistent with hepatic metabolism and biliary excretion of alisertib. Renal clearance of unchanged alisertib was negligible. Based on the results from the radio-labeled human ADME study (C14014) and

the follow-up in investigations, alisertib is metabolized by both oxidation and glucuronidation pathways, and multiple cytochrome P450 (CYP) isozymes (CYP3A4, 2C8, 2C9, 2C19, and 1A2) and UGT isozymes (UGT1A1, 1A3, and 1A8) are involved. Phase 1 oxidative metabolism was identified to be of quantitative importance, with an estimated contribution of CYP3A4 of approximately 60% to overall apparent oral clearance (CL/F) in humans. Therefore, moderate to strong inhibitors of CYP3A4 and clinically significant inducers may alter systemic exposures of alisertib and should be avoided. The pharmacokinetic properties of alisertib in patients with hematologic malignancies were generally consistent with those observed in patients with nonhematologic malignancies. Based on the results of a population PK analysis in 363 adult cancer patients, the CL/F of alisertib was unaffected by age, body weight, BSA, or UGT1A1 genotype (number of *28 alleles). These results support the use of a common fixed starting dose of alisertib in the adult patient population in the ongoing and planned clinical trials. Clinical pharmacokinetic data available as of 29 March 2015 are summarized in the IB.

The effect of a high-fat meal on the single-dose PK of alisertib administered as 5 × 10-mg ECT was evaluated in Study C14017. The geometric mean $AUC_{0\text{-}inf}$ following alisertib single dose administration under fed conditions was 115% of that under fasted conditions (90% CI: 96%, 139%), with a substantial overlap in the range of individual values of $AUC_{0\text{-}inf}$ when dosed in the fed versus fasted states. Based on the relatively minor (15%) increase in alisertib geometric mean $AUC_{0\text{-}inf}$ upon administration with a high-fat meal in relation to overall PK variability (45% coefficient of variation [CV] in $AUC_{0\text{-}inf}$), it is concluded that food does not produce a clinically relevant effect on alisertib PK. The results of this study support a conclusion that alisertib can be administered without regard to the timing of meals in future clinical trials, unless otherwise specified in the clinical study protocol.

The relative BA of the oral solution in reference to PIC in 14 patients was estimated to be 1.26 in reference to the PIC (90% CI: 1.09 – 1.47). The rate of absorption of alisertib from the oral solution was higher than that from the PIC formulation, based on a shorter median time to first maximum plasma concentration ([$T_{max}$] 1 hour for the oral solution vs 2 hours for the PIC). The geometric mean ratio of dose-normalized $C_{max}$ of oral solution vs PIC was 1.90 (90% CI: 1.52 – 2.37).

Across a total of 56 patients from 3 phase 1 studies in Asian patients, the geometric mean dose-normalized steady-state $AUC_{0\text{-}\tau}$ is 750 nM.hr/mg (43% CV), which is approximately 67% higher than the corresponding geometric mean dose-normalized steady-state $AUC_{0\text{-}\tau}$ in the Western population (N = 363).

Co-administration of alisertib with esomeprazole, a proton pump inhibitor (PPI) resulted in a 28% increase in total systemic exposure ($AUC_{0\text{-}inf}$) of alisertib, supporting the conclusion that gastric acid-reducing agents be avoided in patients receiving alisertib.

Co-administration of alisertib with rifampin, a strong metabolic enzyme inducer resulted in a 47% decrease in total systemic exposure ($AUC_{0\text{-}inf}$) of alisertib, supporting the conclusion that chronic use of concomitant strong inducers of pregnane x-receptor (PXR)-inducible enzymes be avoided in patients receiving alisertib.

Alisertib (50 mg) in single doses and after multiple doses BID for 7 days was not associated with any clinically relevant changes or findings in the electrocardiogram (ECG), did not prolong the QT interval, and can be concluded not to affect cardiac repolarization dynamics. No alisertib concentration-effect relationship was identified, consistent with findings from the statistical analyses in supporting a lack of effect on the QT interval.

Pharmacodynamic evaluations have been performed in patient skin and tumor biopsies using assays that reflect Aurora A kinase inhibition. The data collected to date from these biopsies provide evidence that a dominant mechanism of alisertib is inhibition of Aurora A kinase in both skin and tumor, and these effects are generally dose- and/or exposure-dependent.

Adverse events (AEs) observed to date (as of 29 March 2015) are generally reversible, dose-dependent, and are consistent with the pharmacologic profile of alisertib as an anti-mitotic agent with predominant effects in proliferative tissues. The more commonly observed (≥ 30% incidence) treatment-emergent AEs (TEAEs) all grades from pooled data across the alisertib single-agent studies include: neutropenia (48%), anemia (47%), fatigue (46%), diarrhea (44%), alopecia (36%), stomatitis (32%), and nausea (31%).

Central nervous system (CNS) effects, including transient dose-dependent somnolence and/or confusion, have also been observed. These CNS effects may not be associated with Aurora A kinase inhibition but instead likely represent benzodiazepine-like effects of alisertib due to its structural similarity to benzodiazepine. At higher dose levels evaluated in phase 1 studies, severe CNS effects were sometimes considered DLTs, although these effects abated during the planned treatment-free period. In the phase 1 studies, CNS effects appeared to be related to high peak plasma levels resulting from single daily doses of alisertib. The frequency and/or severity of benzodiazepine-associated CNS toxicities may be reduced in adult patients enrolled to recent studies that administered alisertib with divided doses (eg, BID), a schedule designed to reduce peak plasma levels while maintaining overall AUC. CNS effects have been reversible with cessation of alisertib treatment, dose reduction,

and dose modification of other sedative medications.

## 1.6 Potential Risks and Benefits

As of 29 March 2015, 1197 patients (including 23 patients from 2 company-sponsored, non-US IND studies in Japan and excluding patients from ongoing, double-blind study C14018) have been treated with alisertib, in company-sponsored studies. Clinical safety data include experience from patients who received multiple cycles followed by treatment-free periods between each cycle, and from patients who reduced or discontinued treatment. Based on the available clinical data, drug abuse, dependency, and drug withdrawal effects were not observed.

The identified risks associated with alisertib treatment include: reversible myelosuppression including anemia; febrile neutropenia (including fatal febrile neutropenia); leukopenia; lymphopenia; neutropenia (including fatal neutropenia); pancytopenia (including fatal pancytopenia); thrombocytopenia; GI toxicity including abdominal pain, diarrhea, dyspepsia, mucosal inflammation, nausea, oral pain, stomatitis, and vomiting; asthenia; fatigue; pyrexia; infection (including fatal infection); sepsis (including fatal sepsis); liver function test abnormal including aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, alkaline phosphatase (ALP), and gamma-glutamyltransferase (GGT); decreased appetite; dehydration; gait disturbance; sedation; somnolence; confusional state; disorientation (and associated memory loss); alopecia; rash (including bullous dermatitis); and palmar-plantar erythrodysesthesia syndrome.

While all of these toxicities are potentially associated with risk or discomfort to the patient, they are anticipated to be reversible. However, it is possible that alisertib will have other toxicities that have not been observed in or predicted from its evaluation in rats and dogs and from ongoing studies in humans. Alisertib has a very low potential to prolong the QT interval in vivo based upon its extremely weak in vitro binding to hERG ($IC_{50}$ and $K_i$ both > 100 µM).To mitigate the inherent risks in clinical studies of alisertib, patients are evaluated frequently while they are receiving treatment. Guidance for reducing doses is provided in the protocols, and drug dosage can be reduced by either reducing the daily dose administered or by interruption of the scheduled treatment within a cycle.

Because alisertib inhibits Aurora A kinase, it is possible that alisertib may interfere with cancer growth and cause cancer cell death. Preclinical results indicate that alisertib is not a major substrate for efflux mechanisms that have been associated with cross-resistance between some types of anticancer agents. Thus, alisertib has potential through a potentially

non-cross resistant pathway as compared to other agents the patients may have received. Based on laboratory studies with agents that target Aurora A kinase, it is also possible that alisertib will induce cancer cell senescence, leading to a terminal outcome for cancer cells that may be initially represented by stable disease (SD) instead of immediate tumor reduction (response). The clinical utility of these effects will be investigated in current and future studies.

This study will be conducted in compliance with the protocol, applicable regulatory requirements, and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP), guidelines.

## 1.7 Paclitaxel

### 1.7.1 Scientific Background

Paclitaxel is a cytotoxic agent with proven antitumor activity in a variety of solid tumors, including breast cancer, ovarian cancer, and lung cancer. The antitumor activity of paclitaxel is based on tubulin-binding and stabilization of non-functional microtubule bundles, thereby blocking normal mitotic spindle development and subsequent cell division.[31]

### 1.7.2 Clinical Pharmacokinetics and Pharmacodynamics

Paclitaxel demonstrated a biphasic decline in plasma concentrations following intravenous administration. An initial rapid decline represents distribution of the drug to the peripheral compartment as well as elimination, while the second phase represents the slower efflux of drug from the peripheral compartment.[32]

Pharmacokinetic parameters were studied in a phase 3 trial in patients with ovarian cancer, using dosages of 135 mg/m$^2$ IV and 175 mg/m$^2$ IV administered as 3- or 24-hour infusions. Terminal half-life ranged from 13.1 to 52.7 hours, $C_{max}$ ranged from 195 ng/mL to 3650 ng/mL, and total body clearance ranged from 12.2 to 23.8 L/h/m$^2$. The pharmacokinetics of paclitaxel administered as singles doses at 15 to 135 mg/m$^2$ administered as a 1-hour infusion, 30 to 275 mg/m$^2$ by 6-hour infusion, and 200 to 275 mg/m$^2$ as a 24 hour infusion, in adult patients with other cancers were consistent with these values.

Clearance of paclitaxel is primarily through non-renal pathways. A study of radiolabeled paclitaxel showed that 71% of radioactivity was excreted in the feces and 14% through the urine in 120 hours. Paclitaxel is metabolized primarily by the cytochrome P450 isozymes CYP2C8 and CYP3A4.

Additional details regarding the pharmacology of paclitaxel can be found in the package insert.

### 1.7.3 Clinical Experience

In breast cancer, paclitaxel is used both in combination with other agents and as a single agent. In the pivotal Phase 3 trial 2 doses of paclitaxel (135 mg/m$^2$ IV or 175 mg/m$^2$ IV), both administered q3w, were compared in 471 patients who had received 1-2 prior chemotherapy regimens. The ORRs were 29% and 22% for the high and low dose respectively. Median TTP was 4.2 versus 3.0 months (P=.027), and median OS was 11.7 months and 10.5 months (P=.321) for the 175 mg/m$^2$ and 135 mg/m$^2$ dosages, respectively.[32] An ORR of 25% was reported for q3w paclitaxel at a dosage of 175 mg/m2 in another phase 3 trial in patients with MBC that had progressed on an anthracycline-containing regimen, with a median TTP of 3.6 months and a median OS of 12.7 months.[33] Paclitaxel has also been studied in anthracycline-naïve MBC. As first-line therapy, ORRs of 25%-34% have been reported, with median OS ranging from 15.6 months to 22.2 months.[34,35,36]

A weekly (qw) over a three-weekly (q3w) administration schedule has been shown to be more effective in the metastatic as well as in the adjuvant setting after standard chemotherapy.[37,38] In these two large randomized phase 3 studies the overall toxicity profile was similar between the qw and q3w schedule except for neuropathy (higher in the qw arm) while other studies have described a more favorable toxicity profile with the qw administration.[7]

### 1.7.4 Potential Risks of Paclitaxel

The reported toxicity profile of paclitaxel is based upon the experiences of 812 patients with ovarian or breast cancer who received treatment with single agent paclitaxel in 10 clinical studies.[32]

Adverse events that have been observed in patients with paclitaxel include: (1) reversible myelosuppression including neutropenia, leukopenia, thrombocytopenia, and anemia; (2) peripheral neuropathy; (3) GI toxicity including nausea, vomiting, diarrhea, and mucositis; (4) alopecia; (5) myalgia and/or arthralgia; (6) bleeding; (7) infection; (8) abnormal liver function tests (including AST, ALP, and bilirubin; (9) cardiovascular events, including hypotension, bradycardia, and hypertension; (10) abnormal electrocardiogram (ECG) and (11) injection site reaction.

Anaphylaxis and severe hypersensitivity reactions occurred in 2-4% of patients treated with paclitaxel on clinical trials, and fatal reactions have been reported. All patients should be pretreated with corticosteroids, diphenhydramine, and histamine H2-receptor antagonists. Patients who experience severe hypersensitivity reactions to paclitaxel should not be rechallenged with the drug.

Additional details regarding adverse events associated with paclitaxel can be found in the package insert.

