Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

SYNOPSIS

Title of Study:

A Phase II, Multicenter, Open-Label, Randomized Study of YM155 Plus Docetaxel as First-Line Treatment in Patients with HER2 Negative Metastatic Breast Cancer

Investigators/Coordinating Investigator:

[redacted]
[redacted]
[redacted]
[redacted] Germany

Study Center(s):

Thirty sites from the United States, Europe and Russia participated in this study.

Publication Based on the Study:

There are no publications based on this study.

Study Period:

43 months

Study Initiation Date (Date of First Enrollment):

30 Nov 2009

Study Completion Date (Date of Last Evaluation):

27 Jun 2013

Phase of Development:

Phase 2

Objectives:

Primary Objective:

To compare the progression free survival (PFS) between YM155 plus docetaxel (Arm 1) and the docetaxel regimen alone (Arm 2).

Secondary Objectives:

- Objective response rate (ORR)
- Overall survival (OS)

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Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

- Duration of response (DOR)
- Clinical benefit rate (CBR)
- Time to response (TTR)
- Safety and tolerability

[redacted]

Methodology:
This was a phase 2, multicenter, open-label, randomized study of YM155 plus docetaxel in patients with human epidermal growth factor 2 (HER2) non-overexpressing negative metastatic breast cancer. Two treatments YM155 + docetaxel (Arm A) and docetaxel alone (Arm B) were administered in sequential 21-day cycles.

In Arm A, intravenous docetaxel infusion was administered at a dose of 75 mg/m^2 over one hour on day 1 of cycle 1 (21-day duration), followed by YM155 administered at 5 mg/m^2 per day via a central line, port or peripherally-inserted central catheter (PICC) for 168 hours using a portable electronic infusion pump.

In Arm B, docetaxel intravenous infusion was administered at a dose of either 75 mg/m^2 or 100 mg/m^2 over one hour on day 1 of cycle 1 (21-day duration), in accordance with Investigator discretion. Each patient was contacted by the study site for survival status 4 weeks (± 5 days) following the End of Treatment (EOT) Visit.

The sequence and duration of all study periods is shown below:

Flow Chart

Screening Period (Day -28 to Day 1 [Pre-infusion])

Obtained Informed Consent (Start of Study)	**Day - 28 to Day - 1** Performed screening assessments per Schedule of Assessments	**Day 1 (Pre-Infusion)** Baseline Procedures Confirmed inclusion/exclusion criteria

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Each Cycle (21 Days/Cycle = 168 hours of YM155 treatment + 14 [Arm A] / 20 [Arm B] days of observation)

Day 1	**Day 4**	**Day 6**	**Day 8**	**Day 15**	**Days 18-21**
Randomized Administered docetaxel (Arms A and B) Started YM155 infusion	Assessments	(Cycle 1 only) Assessments	Assessments End YM155 infusion (Arm A)	(Cycle 1 only) Assessments	Retreatment Assessments

Other Visits

End of Treatment Visit	**Overall Survival Follow-up**
Procedures were performed within 30 days following the completion of the last infusion of study drug (YM155 or docetaxel). The End of Treatment Visit was completed prior to the initiation of any other systemic anti-breast cancer treatment.	Each patient was contacted by the study site for survival status four weeks (+/-5 days) following the End of Treatment Visit.

The criteria for each cycle was met in accordance with protocol criteria (Protocol Section 3.4, Retreatment Criteria), prior to initiating dosing for that cycle. Each patient was eligible to continue receiving YM155 plus docetaxel or docetaxel alone as randomly assigned in this study until one of the discontinuation criteria was met. Patients who had a complete response (CR), partial response (PR) or continued to show clinical benefit (e.g., stable disease [SD]) were continued on the combination treatment, while those who could no longer tolerate the study regimen due to docetaxel toxicity, were permitted to continue YM155 as monotherapy until one of the discontinuation criteria was met. For patients with a CR or PR, a minimum of 2 additional cycles of combination treatment should have been completed. After completion of at least 2 additional cycles of combination treatment (in the case of a PR if no further tumor regression had been observed), YM155 may have

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

been given as monotherapy at the discretion of the Investigator and upon approval of the Medical Monitor, until the discontinuation criteria was met.

If the patient experienced a toxicity assessed by the investigator to be possibly or probably related to YM155 during the Treatment or Observation Periods, the chart below was referred to regarding infusion interruptions and YM155 dose reductions.

Intensity of Event Based on NCI-CTCAE	Adjustments to YM155
Mild or Moderate (Grade 1 or 2)	None. However, reduction in dose to 3.6 mg/m^2/day for rising serum creatinine (upper limit of normal (ULN) – 3 x ULN) was done at the discretion of the Investigator. The Astellas Medical Monitor was notified of the dose reduction within 24 hours of the reduction.
Severe to Life-Threatening (Grade 3 or 4)	For Grade 3 or 4 toxicity (with the exception of weight loss or gain, anorexia, alopecia, and fatigue), the infusion of YM155 and docetaxel was interrupted until the toxicity resolved to a Grade $\leq$ 1 or baseline. When restarting the infusion of YM155, the dose may have been reduced from 5 mg/m^2/day to 3.6 mg/m^2/day at the Investigator's discretion. The Astellas Medical Monitor was notified of the dose reduction within 24 hours of the reduction.