### 1.8 Paclitaxel plus alisertib – clinical experience

The combination of alisertib plus paclitaxel has been investigated in a Phase 1B dose escalation study (C14008) in patients with previously treated, metastatic or locally recurrent ovarian or breast cancer (N=49; 38 ovarian cancer, 11 breast cancer). The maximum tolerated doses (MTDs) were determined to be paclitaxel 80 mg/m$^2$ IV (days 1, 8, and 15) plus alisertib 10 mg BID (days 1-3,8-10,15-17) and paclitaxel 60 mg/m$^2$ IV (days 1, 8, and 15) plus alisertib 40 mg BID (days 1-3,8-10,15-17) of a 28 day cycle.[39,40] This dosing schedule was selected to maximize concomitant exposure of alisertib and paclitaxel, while providing treatment-free periods for recovery from toxicities like neutropenia and mucositis.[40] The most common dose-limiting toxicities were neutropenia, with or without fever. Thirty-eight patients experienced Grade ≥3 adverse events; the most common were neutropenia (61%) and leukopenia (33%).

Preliminary data from the combination study of alisertib + paclitaxel (C14008) suggest that there is an increased risk of stomatitis for patients receiving the combination of alisertib + paclitaxel, when compared with patients receiving either single-agent alisertib or single-agent paclitaxel.

The effect of alisertib on paclitaxel PK was assessed at the RP2D of 40 mg BID of alisertib + 60 mg/m$^2$ of paclitaxel. In this study, alisertib 40 mg BID was administered for 3 days on/4 days off, repeated weekly for 3 weeks in a 28-day cycle (alisertib administered on Days 1-3, 8-10, 15-17) and weekly paclitaxel at either 60 mg/m$^2$ on Days 1, 8, and 15 or weekly paclitaxel 80 mg/m$^2$ on Days 1, 8, and 15, of a 28-day cycle. Based on the preliminary data, it appears that there is a small (10%-19%) increase in paclitaxel total systemic exposures (AUC) achieved when co-administered with 40-mg BID alisertib. The exposures of paclitaxel achieved at 60 mg/m$^2$ when co-administered with 40-mg BID alisertib are not higher than those achieved with paclitaxel when administered alone at the standard single-

agent weekly dose of 80 mg/m$^2$, indicating the lack of any clinically concerning increases in paclitaxel exposures when co-administered with alisertib at the RP2D of the combination.

One patient with ovarian cancer had a complete response by RECIST as well as CA125.[39] Sixteen patients had a PR, including 10 patients with ovarian cancer and 6 patients with breast cancer. Fourteen additional patients had a best response of SD, including 11 patients with ovarian cancer and 3 with breast cancer.

## 1.9 Study rationale and selection of drug doses

### 1.9.1 Study rationale

The rationale behind assessing the effectiveness of the addition of alisertib to weekly paclitaxel therapy in patients with TNBC and highly proliferative ER+ and HER2- breast cancer is based on the unmet clinical need for effective strategies to prevent or delay resistance to taxane therapy in the metastatic setting. As described in Sections 1.3.2 and 1.3.3, synergistic or additive effects have been observed in breast cancer xenograft models which involved alisertib added to either paclitaxel or docetaxel. Alisertib inhibited the Pgp-mediated efflux of paclitaxel in a cell culture model. In addition, as described in Section 1.1 AURKA is frequently overexpressed in TNBC, and expression levels have been shown to be prognostic in both of these breast cancer subtypes. The combination of alisertib with paclitaxel has also been investigated in a Phase 1 study in patients with locally advanced or metastatic ovarian and breast cancers, with preliminary evidence of activity in both tumor types including 6 PRs and 3 SD in 11 patients with MBC.[40]

### 1.9.2 Dose selection

A Phase 1B dose escalation study investigating the combination of alisertib plus paclitaxel was conducted in patients with metastatic or locally recurrent ovarian or breast cancers.[40,40] Paclitaxel was administered on days 1, 8 and 15 of a 28-day cycle, with alisertib given orally on days 1-3, 8-10, and 15-17. This dosing schedule was selected to maximize concomitant exposure of alisertib and paclitaxel, while providing treatment-free periods for recovery from toxicities like neutropenia and mucositis.[41] Two maximum tolerated doses (MTDs) were determined: MTD1 (paclitaxel 80 mg/m$^2$ IV plus alisertib 10 mg BID), or MTD2 (paclitaxel 60 mg/m$^2$ IV plus alisertib 40 mg BID).

Based on pharmacokinetic and pharmacodynamic analyses, the RP2D is MTD2 (paclitaxel 60 mg/m$^2$ IV plus alisertib 40 mg BID) which demonstrated 4-fold higher dose density compared to MTD1, and this dose density was nearly 80% of the current RP2D/RP3D dosage for single-agent alisertib. In addition, the systemic exposure achieved at this dosage and schedule was similar to the exposures found to be associated with AURKA inhibition in tumors in prior studies. No clinically concerning drug-drug interactions were noted at MTD2, and translational assessment of exposure efficacy relationships in nonclinical xenograft studies predict greater antitumor efficacy for MTD2 compared with MTD1.

Therefore, the initial dose and schedule selected for this study, based on the phase 1B experience with this combination regimen, is paclitaxel 60 mg/m$^2$ IV administered on days 1, 8 and 15 and alisertib 40 mg BID on days 1-3, 8-10, and 15-17 of a 28-day cycle.

### 1.9.3 Rationale for Correlative Biomarker Study

Currently there are no validated biomarkers that predict for the effectiveness of alisertib. FOXM1 is a pro-proliferative cell cycle transcription factor that is upregulated in several cancers. It is responsible for regulating the G2/M phase of mitosis, DNA damage repair, and is required for cell cycle progression. In addition, it drives other G2/M regulatory genes such as survivin, centromere proteins A/B/F, and AURKA.[41] It was recently determined that FOXM1 is downregulated by the p53 tumor suppressor via the p21/Rb/E2F pathway. This indicates that in cancers where p53 is mutated or not functional, FOXM1 contributes to increased proliferation/uncontrolled mitosis and genomic instability.[42] AURKA is a serine/threonine kinase that is important in regulating the transition from G2 in mitosis.[10] FOXM1 transcriptionally regulates AURKA in order for the cell to progress from the G2 to the M phase.[11] In addition to being regulated by FOXM1, AURKA is also responsible for the phosphorylation of p53, which leads to its ubiquitination and degradation. In turn, with the degradation of p53, FOXM1 is also downregulated, thereby regulating cell cycle progression. Genomic instability can be induced in several cancers, including breast cancer, due to increased levels of AURKA. In ovarian cancer, AURKA induces genomic stability, cell cycle progression, and anti-apoptosis by downregulating p21, Rb, and BRCA2.[43]

As described in Section 1.1, FOXM1 and AURKA have been shown to be co-overexpressed in some TNBC tumors, and expression levels of AURKA have demonstrated prognostic value in early-stage breast cancers.

In order to develop hypotheses regarding potential predictive biomarkers for benefit from alisertib, FFPE tissue from study patients' primary breast cancers will be retrospectively

analyzed for expression of FOXM1 and AURKA, p53 mutation status, and degree of genomic instability, as potential predictors of benefit from the combination of alisertib and paclitaxel.

# 2. STUDY OBJECTIVES

## 2.1 Primary Objective

The primary objective of this study is:

- To demonstrate the superiority of alisertib plus paclitaxel compared with paclitaxel alone in PFS in two cohorts of patients with metastatic or locally recurrent breast cancer, one with ER+, HER2- disease and the other with triple-negative (TN) disease

## 2.2 Secondary Objectives

The secondary objectives of this study are:

- To assess the safety of alisertib combined with paclitaxel
- To compare the objective response rates (ORR; complete response [CR] plus partial response [PR]) between the two treatment arms in each of the two cohorts
- To compare the clinical benefit rate (CBR; CR + PR + stable disease [SD] ≥6 months) between the two treatment arms in each of the two cohorts
- To assess overall survival (OS) in each of the treatment arms in each of the two cohorts

## 2.3 Exploratory Endpoints

- To perform genomic profiling of patients' archival primary breast cancer tissue to identify potential predictive markers for benefit from alisertib plus paclitaxel

# 3. INVESTIGATIONAL PLAN

This is an investigator-initiated study. The principal investigator is Joyce O'Shaughnessy, MD, and the study sponsor is Delta Clinical Research, LLC.

## 3.1 Overall Design and Plan of the Study

This will be a randomized, multicenter, parallel group study to evaluate alisertib plus paclitaxel compared with paclitaxel alone in the treatment of metastatic or locally recurrent breast cancer in each of the two patient cohorts. The two cohorts will consist of: 1) ER+, HER2-, disease, and 2) poorly differentiated (and/or Grade 3) TNBC. Up to 1 prior chemotherapy regimen for metastatic disease will be allowed, with no limit on the number of prior endocrine therapies. Prior adjuvant taxane therapy is allowed as long as the patient has been disease-free for at least 1 year from the end of adjuvant chemotherapy to the development of metastatic disease. Prior taxane for metastatic disease is not permitted. Previous therapy with an mTOR inhibitor is allowed. Untreated or progressing brain metastases are not allowed, and patients cannot require steroid therapy for the treatment of brain metastases.

General eligibility criteria may be assessed prior to the formal Screening period. However, per the Schedule of Events, formal screening will occur during the Screening period, which may last for up to 28 days prior to the baseline visit. Following Screening, patients will be assigned to the appropriate Cohort, stratified by number of prior chemotherapy regimens for metastatic disease (0 or 1) and by prior (neo)adjuvant taxane (yes or no), and randomized to receive either paclitaxel alone or paclitaxel in combination with alisertib, in an unblinded manner. Treatment periods will be defined as 28 day cycles, which will be chronologically timed regardless of whether patients are on study medication. Paclitaxel will be administered IV on days 1, 8 and 15, and alisertib will be administered BID on days 1-3, 8-10, and 15-17 of each treatment cycle. Week 4 is a rest week. Patients will remain on treatment until disease progression, unacceptable toxicity, or discontinuation of treatment for other reasons (see section 3.10).

Patients randomized to the paclitaxel and alisertib arm will be seen by their oncology care provider for Cycle 1 on days 1, 8 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only); Cycle 2 on days 1 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only); for Cycle 3 and subsequent cycles, patients will have a

brief physical exam, review of AEs, concomitant medications, and vitals, weight, and performance status on day 1 of each cycle. Additional unscheduled visits may occur as required, such as in the case of an adverse event requiring medical attention. Patients receiving paclitaxel alone will have CBCs on days 1, 8 and 15 and will be seen by their oncology care provider every 28 days. An End of Treatment visit will occur within 30 days of receipt of last dose of study drug(s), and patients will continue to be followed for other follow-up assessments specified in the Schedule of Events, including survival.

The primary endpoint of this study is PFS. ORR, CBR, and OS are secondary endpoints. Patients will undergo computed tomography (CT) scans of the chest, abdomen and pelvis during the Screening period, and will be reassessed with chest and abdominal imaging every 8 weeks following initiation of treatment for the first 32 weeks of study treatment, then every 12 weeks for the duration of the study treatment period (pelvic CT will only be performed if metastatic lesions are detected at baseline). Patients will undergo a whole body Tc-99 bone scan at baseline, and will be reassessed every 12 weeks for the first 32 weeks of study treatment, then every 16 weeks for the duration of the study treatment period only if metastatic lesions are detected at baseline. Patients with a history of treated brain metastases will have a baseline MRI of the brain; reassessment imaging will be performed at 8 week intervals for the first 32 weeks of study treatment, then every 12 weeks for the duration of the study treatment period (CT may be used if MRI is contraindicated). Skin lesions will be documented by color photography and reassessed every 8 weeks for the first 32 weeks of study treatment, then every 12 weeks for the duration of the study treatment period, if present at baseline. Toxicities will be evaluated according to NCI Common Toxicity Criteria for Adverse Events (CTCAE) Version 4.03.

A correlative molecular biomarker study will also be performed. An FFPE archived tumor block (or 20 unstained slides if tumor block is unavailable) from the primary breast cancer will be required from each patient. Samples will be retrospectively analyzed for potential predictors of benefit from the combination of alisertib and paclitaxel, including but not limited to expression of FOXM1 and AURKA, p53 mutation status, and degree of genomic instability.

### 3.2 Selection of Patients

The total number of patients to be enrolled on this study is 252 (Cohort 1 [ER+/HER2-] n=140; Cohort 2 [TNBC] n=112).

### 3.2.1 Registration Procedures

The registration process begins when the coordinator has obtained a signed informed consent from the patient. Please enter patient demographics into the Clinical Trial Management System (CTMS); this is the Web-based intranet system for the delivery of trial information between Delta and it is used across all sites. A unique patient number (UPN) will be assigned to the patient at that time. Entering a patient into CTMS does not signify that you have registered the patient in the study. If you have any difficulty with CTMS please contact the Clinical Trial Manager.

Once the patient has an UPN number, the coordinator can go to their Patient Report and select the patient that they want to register. Located to the left of the patient's UPN will be the letters "Reg" in blue. The coordinator will click on the blue "Reg" to open up that patient's information. Each page that needs to be completed will be in yellow. The site will answer the questions on the Inclusions and Exclusions. Once all questions on each page are answered, that page will turn green. Once all the pages turn green, click on the "verify data" tab, then click the "register" tab. The register page will open, "click to register". An ID number will be directly assigned. For any difficulties with entering the data, please contact the Project Manager of the study.

**Treatment must begin within 5 working days after the patient's registration on the study, not including weekends or holidays.**

### 3.2.2 Inclusion Criteria

Each patient must meet all of the following inclusion criteria to be enrolled in the study:

- Voluntary written informed consent before performance of any study-related procedure not part of normal medical care, with the understanding that consent may be withdrawn by the subject at any time without prejudice to future medical care, and signed Health Insurance Portability and Accountability Act (HIPAA) form.

- Female subject (≥18 years old), who is either:

    - post-menopausal for at least one year before the screening visit, or

    - surgically sterilized, or

- willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide) for the duration of the study.

- Metastatic or locally recurrent breast cancer with histologic confirmation (on either primary or metastatic tumor) of **one of the following**:
  - ER+, HER2- invasive breast cancer (any PgR status)
  - TNBC, defined as:
    - HER2 negative status (based on most recently analyzed biopsy) is defined as immunohistochemistry (IHC) status of 0, 1+ or 2+ (if IHC 2+, a negative FISH test is required, i.e., HER2 fluorescence in situ hybridization (FISH) ratio < 2.0 with an average HER2 copy number <4.0 signals/cell); ER-negative and PR-negative status is defined as ER and PgR <1% nuclei positive by IHC

- Measurable disease by modified Response Evaluation Criteria in Solid Tumors (RECIST) (v1.1) or non-measurable lytic, bone-only disease (mixed blastic/lytic bone disease is allowed); if patient has bone-predominant disease with no measurable disease, there must be a lytic component to the bone metastases that is visible on plain X-ray or CT scan that can be serially followed

- Absolute neutrophil count (ANC) > 1500/mm³, platelets ≥ 100,000/mm³, Hgb ≥ 9 g/dL. Values must be obtained without need for myeloid growth factor or platelet transfusion support within 14 days, however, erythrocyte growth factor is allowed as per published ASCO guidelines (available at: http://www.asco.org/quality-guidelines/asco-ash-clinical-practice-guideline-update-use-epoetin-and-darbepoetin-adult).

- Total bilirubin ≤ 1.5 x upper limit of normal (ULN), SGOT (AST) and SGPT (ALT) < 2.5 x ULN. AST and/or ALT may be up to 5 x ULN if patient has known liver metastases

- Adequate renal function as defined by: Calculated creatinine clearance must be ≥ 30 mL/minute (see Cockcroft-Gault formula in Appendix 5)

- Eastern Cooperative Oncology Group (ECOG) performance status 0 or 1 (refer to Appendix 4)

### 3.2.3 Exclusion Criteria

Patients meeting any of the following exclusion criteria are not to be enrolled in the study.

- More than 1 previous chemotherapy regimen for metastatic disease
    - No limit on previous endocrine therapy
    - Previous mTOR therapy, e.g., everolimus, is allowed
    - Prior adjuvant taxane therapy is allowed, provided the disease-free interval from the end of (neo)adjuvant chemotherapy to the development of metastatic disease was ≥ 1 year
    - No prior taxane for metastatic disease
- Previous radiation therapy covering the whole pelvis
- Suspected brain metastases, untreated brain metastases or current clinical or radiologic progression of known brain metastases or requirement for steroid therapy for brain metastases
    - Patients with treated brain metastases are eligible if they have been stable and off steroids for ≥ 3 weeks
- Prior allogeneic bone marrow or organ transplantation
- Known GI disease or GI procedures that could interfere with the oral absorption or tolerance of alisertib. Examples include, but are not limited to partial gastrectomy, history of small intestine surgery, and celiac disease
- Known history of uncontrolled sleep apnea syndrome and other conditions that could result in excessive daytime sleepiness, such as severe chronic obstructive pulmonary disease; requirement for supplemental oxygen.

- Requirement for administration of proton pump inhibitor, or for constant administration of H2 antagonist, or pancreatic enzymes. Intermittent uses of antacids or H2 antagonists are allowed as described in Section 3.4.

- Systemic infection requiring IV antibiotic therapy within 14 days preceding the first dose of study drug, or other severe infection.

- Myocardial infarction within 6 months prior to enrollment or has New York Heart Association (NYHA) Class III or IV heart failure (see Appendix 3), uncontrolled angina, severe uncontrolled ventricular arrhythmias, or electrocardiographic evidence of acute ischemia or active conduction system abnormalities. Prior to study entry, any ECG abnormality at Screening has to be documented by the investigator as not medically relevant.

- Female subject who is pregnant or breast-feeding. Confirmation that the subject is not pregnant must be established by a negative serum β-human chorionic gonadotropin (β-hCG) pregnancy test result obtained during screening, within 72 hours prior to first dose of study drug(s). Pregnancy testing is not required for post-menopausal or surgically sterilized women.

- Patient has received an investigational agent within 30 days before enrollment

- Serious medical or psychiatric illness likely to interfere with participation in this clinical study.

- Other severe acute or chronic medical and/or psychiatric condition(s), including but not limited to uncontrolled diabetes, malabsorption, resection of the pancreas or upper small bowel, requirement for pancreatic enzymes, any condition that would modify small bowel absorption of oral medications, or laboratory abnormalities that may increase the risk associated with study participation or investigational product administration or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the patient not eligible for enrollment for this study.

- Diagnosed or treated for another malignancy within 3 years of enrollment, with the exception of complete resection of basal cell carcinoma or squamous cell carcinoma of the skin, or an in situ malignancy, or a stage I cancer with a 5-year

DFS of ≥ 90% (survival rates by stage are available for most cancers on the American Cancer Society website).

- Treatment with clinically significant enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine or phenobarbital, or rifampin, rifabutin, rifapentine or St. John's wort within 14 days prior to the first dose of alisertib and during the study.

- Known history of human immunodeficiency virus (HIV) infection, hepatitis B, or hepatitis C. Testing is not required in the absence of clinical findings or suspicion. For guidance in defining active infection for hepatitis B, please refer to the WHO guidelines. (World Health Organization, Global Alert and Response (GAR), Hepatitis B. http://who.int/csr/disease/hepatitis/whocdscsrlyo20022/en/index4.html)

- Prior administration of an Aurora A kinase-targeted agent, including alisertib

- Need for ongoing therapeutic steroid therapy. Intermittent steroid use for the control of nausea and vomiting is allowed. Premedication with dexamethasone prior to paclitaxel administration is allowed. Topical steroid use is permitted. Inhaled steroids are permitted. Replacement doses of hydrocortisone up to 15 mg/day are allowed.

- Inability to swallow oral medication or inability or unwillingness to comply with the administration requirements related to alisertib.

- Administration of myeloid growth factors or platelet transfusion within 14 days prior to the first dose of study treatment.

- Peripheral neuropathy > grade 1

- Known severe hypersensitivity to paclitaxel

## 3.3 Study Treatments

### 3.3.1 Clinical Trial Materials

Alisertib drug product is supplied as the ECT dosage form in 10 mg strength, with dose strength expressed as the milligrams of active drug (free acid). The key formulation

excipients of the alisertib tablet formulation that aid in the in vivo absorption of the drug are the buffer (sodium bicarbonate), the surfactant (sodium lauryl sulfate), and the enteric coating.

Paclitaxel is a commercially available product. If available, generic paclitaxel should be used as part of study treatment, when possible. Paclitaxel will be prescribed by the investigator and obtained as outlined in the investigator Clinical Trial Agreement. Paclitaxel is available in 30 mg (5 mL), 100 mg (16.7 mL) and 300 mg (50 mL) multidose vials. Each mL of sterile nonpyrogenic solution contains 6 mg paclitaxel, 527 mg of purified Cremaphor® EL (polyoxyethylated castor oil) abd 49.7% (v/v) dehydrated alcohol, USP.

### 3.3.2 Preparation, Handling, and Storage of Drugs

Alisertib ECT are packaged in a 60-cc high-density polyethylene (HDPE) bottle with a rayon coil, induction seal, desiccant packs, and a polypropylene child-resistant cap.

Alisertib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling MLN8237.

Per the package insert, Paclitaxel Injection is supplied as a sterile, non-pyrogenic, nonaqueous solution intended for dilution with a suitable parenteral fluid prior to intravenous infusion. Contact of the undiluted concentrate with plasticized polyvinyl chloride (PVC) equipment or devices used to prepare solutions for infusion should be avoided.

In order to minimize patient exposure to the plasticizer DEHP [di-(2-ethylhexyl)phthalate], which may be leached from PVC infusion bags or sets, diluted paclitaxel solutions should preferably be stored in bottles (glass, polypropylene) or plastic bags (polypropylene, polyolefin) and administered through polyethylene-lined administration sets. Paclitaxel should be administered through an in-line filter with a microporous membrane not greater than 0.22 microns. Use of filter devices such as IVEX-2® filters which incorporate short inlet and outlet PVC-coated tubing has not resulted in significant leaching of DEHP.

**Drug Administration and Dosage Schedule**

Patients will be randomized to receive either:

- Weekly paclitaxel (90 mg/m$^2$ IV) (standard arms)

- Weekly paclitaxel (60 mg/m$^2$ IV) plus alisertib (40 mg BID) (experimental arms)

Patients on the standard arms will receive paclitaxel at a dosage of 90 mg/m$^2$ on days 1, 8 and 15 of a 28-day cycle. Patients on the experimental arms will receive paclitaxel at a dosage of 60 mg/m$^2$ on days 1, 8 and 15 of a 28-day cycle. Alisertib will be administered to patients on the experimental arms at a dosage of 40 mg BID on days 1-3, 8-10, and 15-17 of the 28-day cycle. Week 4 is a rest week. Cycle 2 and subsequent cycles, only, there is a **window of +3 days (after the scheduled time)** for treatment administration during the study.

Patients will be treated until disease progression, unacceptable toxicity, death or discontinuation from study treatment due to any other reason.

**Alisertib Administration**

Alisertib will be given PO in a dosage of 40 mg BID on days 1-3, 8-10 and 15-17 of each 28-day treatment cycle.

Patients will be instructed to take each oral dose of alisertib with 8 ounces (1 cup, 240 mL) of water. For BID dosing, the doses must be taken at least 6 hours apart.

Alisertib will be supplied as 10 mg ECT, with the dose strength expressed as milligrams of active drug (free acid). All tablets are to be ingested whole; patients who have difficulty swallowing tablets will be excluded from the study. Antiemetogenic agents may be administered at the discretion of the investigator. Prophylactic antiemetic therapy will not be used in this study unless it becomes clear that alisertib causes acute or delayed nausea and/or vomiting.

Neutralizing antacids and calcium-containing supplements cannot be taken within 2 hours prior to alisertib dosing until up to 2 hours after dosing. PPIs are not permitted for patients on the alisertib arm at any time during the study. H2 receptor antagonists may be used, except within 24 hours prior to the initiation of alisertib administration through the 3-day alisertib administration period. (See Section 3.4 regarding PPIs and H2 receptor antagonists)

Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is strongly discouraged because of the potential benzodiazepine-like effects of alisertib.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified subinvestigator(s).

**Paclitaxel Administration**

Paclitaxel will be administered at a dosage of 90 mg/m$^2$ IV (standard arm) or 60 mg/m$^2$ IV (experimental arm) on days 1, 8 and 15 of a 28-day cycle. Paclitaxel will be administered as a 1-hour intravenous infusion following standard premedications.

Standard premedications prior to each dose of paclitaxel should be administered according to local practice. The following treatment is recommended:

- Dexamethasone 10 mg IV
- Diphenhydramine 25-50 mg IV (αH1 receptor)
- Ranitidine 50 mg IV (αH1 receptor). Note: Cimetidine is a CYP3A4 and CYP1A2 inhibitor and therefore should not be administered.

Standard premedication treatment should be given 30 to 60 minutes before the paclitaxel infusion and may vary according to local standard of care.

All premedication and other concomitant medication given during the study must be recorded on the Concomitant Medication page of the eCRF.

### 3.3.3 Dose Modification and Delay

Toxicity will be evaluated according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE), Version 4.03, effective 14 June 2010.[44] (see Appendix 2)

To manage excessive toxicity, reduction of the total alisertib dose can be done by reducing the daily dose administered and/or by interruption of the scheduled treatment within a cycle. Any dosage deviations (or ongoing dosage changes) must be scrupulously recorded.

### 3.3.4 Criteria for Retreatment and Dose Delays for Paclitaxel Plus Alisertib Combination Arm

Treatment with paclitaxel plus alisertib will be repeated every 28 days. In order for a new cycle of therapy to begin, the patient must meet the following criteria:

- ANC must be $\geq 1{,}500/mm^3$ on day 1
- Platelet count must be $\geq 75{,}000/mm^3$ on day 1
- In addition, all toxicities considered by the investigator to be related to therapy with alisertib and/or paclitaxel must have resolved to ≤ Grade 1 (with exception of fatigue and neuropathy which may be ≤ Grade 2).