NCI-CTCAE: National Cancer Institute-Common Terminology Criteria for Adverse Events

Dose adjustments were also permitted for toxicity assessments considered by the Investigator to be related to docetaxel during the Treatment or Observation Periods as follows:

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Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Docetaxel Dose	Event	Adjustments to Docetaxel
100 mg/m^2 (Arm B only)	• Febrile neutropenia (duration > 1 week). • ANC < 500 cells/mm^3 (duration > 1 week) • Severe or cumulative cutaneous reaction	Reduced to 75 mg/m^2.
75 mg/m^2	• Febrile neutropenia (duration > 1 week) or ongoing febrile neutropenia • ANC < 500 cells/mm^3 (duration > 1 week) or ongoing ANC < 500 cells/mm^3 • Severe or cumulative cutaneous reactions	Reduced to 55 mg/m^2 or discontinued docetaxel
Any dose	• Grade 3 or 4 toxicity (with the exception of peripheral neuropathy, weight loss or gain, anorexia, alopecia and fatigue)	The infusion of docetaxel was interrupted until the toxicity resolved to a Grade < 1 or baseline. When restarting the infusion of docetaxel, the dose was reduced from 100 mg/m^2 to 75 mg/m^2, or from 75 mg/m^2 to 55 mg/m^2. The Astellas Medical Monitor was notified within 24 hours of the reduction.

Assessments and procedures were performed on the same schedule in both Arm A and Arm B. Radiological imaging (diagnostic CT or MRI scans) was used to identify and assess target lesions at Screening, Treatment and End-of-treatment (EOT) visits for primary efficacy evaluation. Bone scans were performed at Screening and repeated every 12 weeks if metastases were present, otherwise scans were not repeated except to confirm CR or PR. Patients with a global deterioration of health status requiring discontinuation of treatment without objective evidence of disease progression at that time were classified as having "clinical progression."

Safety was assessed by adverse events, physical examinations, vital signs, laboratory test results and electrocardiogram (ECG) findings. [redacted] Adverse events of special interest, including events of hepatic origin, abnormal liver function tests and events suggestive of drug-drug interactions (such as interactions with concomitant Coumadin®/warfarin) and drug toxicities were monitored. Patients were discontinued from the study for liver metastases and/or exposure to other agents associated with liver injury, and, in the absence of explanation, for increased liver function tests. The potential for drug induced liver injury (DILI) was considered in accordance with the following:

- ALT or AST > 8X upper limit of normal (ULN)
- ALT or AST > 5X ULN for more than 2 weeks (in patients without liver metastases)
- ALT or AST > 3X ULN and (TBL > 2X ULN or International Normalized Ratio (INR) > 1.5)
- ALT or AST > 5X ULN and (TBL > 2X ULN in patients with liver metastases)
- ALT or AST > 3X ULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash and/or eosinophilia (> 5%)

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Patients were free to withdraw from the study for any reason and at any time without giving reason for doing so and without penalty or prejudice. The Investigator was also free to terminate a patient's involvement in the study at any time if the patient's clinical condition warranted it.

The patient was discontinued from treatment if any of the following occurred:

- Patient developed progressive disease
- Patient developed unacceptable toxicity
- Patient developed ≥ Grade 3 neuropathy
- Female patient was determined to be pregnant
- Investigator decided it was in the patient's best interest to discontinue
- Patient declined further treatment
- Patient was non-compliant with the protocol based on Investigator and/or Medical Monitor opinion
- Patient was lost to follow-up despite reasonable efforts by the Investigator to locate the patient

The patient was discontinued from the survival follow-up if any of the following occurred:

- Death
- Patient declined further study participation (i.e., withdrew consent and no additional contact was made)
- Patient was lost to follow-up despite reasonable efforts by the Investigator to locate the patient
- Sponsor elected to discontinue collection of data

All patients were contacted by the study site for survival 4 weeks (± 5 days) following the EOT Visit.

Number of Patients (Planned, Enrolled and Analyzed):

Planned: Approximately 100 patients were planned for enrollment, in order to observe approximately 67 PFS events.

Randomized: One hundred one patients were randomized 1:1 (50 in Arm A and 51 in Arm B). A total of 99 patients (48 in Arm A and 51 in Arm B) received at least one dose of study drug [Table 1].