If the patient does not meet the above-cited criteria for retreatment, then that 3-day sub-cycle of alisertib dosing should be held and paclitaxel will also be held. At the end of that week, the patient should be re-evaluated to determine whether the criteria for retreatment have been met. If above criteria are met, patient should resume alisertib treatment at the next planned 3-day sub-cycle (Days 8-10) and should resume paclitaxel on Day 8. Should treatment need to be delayed for more than 1 week because of incomplete recovery from treatment-related toxicity, the dose of alisertib will be reduced (Table 3-1 and Table 3-2) to 30 mg BID (Dose Level -1) when therapy resumes on Day 15. The dose of paclitaxel will not be reduced below 60 $mg/m^2$. A second dose reduction of alisertib to 20 mg BID (Dose Level -2) may occur should treatment need to be delayed for more than 1 week because of incomplete recovery from treatment-related toxicity on the reduced dosage of 30 mg BID. Patients who require further dose reductions will be removed from the study. Should treatment need to be delayed for more than 3 weeks at any dose, therapy with alisertib will be discontinued.

On days 8 and 15 of each cycle, the patient must have an ANC $\geq 1000/mm^3$ and platelets $\geq 75{,}000/mm^3$ in order to receive the treatment with paclitaxel and the next sub-cycle of alisertib. If a patient cannot receive the Day 8 or Day 15 dose on time, that dose is postponed until ANC recovers; the patient will then receive that postponed dose (still calling it Day 8 or Day 15) and continue with either Day 15 dose (if Day 8 was postponed) or skipping Day 22 if Day 15 was postponed. If day 8 or 15 is skipped due to myelosuppression, resume therapy at the next scheduled visit with one alisertib dose level reduction.

Skipped doses of alisertib/paclitaxel will not be made up but rather therapy will be resumed when re-treatment criteria are met at the next treatment day. The cycle length will remain constant at 28 days.

**Table 3-1 Table of Alisertib Dose Adjustments**

| Dose Level | Dose | Schedule | Cycle Length |
|---|---|---|---|
| Starting | 40 mg | PO BID | Days 1-3, 8-10 and 15-17 of a 28-day cycle |
| -1 | 30 mg | PO BID | Days 1-3, 8-10 and 15-17 of a 28-day cycle |
| -2 | 20 mg | PO BID | Days 1-3, 8-10 and 15-17 of a 28-day cycle |
| -3 | | Discontinue | |

#### 3.3.4.1 Dose Modifications for Hematologic Toxicity (Combination Arm)

If a patient experiences any of the following hematologic toxicities during the dosing period, alisertib will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment (Table 3-2).

- Grade 4 neutropenia (ANC < 500 cells/$mm^3$) lasting more than 3 consecutive days
- Grade 4 thrombocytopenia (platelet count < 25,000/µL) lasting more than 3 consecutive days
- Platelet count less than 10,000/µL at any time
- Grade 3 or 4 neutropenia with fever or infection, or both, where fever is defined as an oral temperature greater than 38.5°C
- Grade 3 thrombocytopenia with clinically significant bleeding

Paclitaxel may be administered during the remainder of the cycle while alisertib is being held if ANC is ≥ 1000/$mm^3$ and platelets are ≥ 75,000/$mm^3$. Treatment with paclitaxel should be held on a given week for ANC <1000 cells/$mm^3$ or a platelet count < 75,000/$mm^3$.

#### 3.3.4.2 Dose Modifications for Non-Hematologic Toxicities (Combination Arm)

If a patient experiences any of the following toxicities during a cycle, alisertib dosing will be discontinued for the remainder of that cycle and the dose will be decreased 1 level for all subsequent cycles of treatment (Table 3-2). Treatment may resume on Day 1 of the following cycle provided drug-related toxicities have resolved to ≤ Grade 1 or to baseline (with the exception of fatigue and neuropathy which may be ≤ Grade 2).

- Any Grade 3 non-hematologic toxicity that is considered by the investigator to be related to study treatment other than:
    - Grade 3 or greater nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy that includes a 5-hydroxytryptamine 3 [5-HT3] serotonin receptor antagonist;
    - Grade 3 fatigue that lasts less than 2 weeks
- Grade 2 non-hematologic toxicities that are considered by the investigator to be related to study treatment and in the opinion of the investigator require dose reduction. Alisertib dose reductions for Grade 2 non-hematologic toxicity may be made without interrupting alisertib administration.

In general, alisertib treatment should be discontinued if a patient experiences a Grade 4 non-hematologic toxicity. If, in the opinion of the onsite investigator and study Principal Investigator it is in the patient's interest to continue therapy with alisertib, then after recovery from the toxicity or toxicities in question to ≤ Grade 1 or to baseline values, the dose of alisertib should be reduced to 20 mg BID with subsequent cycles of therapy. Retreatment with alisertib in patients who develop Grade 4 non-hematologic toxicity must be discussed with the study Principal Investigator.

When a dose reduction of alisertib is required, no re-escalation of dose will be permitted. If a patient requires more than 2 dose reductions, therapy with alisertib will be discontinued. If alisertib is discontinued patients may continue treatment with paclitaxel days 1, 8 and 15 every 28 days at either 60 mg/m$^2$ IV or 80 mg/m$^2$ IV at the physician's discretion.

Paclitaxel dosing may be reduced on the combination arm by 25% (i.e., to 45 mg/m$^2$) for grade ≥2 peripheral neuropathy. If neuropathy worsens, paclitaxel can be stopped and patients may continue treatment with alisertib.

**Table 3-2 Criteria for Alisertib Dose Modification on Combination Arm**

| Event | Dose Modification |
|---|---|
| Treatment delay >1 week due to incomplete recovery from treatment-related toxicity | 1st Occurrence: Reduce alisertib to Dose Level -1<br><br>2nd Occurrence: Reduce alisertib to Dose Level -2<br><br>3rd Occurrence: Discontinue alisertib |
| Treatment delay >3 weeks due to incomplete recovery from treatment-related toxicity | Discontinue alisertib |
| Hematologic Toxicities:<br>• Grade 4 neutropenia (ANC < 500 cells/$mm^3$) lasting more than 3 consecutive days<br>• Grade 4 thrombocytopenia (platelet count < 25,000/µL) lasting more than 3 consecutive days<br>• Platelet count less than 10,000/µL at any time<br>• Grade 3 or 4 neutropenia with fever or infection, or both, where fever is defined as an oral temperature greater than 38.5°C<br>Grade 3 thrombocytopenia with clinically significant bleeding | 1st Occurrence: Discontinue alisertib for the remainder of that cycle; reduce alisertib dosage to Dose Level -1 for all subsequent cycles of treatment<br>2nd Occurrence: Discontinue alisertib for the remainder of that cycle; reduce alisertib dosage to Dose Level -2 for all subsequent cycles of treatment<br>3rd Occurrence: Discontinue alisertib |
| Grade 2 Non-Hematologic Toxicity (considered related to study treatment and in investigator's opinion requiring a dose reduction)<br><br>NOTE: It is strongly recommended that alisertib be interrupted and the dose be reduced at the first occurrence of grade 2 stomatitis – alisertib may resume once grade 2 stomatitis has recovered at one dose level reduction within the same cycle. | 1st Occurrence: Reduce alisertib dosage to Dose Level -1 (alisertib interruption for remainder of cycle not required)<br>2nd Occurrence: Reduce alisertib dosage to Dose Level -2 (alisertib interruption for remainder of cycle not required)<br>3rd Occurrence: Discontinue alisertib |

| Event | Dose Modification |
|---|---|
| Grade 3 Non-Hematologic Toxicity (excluding ≥Grade 3 nausea or emesis, or both, that occurs in the absence of optimal antiemetic therapy that includes a 5-hydroxytryptamine 3 [5-HT3] serotonin receptor antagonist; or Grade 3 fatigue lasting < 2 weeks) | 1st Occurrence: Discontinue alisertib for the remainder of that cycle; reduce alisertib dosage to Dose Level -1 for all subsequent cycles of treatment[a]<br>2nd Occurrence: Discontinue alisertib for the remainder of that cycle; reduce alisertib dosage to Dose Level -2 for all subsequent cycles of treatment[a]<br>3rd Occurrence: Discontinue alisertib |
| Grade 4 Non-Hematologic Toxicity | Discontinue alisertib[b] |

[a] Treatment may resume on Day 1 of the following cycle provided drug related toxicities have resolved to ≤ Grade 1 or to baseline (with the exception of fatigue and neuropathy which may be ≤ Grade 2).

[b] If, in the opinion of the investigator and study Principal Investigator it is in the patient's interest to continue therapy with alisertib, then after recovery from the toxicity or toxicities in question to ≤ Grade 1 or to baseline values, the dose of alisertib should be reduced to 20 mg BID with subsequent cycles of therapy. Retreatment with alisertib in patients who develop Grade 4 non-hematologic toxicity must be discussed with the study Principal Investigator.

### 3.3.5 Dose Modifications for Paclitaxel Monotherapy Arm

Treatment with paclitaxel will be administered on days 1, 8 and 15 of a 28-day cycle. Paclitaxel administration should be held on a given week if the patient does not meet the following criteria on days 1, 8 and 15:

- ANC must be $\geq 1{,}000/mm^3$
- Platelet count must be $\geq 75{,}000/mm^3$

Treatment with paclitaxel should be held on a given week if ANC or platelet values are below these thresholds. That week's paclitaxel dose should be skipped and treatment resumed at the following planned visit either at a reduced paclitaxel dose of 70 mg/m$^2$ or with the addition of prophylactic Neupogen to the regimen if the physician wishes to keep the paclitaxel dose at 90mg/m$^2$. If the ANC decrease to < 1,000/mm$^3$ in spite of Neupogen use, then the paclitaxel dose will be reduced to 70 mg/m$^2$. Physicians may continue to use Neupogen prophylactically if the paclitaxel dose is reduced to 70mg/m$^2$. If patients' ANC if < 1000/mm$^3$ on a day of treatment at 70mg/m$^2$, with or without Neupogen, the paclitaxel treatment may be discontinued or further reduced to 60 mg/m$^2$ at the physician's discretion. Treatment with paclitaxel should be held for any grade 3 or 4 non-hematologic toxicity until it is resolved to ≤ Grade 1 (with the exception of fatigue and neuropathy which may be ≤ Grade 2), and then resumed at the next scheduled treatment cycle visit at a reduced dose of 70 mg/m$^2$. If a patient cannot receive the Day 8 or Day 15 dose on time, that dose is postponed; the patient will then receive that postponed dose (still calling it Day 8 or Day 15) and continue with either Day 15 dose (if Day 8 was postponed) or skipping Day 22 if Day 15 was postponed. Paclitaxel dose may be further reduced to 60 mg/m$^2$ for a second occurrence of Grade 3 non-hematologic toxicity and discontinued for second occurrence of Grade 4 non-hematologic toxicity. Should treatment need to be delayed for more than 3 weeks at any dose, therapy with paclitaxel will be discontinued.

### 3.3.6 Treatment Assignment

A total of 252 patients will be randomized in this study: 140 patients with ER+/HER2- MBC in Cohort 1 and 112 patients with metastatic TNBC in Cohort 2. Within these groups, patients will be stratified by number of previous chemotherapy regimens for metastatic or recurrent breast cancer (no previous chemotherapy [0]; one previous chemotherapy regimen [1]), and by prior (neo)adjuvant taxane (yes or no), and will be randomized 1:1 to either:

- Arm A: 60 mg/m$^2$ paclitaxel IV days 1, 8, and 15 plus alisertib 40 mg PO BID days 1-3, 8-10, and 15-17 of a 28-day cycle, or
- Arm B: 90 mg/m$^2$ paclitaxel IV days 1, 8 and 15 of a 28-day cycle.

Randomization will be done in blocks of four using SAS software.

### 3.3.7 Packaging and Labeling

The study drug, provided by Millennium, will be labeled and handled at the investigative site as open-label material; packaging labels will fulfill all requirements specified by governing regulations. Alisertib will be supplied as ECT in 10 mg strength. The 60-cc HDPE bottles will have a child-resistant cap and be labeled for take-home use. Patients will receive instructions for home use of Alisertib, including the requirement that Alisertib be administered as intact tablets.

Paclitaxel is a commercially available product. Medication labels will comply with all legal requirements.

## 3.4 Excluded Concomitant Medications and Procedures

The following medications and procedures are prohibited during the study:

- Alternative therapy, including palliative radiotherapy, for treatment of the patient's malignancy
- Any investigational therapy other than alisertib
- Requirement for administration of any proton pump inhibitor (PPI) (paclitaxel/alisertib combination arm only). Patients receiving alisertib are at risk of having a 30% increase in alisertib blood levels with PPIs with a resultant increase in the potential for toxicity. Use of any PPI in either continued or intermittent use will be prohibited on the combination arm during the conduct of the study and patients must discontinue any use of PPI within five days prior to the first dose of alisertib. Patients may be administered alternative agents to manage gastric acidity or reflux (e.g., H2 receptor antagonists, antacids) with exceptions described below. PPI use is allowed for patients on the paclitaxel alone arm.
- Histamine-2 (H2) receptor antagonists are not permitted from within 24 hours of the initiation of alisertib administration through the end of the 3 days of alisertib dosing, except as required for paclitaxel premedication. H2 receptor antagonists are allowed for patients on the paclitaxel alone arm.
- Enzyme inducers, such as the enzyme-inducing antiepileptic drugs phenytoin, carbamazepine or phenobarbital, or rifampin, rifabutin, rifapentine or St. John's Wort within 14 days prior to the first dose of alisertib.