Analyzed: The full analysis set (FAS) consisted of all 101 patients (50 in Arm A and 51 in Arm B) who were randomized into the study. Ninety-nine patients were included in both the per protocol set (PPS) and in the safety analysis set (SAF). [redacted]

Diagnosis and Main Criteria for Inclusion:

Patients were eligible for enrollment into the study if all of the following criteria were met:

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

1. Prior to any study-related procedures (including withdrawal of prohibited medicines, if applicable), the patient had provided IRB/IEC-approved written Informed Consent and privacy language as per national regulations (e.g., HIPAA Authorization for US sites)
2. The patient was female or male age 18 years or older with metastatic breast cancer.
3. The patient had histologically- or cytologically-proven adenocarcinoma of the breast that was HER2 negative defined as one of the following:
    - Negative fluorescence in-situ hybridization (FISH)
    - 0 or 1+ immunohistochemistry (IHC)
    - IHC 2+ with negative FISH.
    - Patients with hormone receptor positive or negative status were eligible. Additionally, patients with triple negative status (estrogen receptor negative, progesterone receptor negative and HER2 negative) were eligible.
4. No prior chemotherapy regimen for metastatic breast cancer
    - Prior treatment with a cytotoxic therapy (other than docetaxel) was allowed if administered in the neoadjuvant or adjuvant setting $\geq$ 3 weeks prior to the Baseline Visit, with all side effects of using prior cytotoxic therapy resolved or back to baseline (with the exception of weight loss or gain, anorexia, alopecia or fatigue).
    - Prior treatment with docetaxel was allowed if administered in the neoadjuvant or adjuvant setting, and the patient has no recurrent disease within 12 months after completing treatment, with all side effects of prior docetaxel use resolved or back to baseline (with the exception of weight loss or gain, anorexia, alopecia or fatigue).
    - Prior treatment with a kinase inhibitor, biologic therapy, vaccine, or investigational treatment other than cytotoxic therapy or procedure for breast cancer was allowed if administered in the neoadjuvant, adjuvant or metastatic setting $\geq$ 4 weeks prior to the Baseline Visit.
    - Prior treatment with hormonal therapy in the neoadjuvant, adjuvant setting or metastatic was allowed if administered $\geq$ 2 weeks prior to the Baseline Visit.
    - Prior treatment with bevacizumab was allowed if administered in the neoadjuvant or adjuvant setting > 4 weeks prior to the Baseline Visit.
5. The patient had completed prior palliative radiation therapy $\geq$ 2 weeks of the Baseline Visit, with side effects of radiation resolved.
6. The patient had an Eastern Cooperative Oncology Group (ECOG) performance status $\leq$ 1 at the Baseline Visit.
7. The patient had at least 1 measurable lesion by Response Evaluation Criteria in Solid Tumors (RECIST, version 1.1). If the selected lesion(s) received prior radiation and/or loco-regional therapy, there must have been evidence of disease progression since the last radiation or loco-regional therapy.

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

8. If a patient had a previous history of non-breast cancer malignancy, he or she was eligible for the study only if the patient met certain criteria for a cancer survivor:
    - Patient having a previous history of a non-invasive carcinoma was eligible if, in the opinion of the Investigator, he/she had successful curative treatment any time prior to enrollment.
    - For all other malignancies, the patient had undergone potentially curative therapy; and the patient had been considered disease free for at least 5 years.
9. The patient's life expectancy was estimated to be greater than 12 weeks at the Baseline Visit.
10. The patient must have been non-pregnant and non-lactating. Each site administered a pregnancy test to any female of childbearing potential during the Screening Period and at the Baseline Visit. Only patients with negative pregnancy test results were eligible. All sexually-active patients of childbearing potential agreed to use an adequate method of contraception throughout the study period.

Patients were excluded from the study if any of the following exclusion criteria were met:

1. The patient had hypersensitivity to docetaxel or polysorbate 80.
2. The patient had a major surgical procedure, substantial open biopsy within 28 days to the Baseline Visit, or significant traumatic injury within 28 days prior to the Baseline Visit or anticipation of need for major surgical procedure during the course of the study.
3. The patient had neuropathy ≥ Grade 2 at the Baseline Visit.
4. The patient had inadequate marrow, hepatic and/or renal function at the Baseline Visit defined as:
    - Serum creatinine ≥ 1.5 x ULN or calculated serum creatinine clearance < 60 mL/min.
    - Absolute neutrophil count < 1500/mm^3.
    - Platelets ≤ 100000/ mm^3.
    - Alanine transaminase (ALT) or aspartate transaminase (AST) > 2.5x ULN. Patients who have documented liver metastases and an ALT or AST > 5x ULN were excluded. Patients were excluded with a hemoglobin < 9 mg/dL. The Sponsor's Medical Monitor should be contacted for further direction if the Investigator suspects a patient had Gilbert's disease.
    - Bilirubin > ULN.
5. The patient had known brain or leptomeningeal metastasis as assessed through medical history review and physical examination.
6. The patient had a known history of positive test for Hepatitis B surface antigen (HBsAg) or hepatitis C antibody or history of positive test for human immunodeficiency virus (HIV). Patients in study sites in Germany were excluded based on a positive test for HBsAg, Hepatitis B core antibody (HBcAb) or Hepatitis C antibody (HCVAb) or positive test for HIV at Screening.
7. The patient had significant and/or uncontrolled cardiac, renal, hepatic or other systemic disorders or significant psychological conditions at Baseline Visit that in the Investigator's judgment jeopardized patient enrollment or compliance with the study procedures.

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Test Product, Dose and Mode of Administration, Batch Numbers:

YM155 was provided as an intravenous solution at a concentration of 10 mg/mL, 7.5 mL volume (10 mL vial).

Duration of Treatment (or Duration of Study, if applicable):

Study drug treatment was for an indefinite period of time. The study duration was 43 months.

Reference Product, Dose and Mode of Administration, Batch Numbers:

Generic docetaxel or Taxotere® was the reference therapy drug administered intravenously at a dose of 75 mg/m^2 or 100 mg/m^2.

Criteria for Evaluation:

Efficacy:

The efficacy data were derived from the results of radiological imaging (e.g., diagnostic CT scans, MRI or bone scans) and objective tumor assessments according to the requirements of the RECIST (v1.1). The primary endpoint for the study was PFS, defined as the time from the date of randomization until objective tumor progression or death. Secondary efficacy variables are listed below. All response assessments were based on responses determined by the independent review committee.

- ORR: the proportion of patients with CR or PR.
- OS: The OS was the time from the date of randomization until death. Patients without a known death date were censored at the earlier of the date of last contact and the data cutoff date.
- DOR: The DOR was the time from the first documentation of response (CR or PR) until objective tumor progression. Patients with a CR or PR and without documented PD were censored at the date of last valid tumor assessment.
- CBR: This included the proportion of patients with CR, PR or SD.
- TTR: TTR was the time from the date of randomization until the first documentation of response (CR or PR).

Other efficacy endpoints included PFS per Investigator assessment, the change/shift from baseline in ECOG performance status and the Functional Assessment of Cancer Therapy-Breast (FACT-B) questionnaire score.

Safety and Tolerability:

Treatment-emergent adverse events (events that occurred following receipt of the first dose of the study drug(s) on day 1 of cycle 1) were recorded on the electronic case report form (eCRF). Since the treatment medications evaluated in this study are known to induce mild and transient myelosuppression, neutropenia was only reported by the Investigator if the condition was considered to be serious. In this event, neutropenia was documented as a serious adverse event (SAE) by the Investigator. Patients with adverse events (AEs) of hepatic origin

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

accompanied by Liver Function Test abnormalities were carefully monitored in accordance with drug-induced liver injury (DILI) criteria.

[redacted]

Statistical Methods:

Descriptive statistics were used to summarize continuous variables, and included the number of patients (n), mean, standard deviation, median, minimum and maximum. Frequencies and percentages were displayed for categorical data. Percentages by categories were based on the number of patients with no missing data, i.e., added up to 100%. All confidence intervals were presented with a two-sided 95% confidence level unless otherwise stated. All data processing, summarization, and analyses were performed using SAS® Version 9.1 or higher on Unix.

Efficacy data were derived from the results of radiological imaging (e.g., diagnostic CT scans, MRI or bone scans) and objective tumor assessments according to RECIST guidelines (v1.1), which were used to determine response to treatment. Patients who did not satisfy the criteria to be counted as responders or who had insufficient data to determine or confirm a response were considered as nonresponders in the final analysis of response rates. No imputation of data was done to determine individual patient response. Response assessments for the secondary variables (ORR, OS, DOR, CBR and TTR) were based on responses determined by an independent review committee.

Visit-by-visit analyses of data excluded patients who did not provide data at the visit in question. An exception to this rule was analysis of retreatment assessment data. If the patient did not provide information during the Retreatment Assessment Period (day 18 to 21 of each treatment cycle), but provided information predose on day 1 of the following cycle, then the day 1 observation was used in place of the day 18 to 21 observation.

Missing ECOG performance status data at end of the study was imputed by using the last observation carried forward, unless the patient was known to have died (Grade 5). For visit-by-visit summary of ECOG, no imputation was made.

Clinical safety data (including AEs, clinical laboratory evaluations, vital signs, 12-lead ECG, physical examinations, ECOG performance status and FACT-B questionnaire score) were summarized using descriptive statistics or frequency distributions, as appropriate, for the SAF. For continuous variables (e.g., clinical laboratory measurement, vital signs), patients with missing baseline variable were excluded from the analysis of change from baseline. Missing EOT data were imputed by using the last observation carried forward. Treatment-emergent AEs (TEAEs) were coded using MedDRA (v12.1) and summarized by system organ class

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

preferred term, by relationship to study regimen, and by severity (NCI- CTCAE grade). Similar summaries were also provided for drug regimen-related TEAEs, serious TEAEs, serious drug regimen related TEAEs and TEAEs that lead to study discontinuation. A drug regimen-related TEAE was defined as any TEAE with possible, probable, or missing relationship as assessed by the Investigator. AEs with missing National Cancer Institute – Common Terminology Criteria for Adverse Events (NCI-CTCAE) grade were treated as having the highest observed grade among AEs with the same preferred term for each patient.

For all analyses [redacted] all values were included in the analyses. [redacted]

Summary of Results/Conclusions:

The demographic characteristics of the population studied is shown in [Table 2].

Efficacy/[redacted]/Pharmacodynamic Results:

The final analysis was to be performed after 67 PFS events (progressions or deaths) had been observed. However, the needed number of events was not observed within the duration of the trial. Accordingly, the actual analysis described below was performed on fewer than the planned 67 PFS events, and the trial was considered not to have attained the planned primary objective.