- Antacids are permitted; however, they should not be administered within 2 hours before or 2 hours after administration of alisertib.

### 3.5 Permitted Concomitant Medications and Procedures

Myeloid growth factors to treat patients with neutropenia are permitted, and given prophylactically as needed at the discretion of the physician. Patients who receive prophylactic myeloid growth factors whose ANC >1000 can continue with Neupogen and maintain the current treatment dose of paclitaxel. Patients should undergo alisertib dose reduction if ANC is not adequate for treatment. Antiemetic agents may be administered at the discretion of the investigator but are not generally required as a prophylactic agent. All other manifestations of the patient's malignancy should be treated at the discretion of the investigator.

Antacids are permitted; however, they should not be administered within 2 hours before or 2 hours after administration of alisertib.

Medications with potential CNS effects are not prohibited in this study, but it is recommended that their use be minimized to avoid confusion in the interpretation of CNS effects should they occur during the course of treatment with alisertib. Because of alisertib's structural and pharmacological similarity to the benzodiazepines, concomitant therapy with benzodiazepines is strongly discouraged.

Because paclitaxel is metabolized by CYP2C8 and CYP3A4 enzymes, caution should be used when concomitantly administering paclitaxel with known CY3A4 substrates, CYP3A4 inhibitors, and CYP3A4 inducers, as well as CYP2C8 substrates, inhibitors, and inducers.

All other medical conditions should be treated at the discretion of the investigator in accordance with local community standards of medical care.

### 3.6 Precautions and Restrictions

Patients should not drive, operate dangerous tools or machinery, or engage in any other potentially hazardous activity that requires full alertness and coordination if they experience sedation while enrolled in this study.

Patients are to be instructed to limit the use of alcohol while enrolled in this study. Patients should consume no more than 1 standard unit of alcohol per day during the study and for

30 days from the last dose of alisertib. A standard unit of alcohol is defined as one 12 oz beer (350 mL), 1.5 oz (45 mL) of 80-proof alcohol, or one 6-oz (175 mL) glass of wine.

It is not known what effects alisertib has on human pregnancy or development of the embryo or fetus. Therefore, female patients of childbearing potential must be surgically sterilized or be willing to use an acceptable method of birth control (i.e., a hormonal contraceptive, intra-uterine device, diaphragm with spermicide, or condom with spermicide) for the duration of the study.

## 3.7 Management of Clinical Events

### 3.7.1 Nausea and Vomiting

Prophylactic antiemetic therapy will not be used in this study unless it becomes clear that alisertib causes acute or delayed nausea and/or vomiting. If prophylactic antiemetic therapy is needed, 5-$HT_3$ receptor antagonists should be tried first. Because of the potential of benzodiazepines to cause sedation, the use of benzodiazepines for antiemetic prophylaxis should be reserved for patients who cannot be satisfactorily managed otherwise.

Although this study will not initially employ prophylactic antiemetics in cycle 1, there is no prohibition against antiemetic use in the management of a patient who develops nausea or vomiting, or both.

### 3.7.2 Diarrhea

Antidiarrheal medications will not be used prophylactically; however, patients will be instructed to take loperamide, 4 mg, at the occurrence of the first loose stool and then 2 mg every 2 hours until they are diarrhea-free for at least 12 hours. During the night, patients may take 4 mg of loperamide every 4 hours. Fluid intake should be maintained to avoid dehydration.

### 3.7.3 Central Nervous System Effects

If a patient experiences excessive sedation believed to be related to alisertib, treatment with alisertib should be interrupted. Patients whose sedation is not considered immediately life-threatening should be carefully monitored and given appropriate supportive care.

If the patient's level of consciousness is considered to be life-threatening, necessary measures should be instituted to secure the airway, ventilation, and intravenous access.

Flumazenil (Romazicon®) is a selective benzodiazepine receptor antagonist that is intended as an adjunct to, not as a substitute for, the proper management of benzodiazepine overdose. Although there is neither preclinical nor clinical experience with flumazenil and alisertib, the use of flumazenil should be considered if the level of alisertib-associated sedation is considered to be life-threatening. Patients treated with flumazenil should be monitored for resedation, respiratory depression, and other residual benzodiazepine effects for an appropriate period after treatment. Continued monitoring is particularly important in the case of alisertib given its half-life and the comparatively brief half-life of flumazenil in the CNS (20-30 minutes). Flumazenil should be administered according to its label.

### 3.7.4 Treatment Compliance

All drug(s) will be administered to eligible patients under the supervision of the investigator or identified sub-investigator(s). The pharmacist will maintain records of drug receipt (if applicable), drug preparation, and dispensing, including the applicable lot numbers, patients' height, body weight, and body surface area (see Appendix 5), and total drug administered in milliliters and milligrams. Any discrepancy between the calculated dose and dose administered and the reason for the discrepancy must be recorded in the source documents.

## 3.8 Duration of Treatment and Patient Participation

Patients will remain on study treatment until disease progression, intolerable toxicity, or any other reason mentioned in section 3.10, whichever is earlier. Patients will continue to be followed on study for survival after they have discontinued treatment for up to 2 years from the date of registration.

## 3.9 Schedule of Assessments

### 3.9.1 Prestudy assessments

The following assessments will be performed prior to registration:

1. A signed Patient Informed Consent Form must be obtained prior to registration.
2. A signed Patient Authorization Form (HIPAA) has been obtained prior to registration.
3. It has been confirmed that the patient meets **all** inclusion criteria and **none** of the exclusion criteria. All data for the Inclusion/Exclusion criteria must be verifiable in the patient's source document.
   Note: Receptor status (ER, PgR, HER2) and Ki67 status may be obtained anytime before randomization to the study.
4. A complete medical history must be obtained **within 4 weeks prior to registration**.

5. A complete physical examination (including vital signs, height and body weight) must be obtained **within 4 weeks prior to registration**.
6. Assessment of performance status on the ECOG scale (Appendix 4) must be obtained **within 4 weeks prior to registration**.
7. Assessment of concomitant medications must be obtained **within 4 weeks prior to registration**.
8. A complete blood count (CBC) with differential and platelet count **within 4 weeks prior to registration**.
9. Complete metabolic profile (CMP) including: serum chemistries (creatinine, glucose, total protein, blood urea nitrogen [BUN], total bicarbonate [$CO_2$], albumin, total bilirubin, alkaline phosphatase, and aspartate transaminase [AST] and alanine transaminase [ALT] and electrolytes (total calcium, chloride, potassium, sodium), must be performed **within 4 weeks prior to registration**.
10. Calculation of creatinine clearance based on the creatinine values obtained from the CMP **within 4 weeks prior to registration**, (see Appendix 5).
11. Women of childbearing potential must have a documented negative serum or urine pregnancy test performed **within 3 business days prior to first dose of paclitaxel or paclitaxel plus alisertib**.
12. A clinical assessment of the patient's disease (specifically, by physical examination) must be performed **within 4 weeks prior to registration**.
13. Radiologic assessment of tumors: patients must have a CT of the chest, abdomen and pelvis, and a bone scan, **within 4 weeks prior to registration**. Only patients with a documented history of treated brain metastases should have an MRI or CT of the brain performed **within 4 weeks prior to registration** (CT may be used if MRI is contraindicated). Patients with skin lesions should have the lesion documented by color photography. Please see Appendix 6 for RECIST criteria for measurable disease performed **within 4 weeks prior to registration**. **Under RECIST criteria, PET cannot be used to assess measurable disease.** The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time.
14. Determine if FFPE tissue block (or 20 slides) is available for analysis and storage, **prior to registration**. Collection and shipment of tumor sample (new biopsy or archived tissue) to designated lab (check CTI) should occur as soon as possible and **no later than Day -1**.
15. Review of toxicity assessments, including assessment of peripheral neuropathy, must be performed **within 4 weeks prior to registration.**

Note: Information from procedures that may have been previously performed as part of the patient's routine disease care (prior to enrolling in the trial) is allowed to be used to satisfy inclusion criteria as long as the procedures were performed within 28 days of registration.

### 3.9.2 Assessments during treatment

The following evaluations will be performed during therapy at the start of each cycle, unless otherwise specified. There is a window (**up to 3 business days prior to the scheduled time; ± 7 business days for radiologic assessments**) for assessments during the study.

Cycle 2 and subsequent cycles, only, there is a **window of +3 business days (after the scheduled time)** for treatment administration during the study. Any delay within this window is NOT a deviation.

**Note:** Cycle 1 only, the baseline values for those assessments that are to be done prior to every cycle may be used for Cycle 1 assessments as long as they are completed within 3 business days prior to the patient receiving their first dose of study drug. If more than 3 business days have elapsed since the baseline assessment, the assessment must be repeated.

Assessments that are to be done on days when study drug is administered must be done prior to dosing as these assessments (CBC, CMP, assessment of response, PS, etc.) may determine whether or not drug is administered, or if a dose reduction is necessary.

1. A brief medical history must be done to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history, specifically those that have occurred **since** baseline, should be recorded on the AE page of the eCRF.
2. A brief physical examination, including vital signs and body weight
   ***Note:** Patients randomized to the paclitaxel and alisertib arm will be seen for Cycle 1 on days 1, 8 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only). Cycle 2 on days 1 and 15 to have a brief physical exam, review of AEs, concomitant medications, vitals, weight (day 1 of each cycle only), and performance status (day 1 of each cycle only). And cycles 3 and subsequent cycles, patients will have a brief physical exam, review of AEs, concomitant medications, and vitals, weight, and performance status on day 1 of each cycle. Patients receiving paclitaxel alone will be seen day 1 of each cycle to have a brief physical exam, review of AEs, concomitant medications, vitals, weight, and performance status.
3. Assessment of PS on the ECOG scale (Appendix 4)
4. Assessment of concomitant medications
5. A CBC with differential and platelet count*
   ***Note:** CBCs are to be done within 3 business days prior to scheduled dosing on Day 1 of each Cycle for both treatment arms; CBCs also need to be done on Days 8 and 15 of each cycle. Results of the CBC must be known prior to dosing the patient on days when these assessments are done.
6. Serum chemistries (CMPs)*
   ***Note:** CMP are to be done within 3 business days prior to scheduled dosing on Day 1 of each Cycle for both treatment arms.
7. Tumor response by clinical assessment of the patient's disease (specifically, by physical examination) must be performed Day 1 of each cycle.
8. Radiological assessment of tumors to follow measurable disease will be performed for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time. **Under RECIST criteria, PET cannot be used to assess measurable disease**.

- Chest and abdominal CT imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. Pelvic imaging will be continued at subsequent tumor assessments only if pelvic metastases are identified at screening. **Note:** Patients who have a PET/CT scan do not need to have a dedicated CT scan if they have disease measurable on the CT part of the PET/CT scan. This applies throughout the study
- Bone lesions presented at screening, bone scans will then be repeated every 12 weeks after initiation of treatment for the first 32 weeks of treatment and every 16 weeks thereafter for the duration of the treatment period.
- Patients with previously treated brain metastases identified at screening, a brain MRI or CT will be performed every 8 weeks after initiation of treatment for the first 32 weeks of treatment and every 12 weeks thereafter for the duration of the treatment period. .

9. Assessments of other sites of disease, (full staging CT scan), must be performed **only to confirm a CR**.
10. A toxicity assessment, including assessment of peripheral neuropathy, must be performed.
11. Review of patient oral medication diary (Appendix 8).

For details on required assessments, please refer to Schedule of Events.

### 3.9.3 End of Treatment assessments

This is a single assessment that will be performed when a patient finishes treatment, either due to PD or toxicity that places patients off treatment, or in cases of MD decision or where patient withdraws consent. Patients who withdraw consent may not want any further assessment; however, they should be encouraged to have these final assessments done.

There is a window (up to 7 business days) following determination that patient is "off treatment" for assessments following last treatment. Any delay within this window is NOT a deviation.

The following evaluations will be performed following the last treatment:

1. A brief medical history should be done to capture events that have occurred since the last cycle. Events that were not captured in the baseline complete medical history should be recorded on the AE page of the eCRF.
2. A brief physical examination, including vital signs and body weight
3. Assessment of PS on the ECOG scale (Appendix 4)
4. Assessment of concomitant medications
5. A CBC with differential and platelet count
6. A CMP

7. A tumor clinical assessment of the patient's disease (specifically, by physical examination)
8. Radiological assessment of tumors. There is a window (± 7 business days for radiologic assessments) for end of treatment. Any delay within this window is NOT a deviation.
    - Chest and abdominal CT imaging will then be performed at End of Treatment. Pelvic imaging will be continued at subsequent tumor assessments only if pelvic metastases are identified at screening. The methods used for prestudy assessments should be used throughout the study. If possible, the same equipment should be used each time. **Under RECIST criteria, PET cannot be used to assess measurable disease**.

      * Note* For patients who come off-study treatment for reasons other than progression, imaging assessments should be performed per standard of care for the practice until progressive disease is documented. Progression free survival and overall survival dates will be collected from patient's chart until progressive disease is documented.
    - Bone scan is required only if the patient has bone metastases present at screening, or has developed progressive disease in the bone during study treatment.
    - Brain MRI or CT is required only for patients with historically treated brain metastases present at screening, or have developed brain metastases as part of their progressive disease during study treatment.
    - Skin lesion assessments are required only for patients with a documented history of skin lesions, or for patients who developed skin using a digital camera (color photography).
9. A toxicity assessment
10. Review of patient oral medication diary (Appendix 8)
11. Survival status

For details on required assessments, please refer to Schedule of Events.

### 3.9.4 Follow-up assessments

After the end of treatment visits, all patients will be followed for safety up to 30 days after the last dose of study treatment with paclitaxel and/or alisertib. There is a +/- 7 business day window for follow up visit assessments. Any delay within this window is NOT a deviation.

All patients who discontinue from study treatment due to disease progression must have their progression clearly documented according to the criteria specified in RECIST 1.1 (Appendix 6).

If a patient did not discontinue study treatment due to disease progression, death, adverse event, start of new anti-neoplastic therapies, lost to follow-up, or withdrawal of consent for efficacy follow-up then tumor assessments should continue to be performed per standard of

care until the start of new anti-cancer therapy, disease progression, death, lost to follow-up or withdrawal of consent for efficacy follow-up.

All patients will be followed for survival every 3 months from last date of treatment regardless of treatment discontinuation reason (except if consent is withdrawn or patient is lost to follow-up) until death or for up to 2 years from date of registration. Survival information can be obtained via phone and information will be documented in source document.

## 3.10 Discontinuation of Treatment and/or Study Participation

Patients will be informed that they have the right to withdraw from study treatment at any time for any reason, without prejudice to their medical care.

### 3.10.1 Reasons Off Treatment

Patients will be taken off treatment if any of the following occur:

1. Disease progression
2. Intolerable toxicity

   Note: If patients go off study treatment due to any adverse event, regardless of grade, the reason off treatment will be documented as "Adverse event" in eDC; the toxicity (regardless of grade) must be documented in the toxicity section of eDC with the action code entered that is appropriate for discontinuation of study treatment.
3. Treatment is interrupted for more than 3 consecutive weeks for any reason (**Note**: Delays do not count scheduled weeks of rest).
4. An intercurrent illness, which would in the judgment of the Investigator, affect assessments of clinical status to a significant degree or require discontinuation of study treatment
5. Non-protocol therapy (chemotherapy, radiation therapy, hormonal therapy, immunotherapy, or surgery) is administered during study treatment
6. Noncompliance with protocol or treatment
7. Becomes pregnant
8. Refuses to continue treatment (patient will continue to be followed for survival)
9. Physician decision
10. Other

The date of and reason for discontinuation must be noted on the Change of Status page of the electronic Case Report Form (eCRF). Every effort should be made to complete the appropriate assessments.

### 3.10.2 Reasons Off Treatment

Patients will be considered off study if any of the following occur:

1. Termination of study by Delta and/or Millennium Pharmaceuticals, Inc.
2. Withdrawal of consent for study participation (patient will not be contacted and no further information will be collected); patient must sign a change in status of consent form

   **Note:** If the patient withdraws consent, then no additional data will be collected without her explicit consent; all data collected prior to withdrawal of consent may be used in the data analysis. The only exception to the collection of data after withdrawal of consent is collection of **date of death** and cause of death (if available) when the endpoint of the study is mortality.

   **Note:** Patients who decide to stop study therapy before progression of disease will be considered to have withdrawn consent for study therapy but not to have withdrawn consent for study participation and follow-up.
3. Lost to follow-up (3 attempts should be documented in the patient's source document before the site considers the patient as LFU.)
4. Death

The appropriate information must be completed on the Change of Status page of the eCRF.

## 3.11 Efficacy, Correlative Studies, and Safety Measurements

### 3.11.1 Efficacy Measurements

Tumor response will be assessed locally according to Response Evaluation Criteria in Solid Tumors (RECIST), based on RECIST Version 1.1 (Appendix 6). The local investigator's assessment will be used for all endpoint analyses and for treatment decision making.

The following imaging assessments will be performed:

- CT of chest, abdomen, and pelvis at screening. Chest and abdominal CT imaging should then be performed every 8 weeks after initiation of treatment for the first 32 weeks, then every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment. Pelvic imaging should be continued at subsequent tumor assessments if pelvic lesions are identified at screening, or as clinically indicated.

- A whole body TC-99 bone scan at screening for bone lesions according to institutional guidelines. If bone lesions are present at screening, bone scans should be repeated every 12 weeks after initiation of treatment for the first 32 weeks, then every 16 weeks thereafter for the duration of the treatment period, and at End of Treatment (only patients with bone metastases at baseline or those who develop bone metastases as part of their disease progression), using the same methodology used at screening. Patients whose first follow-up bone scan is read as progressive disease may stay on study therapy if the treating physician does not think the patient's disease has progressed clinically, ie, no new bone pain or deterioration in performance status and no progression of disease in other sites. Subsequent bone scans that are read as demonstrating progressive disease will lead to termination of study therapy.

- A baseline brain MRI is necessary for patients with a documented history of treated brain metastases (CT is allowed if MRI is contraindicated). A baseline brain MRI or CT scan is not required if patients do not have a documented history of brain metastases. Brain MRI or CT will be obtained at each tumor assessment only in patients with a documented history of treated brain metastases. Imaging will then be performed every 8 weeks after initiation of treatment for the first 32 weeks, then every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment (only patients with documented history of brain metastases at baseline or those who develop brain metastases as part of their disease progression).

- Skin lesions should be documented at screening using a digital camera (color photography) in clear focus including a ruler or calipers in such a way that the size of the lesion(s) can be determined from the photograph. Skin photographs should be continued at subsequent tumor assessments for any lesions that were photographed at screening. Skin lesion assessments should be performed every 8 weeks after initiation of treatment for the first 32 weeks, then every 12 weeks thereafter for the duration of the treatment period, and at End of Treatment (only for patients with skin lesions at baseline or those who develop skin lesions as part of their disease progression).

### 3.11.2 Correlative Biomarker Study

One formalin fixed paraffin embedded tumor block (or 20 unstained slides if tumor block is not available) from the primary breast cancer, and will be stored for future analysis of

potential biomarkers of benefit from paclitaxel plus alisertib, including but not limited to FOXM1 and AURKA expression, p53 mutation status, and genomic instability. A metastatic lesion is preferred for FFPE analysis if the lesion was resected (no core biopsies). If resected metastatic lesion is unavailable, an FFPE block from the primary breast cancer may be submitted (from definitive surgery unless diagnostic core biopsy had more cancer than the definitive breast surgery specimen).

Since the archived sample may not be located at the institution where the original diagnosis was rendered, the investigational sites will be responsible for locating it. For all tumor samples, the sample collection information must be captured on the relevant eCRF page(s) and laboratory requisition form(s).

Tumor samples will be sent to a designated lab (check CTI) for storage and future analysis. See Collection of Shipping Information provided by sponsor for more detailed instructions on sample preparation and submission information (see Appendix 7).

### 3.11.3 Safety Measurements

Safety assessments will consist of the following: monitoring and recording of all adverse events and serious adverse events; regular monitoring of hematology, and blood chemistry; regular measurement of vital signs, physical examination (including weight); and performance status.

These assessments should be performed periodically throughout the study, as indicated in the Schedule of Events, except for adverse events which will be evaluated continuously.

All patients who receive at least one dose of study drug will be evaluated for safety. Toxicities will be graded and reported from the start of treatment according to the NCI CTCAE Version 4.03 (Appendix 2). Incidence and type of adverse events will be tabulated and summarized using descriptive statistics.

## 3.12 Study Drug Administration

Alisertib will be administered PO at a dosage of 40 mg BID on days 1-3, 8-10, and 15-17 of each 28-day cycle.

Patients will be instructed to take each oral dose of alisertib with 8 ounces (1 cup, 240 mL) of water. For BID dosing, the doses must be taken at least 6 hours apart.

Alisertib will be supplied as 10 mg ECT, with the dose strength expressed as milligrams of active drug (free acid); higher strengths may be supplied depending on the observed MTD. All tablets are to be ingested whole; patients who have difficulty swallowing tablets will be excluded from the study. Antiemetic agents may be administered at the discretion of the investigator. Although not prohibited, the use of benzodiazepines for the prophylaxis or treatment of nausea or vomiting is strongly discouraged because of the potential benzodiazepine-like effects of alisertib.

Study drug will be administered only to eligible patients under the supervision of the investigator or identified sub-investigator(s).

### 3.13 Description of Investigational Agents

Alisertib drug product is supplied as the ECT dosage form in 10 mg strengths with dose strength expressed as the milligrams of active drug (free acid); other strengths may be supplied based on the observed MTD. The key formulation excipients of the alisertib tablet formulation that aid in the in vivo absorption of the drug are the buffer (sodium bicarbonate), the surfactant (sodium lauryl sulfate), and the enteric coating.

### 3.14 Preparation, Reconstitution, and Dispensation

Alisertib ECT are packaged (10 tablets to a bottle) in a 60-cc high-density polyethylene (HDPE) bottle with a child-resistant cap.

Alisertib is an anticancer drug, and as with other potentially toxic compounds, caution should be exercised when handling alisertib.

### 3.15 Packaging and Labeling

The packaged and labeled study drug, alisertib ECT, will be provided by Millennium and will be handled at the investigative site as open-label material. The labels on the study drug will fulfill all requirements specified by governing regulations. Ten alisertib ECT are packaged into each 60-cc HDPE bottle. Alisertib will be supplied as ECT in 10 mg strength. The bottles will have a child-resistant cap and be labeled for take-home use. Patients will receive instructions for home use of alisertib, including the requirement that alisertib be administered as intact tablets.

As required by local regulations, any modifications to the plan for drug supply or storage will be communicated to the investigator and detailed in the Study Manual.

### 3.16 Storage, Handling, and Accountability

Tablets should remain in the bottle provided until use. The container should be stored at the investigative site at controlled room temperature (20-25°C; 68-77°F; excursions are permitted from 15-30°C; 59-86°F) and used before the retest expiry date provided by Millennium. Containers should be kept closed during storage.

Because alisertib is an investigational agent, it should be handled with due care. In case of contact with broken tablets, raising dust should be avoided during the cleanup operation.

The product may be harmful by inhalation, ingestion, or skin absorption. If tablets are broken or crushed, gloves and protective clothing should be worn during the cleanup operation. The area should be ventilated and the site washed after material pick-up is complete. The broken/crushed material should be disposed of as hazardous medical waste in compliance with federal, state, and local regulations.

In case of contact with the powder (e.g., from a broken tablet), skin should be washed immediately with soap and copious amounts of water for at least 15 minutes. In case of contact with the eyes, copious amounts of water should be used to flush the eyes for at least 15 minutes. Medical personnel should be notified.

Patients are to be instructed on proper storage, accountability, and administration of alisertib, including that alisertib is to be taken as intact tablets.

# 4. ADVERSE EVENTS

## 4.1.1 Adverse Event Definition

Adverse event (AE) means any untoward medical occurrence in a patient or subject administered a pharmaceutical product; the untoward medical occurrence does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product whether or not it is related to the medicinal product. This includes any newly occurring event, or a previous condition that has increased in severity or frequency since the administration of study drug.

For this protocol an abnormal laboratory value will not be assessed as an AE unless that value leads to discontinuation or delay in treatment, dose modification, therapeutic intervention, or is considered by the investigator to be a clinically significant change from baseline.

## 4.1.2 Serious Adverse Event Definition

Serious adverse event (SAE) means any untoward medical occurrence that at any dose:

- Results in **death**.
- Is **life-threatening** (refers to an AE in which the patient was at risk of death at the time of the event. It does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires **inpatient hospitalization or prolongation of an existing hospitalization** (see clarification below on planned hospitalizations in Section 4.2).
- Results in **persistent or significant disability or incapacity**. (Disability is defined as a substantial disruption of a person's ability to conduct normal life functions).
- Is a **congenital anomaly/birth defect**.
- Is a **medically important event**. This refers to an AE that may not result in death, be immediately life threatening, or require hospitalization, but may be considered serious when, based on appropriate medical judgment, may jeopardize the patient,

require medical or surgical intervention to prevent 1 of the outcomes listed above, or involves suspected transmission via a medicinal product of an infectious agent. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse; any organism, virus, or infectious particle (e.g., prion protein transmitting Transmissible Spongiform Encephalopathy), pathogenic or nonpathogenic, is considered an infectious agent.

- Clarification should be made between a serious AE (SAE) and an AE that is considered severe in intensity (Grade 3 or 4), because the terms serious and severe are NOT synonymous. The general term *severe* is often used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor medical significance (such as a Grade 3 headache). This is NOT the same as *serious*, which is based on patient/event outcome or action criteria described above, and is usually associated with events that pose a threat to a patient's life or ability to function. A severe AE (Grade 3 or 4) does not necessarily need to be considered serious. For example, a white blood cell count of 1000/$mm^3$ to less than 2000 is considered Grade 3 (severe) but may not be considered serious. Seriousness (not intensity) serves as a guide for defining regulatory reporting obligations.