There was no significant improvement in PFS as judged by an independent review committee (IRC) in patients treated with YM155 and docetaxel compared to docetaxel alone, with or without stratification [Table 3] and [Figure 2]. Arm B (docetaxel alone) patients had an advantage in PFS compared to patients in Arm A (YM155 and docetaxel) in both the stratified (hazard ratio [HR] = 1.53) and unstratified (HR = 1.55) analyses. However, the differences in treatment arms did not reach statistical significance regardless of stratification or sensitivity analysis. Comparable treatment responses were observed when PFS was evaluated by Investigators. In the analysis of secondary variables, including Best Overall Response evaluated by IRC, OS, DOR, and TRR the addition of YM155 to docetaxel was not seen to have any effect.

Safety Results:

All patients (100%) in this study experienced TEAE's [Table 4]. Overall, the most frequent TEAEs were neutropenia (83.8%), alopecia (57.6%), fatigue (45.5%), nausea (39.4%), leukopenia (30.3%), dyspnea (23.2%), diarrhea (21.2%) and peripheral edema (21.2%). In the YM155 and docetaxel treatment group, the most frequent TEAEs included neutropenia (83.3%), alopecia (62.5%), fatigue (50.0%), nausea (37.5%), dyspnea (33.3%), leukopenia (27.1%), anemia (27.1%), diarrhea (22.9%), febrile neutropenia (22.9%) and stomatitis (22.9%). In the docetaxel alone group, the most frequent TEAEs reported were neutropenia (84.3%), alopecia (52.9%), fatigue (41.2%), nausea (41.2%), leukopenia (33.3%), peripheral neuropathy (23.5%) and peripheral edema (23.5%) [Table 5]. Twenty-three patients experienced TEAEs resulting in discontinuation of study drug.

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Among these, fourteen (29.2%) patients were treated with YM155 and docetaxel compared to 9 (17.6%) patients treated with docetaxel alone.

A total of 56 (56.6%) patients died during the study, 87.5% of whom died due to breast cancer disease or disease progression. The remaining patients died of various unrelated causes. Three deaths occurred associated with TEAEs. None of the deaths was considered related to study drug.

Study-drug related TEAEs were analyzed under 4 categories: those related to YM155 only, those related to docetaxel only, those related to YM155 and docetaxel, and those related to YM155 or docetaxel [Table 6].

Treatment-emergent SAEs were experienced by 42 (42.4%) of patients. The most frequent treatment-emergent SAEs in the YM155 and docetaxel group compared to docetaxel alone were febrile neutropenia (20.8% vs. 7.8%) and neutropenia (10.4% vs. 7.8%) [Table 7].

Laboratory evaluations showed that most hematology and some chemistry parameters changed from baseline in both treatment groups and that the differences were comparable; and thus not likely attributable to YM155 alone. In this study, clinically significant INR increases occurred in 3 patients given YM155 and docetaxel (vs 3 given docetaxel alone), and thus findings from studies of YM155 in combination with medications other than docetaxel suggesting cautionary co-administration with Coumadin/warfarin were not supported in this study.

Overall, vital signs showed minor but clinically insignificant excursions in mean blood pressure parameters and mean heart rate, which were comparable between treatment groups. There was an increase in mean body weight in the YM155 and docetaxel group; there was a slight loss in the docetaxel alone group. No cardiac safety signals were detected during the study; however, 11 patients (YM155 and docetaxel, n = 7; docetaxel alone, n = 4) experienced clinically significant arrhythmias most of which were attributed to atrial or sinus node irritability, including atrial fibrillation, atrial or supraventricular ectopy and sinus tachycardia. One patient experienced T-wave inversion.

The findings of this study suggest that, in general, YM155 at 5 mg/m^2/day can be administered in combination with docetaxel and was generally tolerated.

CONCLUSIONS:

This was a phase 2, multicenter, open-label study of YM155 and docetaxel as first line treatment in patients with human epidermal growth factor 2 non-overexpressing (HER2 negative) metastatic breast cancer. Patients were randomized to one of two treatment groups consisting of intravenously-administered YM155 and docetaxel (Arm A) or docetaxel alone (Arm B) and evaluated over 21-day cycles. In Arm A, administration of docetaxel took place over one hour on Day 1 of the Treatment Period followed by continuous administration of YM155 for 168 hours. In Arm B, docetaxel (75 mg/m^2 or 100 mg/m^2) was administered over one hour on Treatment Period Day 1. Patients were enrolled in additional 21-day cycles (Retreatment Periods) provided all specified criteria were met for continuation (Protocol Section 3.4).

Name of Sponsor/Company: Astellas Pharma Global Development - US		
Name of Finished Product: Not Applicable		
Name of Active Ingredient: YM155		

Baseline patient characteristics were similar across study groups and consistent with the target patient population. There were no protocol deviations that affected the conclusions drawn from this study.

There was a trend for a longer duration of PFS in the patients treated with docetaxel alone (Arm B) compared to those treated with YM155 and docetaxel (Arm A), that was consistent regardless of the evaluation criterion (IRC or investigator assessment) or whether the data were stratified by prior taxane treatment and triple-negative breast cancer. However, the differences in treatment arms did not reach statistical significance.

In the analysis of secondary variables, there was no difference between the arms in ORR, CBR, OS, DOR nor TTR regardless of evaluation criterion or stratification..

YM155 in combination with docetaxel was generally tolerated. The most frequent TEAEs for YM155 and docetaxel-treated patients included neutropenia (83.3%), alopecia (62.5%), fatigue (50.0%), nausea (37.5%), dyspnea (33.3%), anemia (27.1%), leukopenia (27.1%), febrile neutropenia (22.9%), stomatitis (22.9%) and diarrhea (22.9%). The most common TEAEs in the docetaxel treatment group included neutropenia (84.3%), alopecia (52.9%), fatigue (41.2%), nausea (41.2%), leukopenia (33.3%), peripheral neuropathy (23.5%) and peripheral edema (23.5%). AEs resulting in discontinuation included laboratory tests results out of range (increased creatinine, GGT levels, urea levels), platelet disorder, ECG abnormality, central line infection, fatigue and pulmonary emboli.

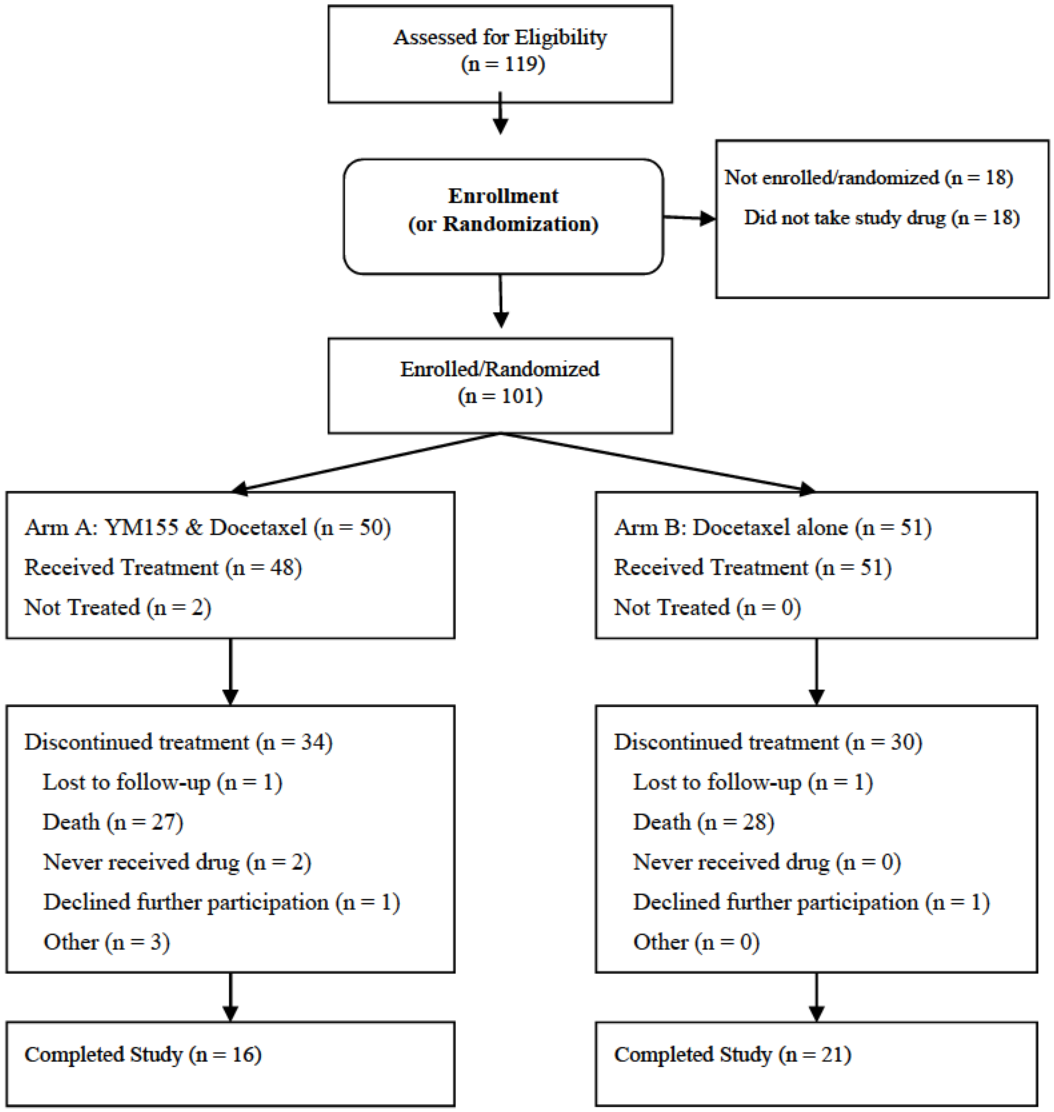
Fifty-six (56.6%) patients died during the study. None of the deaths was attributable to study drug. The majority of deaths (87.5%) were due to breast cancer disease or disease progression. The remaining deaths were attributable to hepatic failure (2 patients), sepsis (1 patient), cerebrovascular accident (1 patient) and general state degradation (1 patient). The cause of death of two patients was unknown.