## 4.2 Procedures for Reporting Serious Adverse Events (SAEs)

AEs may be spontaneously reported by the patient and/or in response to an open question from study personnel or revealed by observation, physical examination, or other diagnostic procedures. Any clinically relevant deterioration in laboratory assessments or other clinical finding is considered an AE. When possible, signs and symptoms indicating a common underlying pathology should be noted as one comprehensive event. AEs which are serious must be reported to Delta Pharmaceuticals Drug Safety and Epidemiology Department from the first dose of alisertib up to and including 30 days after administration of the last dose of alisertib. Any SAE that occurs at any time after completion of alisertib treatment or after the designated follow-up period that the sponsor-investigator and/or sub-investigator considers to be related to any study drug must be reported to Delta Central Safety Department. Planned hospital admissions or surgical procedures for an illness or disease that existed before the patient was enrolled in the trial are not to be considered AEs unless the condition deteriorated in an unexpected manner during the trial (e.g., surgery was performed earlier or

later than planned). All SAEs should be monitored until they are resolved or are clearly determined to be due to a patient's stable or chronic condition or intercurrent illness(es).

Instructions for Reporting SAEs to Delta Central Safety Department

The investigator has the obligation to report all serious adverse events to the IRB and the sponsor, (Delta Pharmaceuticals Drug Safety and Epidemiology Department (DS&E)). Serious adverse events should also be reported to the FDA and IRB in accordance with regulations and IRB policy.

The investigator must complete the FDA MedWatch 3500A form and Delta SAE coversheet in English, assess the relationship to study treatment and send the initial completed MedWatch form and Delta SAE coversheet by Fax to (877) 571-8934 within 24 hours to the local Delta Drug Safety & Epidemiology (DS&E) Department. The investigator must then ensure that the form and coversheet are accurately and fully completed with follow-up information and fax those to Delta DS&E Department within 2 to 3 calendar days for deaths or life-threatening events and 4 calendar days for other serious adverse events. The original and the duplicate copies of the FDA MedWatch form, Delta SAE coversheet, and the fax confirmation sheet should be kept with the site's regulatory binder.

In addition, all SAEs will be reported by telephone to the Delta Central Safety Department as soon as study personnel become aware of the SAE. The SAEs should be reported by facsimile within 24 hours to the Delta Central Safety Department. The site will supply as much information as is available at the time of the initial Fax to the Delta Central Safety Department (study number, subject initials, subject study number, event), during both business and non-business hours, to:

**Delta Clinical Research Safety Department**
10101 Woodloch Forest
The Woodlands, TX 77380
SAE Hotline: (281) 863-6503
Safety Fax: (877) 571-8934

Follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or discontinued study participation. The MedWatch form, Delta SAE coversheet, and fax confirmation sheet must be retained by the investigator.

Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous termination, details of the birth, and the presence or absence of any congenital abnormalities or birth defects.

Adverse events will be recorded for the duration of a patient's study treatment. All AEs, regardless of causal relationship, are to be recorded in the source documentation. The Investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. The diagnosis should be documented as the AE/SAE and not the individual signs/symptoms.

All AEs will be graded and reported according to the NCI CTCAE (version 4.03). The relationship of each event to the study drug will be assessed by the Investigator and recorded on the eCRF. Additional information about each event, such as treatment required, whether or not the study drug had to be discontinued, and eventual outcome will also be recorded on the eCRF.

### 4.3 Procedures for Reporting Drug Exposure during Pregnancy and Birth Events

If a woman becomes pregnant or suspects that she is pregnant while participating in this study, she must inform the investigator immediately and must permanently discontinue study drug(s). The sponsor-investigator must fax a completed Pregnancy Form to the Millennium Department of Pharmacovigilance or designee (or designee; see Section 4.2 for contact information) immediately. The pregnancy must be followed for the final pregnancy outcome (ie, delivery, still birth, miscarriage) and Millennium Pharmacovigilance will request this information from the investigator.

### 4.4 Product Complaints

A product complaint is a verbal, written, or electronic expression that implies dissatisfaction regarding the identity, strength, purity, quality, or stability of a drug product. Individuals who identify a potential product complaint situation should immediately contact MedComm Solutions (see below), as well as Delta Clinical Research, LLC, and report the event. Whenever possible, the associated product should be maintained in accordance with the label instructions pending further guidance from a Millennium Quality representative.

| |
|---|
| **For Product Complaints,**<br>call MedComm Solutions at<br>877-674-3784 (877 MPI DRUG)<br>(US and International) |

Product complaints in and of themselves are not AEs. If a product complaint results in an SAE, an SAE form should be completed and sent to the Delta Central Safety Department (refer to Section 8.2).

# 5. STATISTICAL PROCEDURES

## 5.1 Study Design and Overview of Primary and Secondary Endpoints

This is a Phase II, multicenter, randomized, parallel group study to demonstrate the superiority of alisertib plus paclitaxel compared to paclitaxel alone in PFS in two cohorts of patients with metastatic or locally recurrent breast cancer, one with ER+/HER2- disease and the other with TN disease. It is estimated that the median PFS time with paclitaxel alone treatment will be 3.5 months in TN patients and 6 months in ER+/HER2- patients. With the addition of alisertib to paclitaxel, the primary endpoint of this study hypothesizes that the median PFS times will increase to 5.8 months and to 10 months, respectively, with a PFS hazard ratio (HR) of 0.6 in these two cohorts. OS, ORR, CBR and toxicities are the secondary objectives. Molecular analyses of patients' archival breast cancer tissue to investigate potential predictive markers will be proposed and it is also the one of secondary endpoints.

## 5.2 Sample Size Estimation/Accrual Rate

In the pivotal trial of ECOG 2100, first-line weekly paclitaxel resulted in a median PFS of 4.6 months in TN patients, and of approximately 9 months in ER+ patients.[8] In this trial the first-line and second-line patients will be enrolled and we estimate that the median PFS in patients with paclitaxel alone will be 3.5 months in the TN cohort and 6 months in the ER+/HER2- cohort. To demonstrate a HR of 0.6 with 80% power and one-sided alpha = 5% with the addition of alisertib to paclitaxel in each of the two cohorts, 104 TN and 118 ER+/HER2 patients would be required for a single final analysis of each cohort.

However, a 2-stage sequential design with futility boundaries for each group is employed for this study. Using ADDPLAN, 112 patients with 103 events (progressions or deaths) are needed for the TN population. The first analysis will be performed when the cumulative events are 34 with a corresponding accumulative information of 33% and an approximate sample size of 64. The statistics resulting from the first stage will be compared with acceptance and rejection boundaries given for the first stage. That is, using the Log-rank test for PFS between two groups in the first stage, if the Z-value is greater than 2.808, superiority of alisertib/paclitaxel can be declared compared to paclitaxel alone. If the Z-value is less than 0, futility of the combination compared to paclitaxel alone will be declared. The study for the TN cohort will be stopped if either superiority or futility is declared. Otherwise, the trial for the TN cohort will continue to the second stage.

The first-stage analysis for the ER+/HER2- cohort will be performed independently of analysis in the TNBC cohort. The 2-stage sequential design for the ER+/HER2- cohort requires a total of 113 events and 140 patients, with 23 events and approximately 68 patients for the first analysis. The corresponding accumulative information is 20% and the rejection boundary is 3.482 for this stage. Similar to the TN cohort, using the Log-rank test, the superiority or the futility will be declared if Z-value is greater than 3.482 or less than 0, respectively, and the study for this cohort will be stopped. Otherwise, the trial for the ER+/HER2- cohort will continue to the second stage.

The total sample size for the evaluable patient population is 252 (ER+/HER2-: n=140; TN: n=112), of which 126 patients will receive alisertib. If the study stops after stage I in each cohort, then the total sample size will be reduced to 132 (ER+/HER2-, n=68; TR, n=64), of which 66 patients will be treated with alisertib.

An accrual rate of 12-15 patients per month is anticipated with similar distribution between cohorts; thus the accrual phase will be approximately 24 months. The last patient will be followed for approximately 12 months after enrollment, until disease progression or treatment-limiting toxicity occurs. Therefore, the anticipated total length of the study is approximately 36 months.

### 5.3 Randomization and Stratification Factors

Patients in each cohort will be randomly assigned to alisertib/paclitaxel or paclitaxel alone arms and stratified by the number of previous chemotherapy regimens for metastatic or locally recurrent breast cancer (0 vs. 1 previous chemotherapy regimen) as well as by previous (neo)adjuvant paclitaxel (yes or no).

### 5.4 Evaluation of Efficacy

The primary efficacy endpoint is progression-free survival (PFS). PFS is defined as the time from the date of the randomization to the date of first documented disease progression or death from any cause. Patients who do not exhibit progression or death at the date of the analysis cut-off will be censored at the date of last contact. In patients with lytic bone-only disease at study entry, progressive disease will be defined as documentation of progressive lytic/destructive disease on CT scan, MRI, or X-ray.

PFS will be estimated using Kaplan-Meier method with 95% confidence intervals (CI) in Intent-to-treat (ITT) population, which includes all patients registered on the study (eligible

and ineligible). The stratified logrank test will be used for comparing the distributions of the two treatment arms. A Cox proportional hazards analysis will be performed to assess the association of potential prognostic factors with PFS and to adjust the treatment comparisons for those factors. The results will be presented in terms of adjusted hazard ratios together with associated 95% CI and p-values.

Secondary efficacy endpoints include OS, ORR, CBR, toxicities and molecular analyses of patients' archived breast cancer tissue to investigate potential predictive markers (see Correlative Study Section).

OS will be measured from the date of the randomization to the date of death for patients who die. If a patient is still alive or is lost to follow up, the patient will be censored at the last contact date. OS in each arm will also be summarized using the Kaplan-Meier method in the ITT population.

ORR, defined as the percentage of CR plus PR, and CBR, defined as the percentage of ORR plus SD greater than 6 months, will be examined using univariate and multivariate approaches in the evaluable population, which includes all eligible patients who received at least 1 dose of study drug. Fisher's exact test will be employed in the univariate comparison of treatment arms with each outcome rate. Logistic regression will be performed to assess the association of potential risk factors with each outcome rate and to adjust the treatment comparisons for those factors. The results will be presented in terms of adjusted risk ratios together with associated 95% CI and p-values. Time to response and duration of response will be calculated in each group.

In addition, patient characteristics including demographics and pre-treatment characteristics such as race, sex, ECOG PS, and age will be described and compared between the two arms in each cohort. Disease histology at baseline, medical history, and prior therapies will be summarized and compared, too. Mean, standard deviation, median, minimum and maximum values will be presented for continuous variables, and frequency tables showing numbers and percentages will be presented for categorical variables.

## 5.5 Evaluation of Safety

The safety profile of the treatment will be assessed through dose exposure, summaries of adverse events, serious adverse events, adverse events leading to study therapy discontinuation, and treatment-related deaths. Toxicity events will be reported using the worst NCI CTCAE grade adverse event per patient. Safety population, defined as all patients

who received at least 1 dose of study treatment, will be included in the analysis for safety. The safety evaluation will summarize numbers and frequencies of all study related adverse events, as well as dose interruptions, dose reductions, and treatment discontinuations due to toxicities.

A Bayesian continuous interim monitoring rule for toxicity will be applied to the first 40 patients in the experimental arm beginning after the first five patients have been randomized to this arm, using the methodology by Thall, Simon, and Estey.[45] We will monitor the probability of a 30% toxicity rate, where toxicity is defined as patients who require 2 or more dose reductions or delays due to toxicity during Cycles 1 and 2. If there is more than a 95% chance that this toxicity rate is greater than 30% in the experimental arm, accrual will be suspended and appropriate modifications will be discussed by the Delta safety team and Millenium Pharmaceuticals, Inc.

The stopping boundaries corresponding to this monitoring rule are:

| # Patients Randomized to Experimental Arm | Suspend Accrual if there are this many Patients with toxicity (2 or more dose reductions or delays in first two cycles) |
|---|---|
| 1-4 | Never stop with this many patients |
| 5 | 4-5 |
| 6-8 | 5-8 |
| 9-10 | 6-10 |
| 11-12 | 7-12 |
| 13-15 | 8-15 |
| 16-18 | 9-18 |
| 19-20 | 10-20 |
| 21-23 | 11-23 |
| 24-25 | 12-25 |
| 26-28 | 13-28 |
| 29-31 | 14-31 |
| 32-34 | 15-34 |
| 35-36 | 16-36 |
| 37-39 | 17-39 |
| 40 | 18-40 |

The operating characteristics of this rule are summarized below. If the true toxicity rate is very high at 50% or 60%, the chances of stopping early for toxicity are 90% and 99%, respectively. With this rule, if the true toxicity rate is 30%, there is a 16% chance of stopping early for toxicity.

| True toxicity rate | Early stopping probability | Average number of patients treated |
|---|---|---|
| 0.10 | 0.0008 | 40+ |
| 0.20 | 0.0207 | 40+ |
| 0.30 | 0.1622 | 38 |
| 0.40 | 0.5500 | 28 |
| 0.50 | 0.8980 | 17 |
| 0.60 | 0.9932 | 10 |

This rule incorporates a prior beta (0.6, 1.4) for the experimental toxicity rate, corresponding to a 30% toxicity rate, and a constant 30% rate was assumed for the comparison to the standard treatment. These stopping boundaries and operating characteristics were obtained using the publically available software Multc Lean Desktop version 2.1.0 developed by the Biostatistics Department of the University of Texas M.D. Anderson Cancer Center.