Overall changes in vital signs were comparable between treatment groups and did not represent clinically-meaningful excursions from baseline. Comparable increases from baseline to maximum NCI-CTCAE grade were observed in both treatment groups in most hematology and chemistry parameters. For the majority of patients, no change in shift from baseline to worst outcome in overall ECG was observed in either treatment group.

In summary, the primary endpoint in the study, increased PFS after administration of YM155 and docetaxel compared to docetaxel alone, was not achieved. Instead, the outcome favored the arm given docetaxel alone. This trend was consistent in both the IRC and investigator assessed PFS, as well as in both stratified and unstratified analyses. The difference between the treatment arms did not reach statistical significance. Although the number of PFS events required for the planned analysis was not attained (resulting in a loss of power to detect differences between the treatment arms), this study provided no evidence of an advantage of adding YM155 to docetaxel therapy for this population.

Date of Report:
March 31, 2014

Figure 1 Disposition of Patients



Source: Tables 12.1.1, 12.1.1.2, 12.1.1.4.2

Table 1 Patient Disposition and Analysis Sets

Analysis Set	Arm A YM155 5.0 mg/m^2/day and Docetaxel† n = 50 (%)	Arm B Docetaxel‡ n = 51 (%)	Total n = 101 (%)
Randomized + Drug Taken§	48 (96.0)	51 (100)	99 (98.0)
Full Analysis Set¶	50 (100)	51 (100)	101 (100)
Per Protocol Set††	48 (96.0)	51 (100)	99 (98.0)
Safety Analysis Set‡‡	48 (96.0)	51 (100)	99 (98.0)
[redacted]	[redacted]	[redacted]	[redacted]

† Patients with docetaxel initiated at 75 mg/m^2.

‡ Patients with docetaxel imitated at 75 or 100 mg/m^2.

§ All randomized patients with at least 1 dose of drug taken/started drug intake.

¶ All patients who were randomized into the study.

††All patients in the full analysis set who also met the criteria for per protocol set defined in the protocol.

‡‡ All randomized patients who initiated at least 1 dose of study regimen.

[redacted].

Source: Table 12.1.1.2

Table 2 Demographic Characteristics

Parameter Category/Statistics	Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 48 (%)	Arm B Docetaxel n = 51 (%)	Total n = 99 (%)
Sex, n (%)			
Male	0	0	0
Female	48 (100)	51 (100)	99 (100)
Race, n (%)			
White	46 (95.8)	48 (94.1)	94 (94.9)
Black or African American	0	1 (2.0)	1 (1.0)
Asian	1 (2.1)	0	1 (1.0)
Other	1 (2.1)	2 (3.9)	3 (3.0)
Ethnicity, n (%)			
Not reported	41 (85.4)	44 (86.3)	85 (85.9)
Not Hispanic or Latino	6 (12.5)	7 (13.7)	13 (13.1)
Hispanic or Latino	1 (2.1)	0	1 (1.0)
Age, years			
Mean (SD)	53.8 (10.19)	53.5 (13.13)	53.6 (11.73)
Median	57.0	55.0	55.0
Range	36 - 79	25 – 77	25 - 79
Body Weight (kg)			
Mean (SD)	68.43 (12.472)	68.21 (15.575)	68.31 (14.085)
Median	66.90	66.30	66.80
Range	46.8 – 93.0	42.0 - 110	42.0 – 110
Height (cm)			
Mean (SD)	160.99 (6.887)	162.69 (7.166)	161.86 (7.048)
Median	159.50	163.50	161.80
Range	145.0 – 175.3	148.0 – 182.8	145.0 – 182.8
BSA (m^2)			
Mean (SD)	1.71 (0.163)	1.73 (0.228)	1.72 (0.198)
Median	1.70	1.70	1.70
Range	1.4 – 2.1	1.3 – 2.3	1.3 – 2.3

All enrolled patients who received at least one dose of study drug (Safety Analysis Set, SAF).

BSA: body surface area.

Source: Table 12.1.2.1.3

Table 3 Primary Analysis of Progression-free Survival by Treatment per IRC (Full Analysis Set)

Parameter	Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 50	Arm B Docetaxel n = 51	P Value	Hazard Ratio	95% CI
Stratified Analysis					
Progression-free survival†	**50**	**51**	0.172‡	1.53§	(0.83, 2.83)§
Number of Events	25	19			
Median (days)¶	251.0	315.0			
95% CI¶	(172, 333)	(202, 433)			
Unstratified Analysis					
Progression-free survival†	**50**	**51**	0.156††	1.55‡‡	(0.84, 2.86)‡‡
Number of events	25	19			
Median (days)¶	251.0	315.0			
95% CI¶	(172, 333)	(202, 433)			

All patients who were randomized into the study.