### 5.6 Correlative Studies

The objectives of this correlative study include the measurement of FOXM1 and AURKA in the primary or metastatic tumor, which will be assessed by RT-PCR expression levels on tumor FFPE sections. High coordinate expression of both FOXM1 and AURKA will be the main biomarkers correlated with PFS obtained with paclitaxel plus alisertib vs. paclitaxel alone in the combined analyses of the ER+/HER2- and TN cohorts, as well as in the ER+/HER2- and TN cohorts separately. PFS with paclitaxel plus alisertib vs. paclitaxel alone will also be evaluated in patients with FOXM1 and/or AURKA levels below the median for ER+/HER2- and TN disease cohorts evaluated together and separately.

### 5.7 Interim Analysis

The interim analysis will be performed when the number of PFS events is 34 with a corresponding accumulative information of 33% and an approximate sample size of 64 for

the TN cohort. For the ER+/HER2- cohort, the interim analysis will be initiated when the number of PFS events is 23 with an approximate sample size of 68 patients in the first stage.

# 6. ADMINISTRATIVE REQUIREMENTS

## 6.1 Good Clinical Practice

The study will be conducted in accordance with the International Conference on Harmonisation (ICH) for Good Clinical Practice (GCP) and the appropriate regulatory requirement(s). The investigator will be thoroughly familiar with the appropriate use of the drug as described in the protocol and Investigator's Brochure. Essential clinical documents will be maintained to demonstrate the validity of the study and the integrity of the data collected. Master files should be established at the beginning of the study, maintained for the duration of the study and retained according to the appropriate regulations.

## 6.2 Ethical Considerations

The study will be conducted in accordance with ethical principles founded in the Declaration of Helsinki (see Appendix 1). The IRB/IEC will review all appropriate study documentation in order to safeguard the rights, safety and well-being of the patients. The study will only be conducted at sites where IRB/IEC approval has been obtained. The protocol, Investigator's Brochure, informed consent, advertisements (if applicable), written information given to the patients (including diary cards), safety updates, annual progress reports, and any revisions to these documents will be provided to the IRB/IEC by the investigator. Informed consent documents will be reviewed by Delta and/or Millennium or designee prior to IRB/IEC submission.

## 6.3 Patient Information and Informed Consent

After the study has been fully explained, written informed consent will be obtained from either the patient or his/her guardian or legal representative prior to study participation. The method of obtaining and documenting the informed consent and the contents of the consent will comply with ICH-GCP and all applicable regulatory requirement(s).

## 6.4 Patient Confidentiality

In order to maintain patient privacy, all data capture records, drug accountability records, study reports and communications will identify the patient by initials and the assigned patient number. The investigator will grant monitor(s) and auditor(s) from Delta,

Millennium or its designees and regulatory authority(ies) access to the patient's original medical records for verification of data gathered on the data capture records and to audit the data collection process. The patient's confidentiality will be maintained and will not be made publicly available to the extent permitted by the applicable laws and regulations.

## 6.5 Protocol Compliance

The investigator will conduct the study in compliance with the protocol given approval/favorable opinion by the IRB/IEC and the appropriate regulatory authority(ies). Changes to the protocol will require approval from Delta, Millennium and written IRB/IEC approval/favorable opinion prior to implementation, except when the modification is needed to eliminate an immediate hazard(s) to patients. The IRB/IEC may provide, if applicable regulatory authority(ies) permit, expedited review and approval/favorable opinion for minor change(s) in ongoing studies that have the approval /favorable opinion of the IRB/IEC. The investigator will submit all protocol modifications to Delta, Millennium and the regulatory authority(ies) in accordance with the governing regulations.

Any departures from the protocol must be fully documented in the source documents.

## 6.6 On-site Audits

Regulatory authorities, the IEC/IRB, Delta, and/or Millennium's clinical quality assurance group may request access to all source documents, data capture records, and other study documentation for on-site audit or inspection. Direct access to these documents must be guaranteed by the investigator, who must provide support at all times for these activities.

## 6.7 Drug Accountability

Accountability for alisertib at all study sites is the responsibility of the Principal Investigator. The investigator will ensure that the drug is used only in accordance with this protocol. Drug accountability records indicating the drug's delivery date to the site (if applicable), inventory at the site (if applicable), use by each patient, and return to Delta and/or Millennium or disposal of the drug (if applicable and if approved by Millennium) will be maintained by the clinical site. Accountability records will include dates, quantities, lot numbers, expiration dates (if applicable), and patient numbers.

Drug compliance should be recorded in the eCRF. Patients on the paclitaxel plus alisertib arm should be given a copy of the Oral Medication Patient Diary (Appendix 8), and adherence to therapy should be reviewed at each office visit.

## 6.8 Premature Closure of the Study

This study may be prematurely terminated, if in the opinion of the investigator, Delta, or Millennium, there is sufficient reasonable cause. Written notification documenting the reason for study termination will be provided to the investigator, Delta, or Millennium by the terminating party.

Circumstances that may warrant termination include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to patients
- Failure to enter patients at an acceptable rate
- Insufficient adherence to protocol requirements
- Insufficient complete and/or evaluable data
- Plans to modify, suspend or discontinue the development of the drug

Should the study be closed prematurely, all study materials must be returned to Millennium.

## 6.9 Record Retention

The investigator will maintain all study records according to ICH-GCP and applicable regulatory requirement(s).

## 7. USE OF INFORMATION

All information regarding alisertib supplied by Delta and/or Millennium to the investigator is privileged and confidential information. The investigator may use this information to accomplish the study, but may not use it for other purposes without consent from Delta and Millennium. In accordance with the agreement between Delta, Millennium and the investigator sponsor, complete study data must be provided to Delta and Millennium. This data and other information obtained from the clinical study may be used by Millennium for the development of alisertib and may be disclosed by Delta and/or Millennium to regulatory authority(ies), other investigators, corporate partners, or consultants as deemed necessary by Delta and/or Millennium.

Upon completion of the clinical study and evaluation of results by Delta and Millennium, the hospital or institution and/or investigator may publish or disclose the clinical trial results pursuant to the terms contained in the applicable Clinical Trial Agreement.

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# 9. APPENDICES

## 9.1 Appendix 1: Declaration of Helsinki

### World Medical Association Declaration of Helsinki:

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amended by the 29th WMA General Assembly, Tokyo, Japan, October 1975 35th WMA General Assembly, Venice, Italy, October 1983 41st WMA General Assembly, Hong Kong, September 1989 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996 and the 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

**A. INTRODUCTION**

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.
2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfillment of this duty.
3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."
4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.
5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.
6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.
7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.
8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.
9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to

reduce or eliminate any of the protections for human subjects set forth in this Declaration.

**B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH**

1. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.
2. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.
3. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.
4. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.
5. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.
6. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.
7. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.
8. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.
9. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.
10. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.
11. The subjects must be volunteers and informed participants in the research project.
12. The right of research subjects to safeguard their integrity must always be respected.

Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

13. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.
14. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.
15. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.
16. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the investigator must obtain that assent in addition to the consent of the legally authorized representative.
17. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.
18. Both authors and publishers have ethical obligations. In publication of the results of research, the investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

**C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE**

1. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

2. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.
3. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
4. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.
5. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

## 9.2 Appendix 2: Common Terminology Criteria for Adverse Events Version 4.03

**NCI COMMON TERMINOLOGY CRITERIA**

**FOR ADVERSE EVENTS (CTCAE)**
**Version 4.0**
**Published: May 28, 2009 (v4.03: June 14, 2010)**

http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf

**DO NOT USE CTC VERSION 2.0 OR 3.0 TO GRADE TOXICITIES IN THIS STUDY!**

## 9.3 Appendix 3: New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease.

| Class | Functional Capacity | Objective Assessment |
|---|---|---|
| I | Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain. | No objective evidence of cardiovascular disease. |
| II | Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of minimal cardiovascular disease. |
| III | Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain. | Objective evidence of moderately severe cardiovascular disease. |
| IV | Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased. | Objective evidence of severe cardiovascular disease. |

Source: The Criteria Committee of New York Heart Association. Nomenclature and Criteria for Diagnosis of Diseases of the Heart and Great Vessels. 9th Ed. Boston, MA: Little, Brown & Co; 1994:253-256.

## 9.4 Appendix 4: Eastern Cooperative Oncology Group Scale for Performance Status

| Grade | Description |
|---|---|
| 0 | Normal activity. Fully active, able to carry on all predisease performance without restriction |
| 1 | Symptoms but ambulatory. Restricted in physically strenuous activity, but ambulatory and able to carry out work of a light or sedentary nature (eg, light housework, office work) |
| 2 | In bed < 50% of the time. Ambulatory and capable of all self-care, but unable to carry out any work activities. Up and about more than 50% of waking hours. |
| 3 | In bed > 50% of the time. Capable of only limited self-care, confined to bed or chair more than 50% of waking hours. |
| 4 | 100% bedridden. Completely disabled. Cannot carry on any self-care. Totally confined to bed or chair. |
| 5 | Dead. |

Source: Oken MM, Creech RH, Tormey DC, Horton J, Davis TE, McFadden ET et al. Toxicity and response criteria of the Eastern Cooperative Oncology Group. Am J Clin Oncol 1982; 5 (6):649-55.

## 9.5 Appendix 5: Body Surface Area and Creatinine Clearance Calculations

Body surface area (BSA) should be calculated using a standard nomogram that yields the following results in meters squared ($m^2$):

$$\text{BSA} = \sqrt{\frac{Ht(inches) \times Wt(lbs)}{3131}}$$

or

$$\text{BSA} = \sqrt{\frac{Ht(cm) \times Wt(kg)}{3600}}$$

Creatinine clearance (CrCl) can be calculated using the Cockroft-Gault equation as follows:

$$\text{CrCl (ml/min)} = \frac{(140\text{-age}) \text{ (body weight in kg)}}{(72 \times \text{serum creatinine in mg/dL})}$$

OR

$$\frac{(140\text{-age})(\text{body weight in kg})}{(0.81 \text{ x serum creatinine in } \mu\text{mol/L})}$$

**For females, use 85% of calculated CrCl value.**

Source: Cockcroft DW, Gault MH. Prediction of creatinine clearance from serum creatinine. Nephron 1976;16(1):31-41.

Note: In markedly obese patients, the Cockroft-Gault formula will tend to overestimate the creatinine clearance. (Adipose tissue tends to contribute little creatinine requiring renal clearance.)

## 9.6 Appendix 6: Response Evaluation Criteria in Solid Tumors (RECIST) v1.1

**New response evaluation criteria in solid tumours: Revised RECIST guideline (version 1.1) Eisenhauer EA, Therasse P, Bogaerts J, et al. Eur J Cancer. 2009 Jan;45(2):228-47.**

**http://ctep.cancer.gov/protocolDevelopment/docs/recist_guideline.pdf**

## 9.7 Appendix 7: Collection and Shipping Instructions for Tumor Blocks

**Collection of FFPE archival tissue from patients' resected breast cancer (metastasis or primary breast cancer) will be tested for potential biomarkers of benefit from paclitaxel plus alisertib, including but not limited to FOXM1 and AURKA expression, p53 mutation status, and genomic instability.**

**An FFPE TUMOR BLOCK WILL BE COLLECTED in the following order of priority:**

1. **Resected metastatic lesion (not a core biopsy or FNA of metastatic lesion);**
2. **Primary breast cancer resection (unless diagnostic core biopsy has more cancer than the definitive breast surgery specimen). If a tumor block is not available, 20 unstained slides cut at standard 4-5 microns will be submitted.**

The following materials must be submitted for each patient entered on the study.

- One paraffin block from a representative area of the tumor Surgical Pathology Report
- Specimen Requisition Form

Ship all samples directly to the designated lab (check CTI).The Specimen Requisition Form must be completed and submitted even if the patient pathology specimens are not available for submission. Please place a copy of the Specimen Requisition Form in the patient study record. To maintain uniform sample handling, samples should not be shipped on Fridays. Please indicate on the package "PATHOLOGY SPECIMENS ENCLOSED".

## 9.8 Appendix 8: Oral Medication Patient Diary

Make copies of the following page and give to patients who are randomized to the paclitaxel plus alisertib arm, to track oral medication compliance.

US Oncology, Inc Study# 13-033

**Drug Administration Record – to be completed by patient and returned at each visit**

**Please begin entries by checking the appropriate box that corresponds to the date treatment was started (Calendar Date). For example: If the patient starts treatment on January 24, 2014, check the box next to "24" under Calendar Date and continue entries from that date forward.**

| | |
|---|---|
| **Patient Initials** | |
| **Arm** | |
| **Patient ID #** | |
| **Month** | |
| **Year** | |

Please return all copies of this form to the Clinical Research Coordinator at each clinic visit.

| Calendar | Drug Taken | |
|---|---|---|
| Date | Yes | No |
| 1 | | |
| 2 | | |
| 3 | | |
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| 6 | | |
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