IRC: independent review committee.

† Disease progression assessment was based on RECIST v1.1 Criteria.

‡ Log-rank test was applied for comparison of survival curves between 2 treatments stratified by prior taxane therapy (yes versus no) and triple negative status (yes versus no).

§ Cox proportional hazard model was applied to calculate hazard ratio of treatment YM155 5.0 mg/m^2/day + docetaxel versus docetaxel, corresponding 95% CI and P value stratified by prior taxane therapy (yes versus no) and triple negative status (yes versus no).

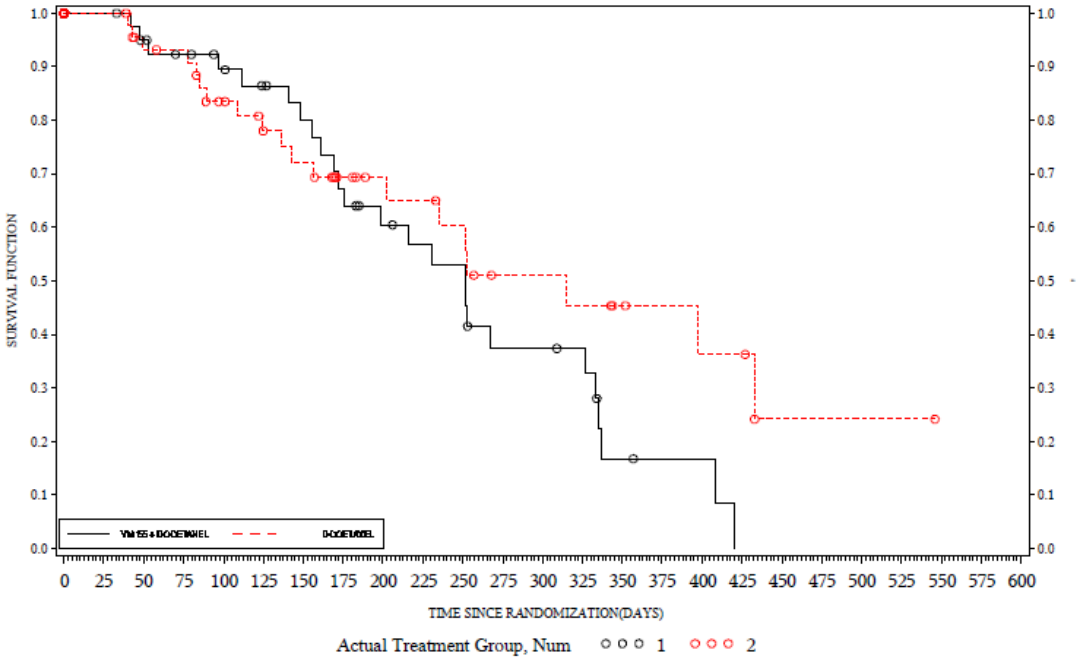
¶ Calculated using Kaplan Meier estimate.

†† Log-rank test was applied for comparison of survival curves between the 2 treatments.

‡‡ Cox proportional hazard model was applied to calculate hazard ratio of treatment YM155 5.0 mg/m^2/day + docetaxel versus docetaxel, corresponding 95% CI and P value.

Source: Tables 12.3.1.1 and 12.3.1.1.1

Figure 2 Kaplan Meier Plot for Progression-free Survival per IRC (Full Analysis Set)



All patients who were randomized into the study,

IRC: independent review committee.

Source: Figure 12.3.2.3.1

Table 4 Overview of the Incidence of Treatment-emergent Adverse Events (Safety Analysis Set)

Category	Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 48 (%)	Arm B Docetaxel n = 51 (%)	Total n = 99 (%)
Any Treatment-emergent AE	48 (100)	51 (100)	99 (100)
YM155 Related† TEAEs	40 (83.3)	0	40 (40.4)
Docetaxel Related† TEAEs	46 (95.8)	51 (100)	97 (98.0)
YM155 and Docetaxel Related† TEAEs	35 (72.9)	0	35 (35.4)
YM155 or Docetaxel Related† TEAEs	47 (97.9)	51 (100)	98 (99.0)
Deaths	2 (4.2)	1 (2.0)	3 (3.0)
Serious TEAEs	25 (52.1)	17 (33.3)	42 (42.4)
YM155 Related† Serious TEAEs	14 (29.2)	0	14 (14.1)
Docetaxel Related† Serious TEAEs	17 (35.4)	9 (17.6)	26 (26.3)
YM155 and Docetaxel Related† Serious TEAEs	12 (25.0)	0	12 (12.1)
YM155 or Docetaxel Related† Serious TEAEs	19 (39.6)	9 (17.6)	28 (28.3)
TEAEs Leading to Discontinuation of Study Drug	14 (29.2)	9 (17.6)	23 (23.2)
YM155 Related Adverse Events Leading to Permanent Discontinuation of Study Drug	8 (16.7)	0	8 (8.1)
Docetaxel Related Adverse Events Leading to Permanent Discontinuation of Study Drug	10 (20.8)	9 (17.6)	19 (19.2)
YM155 and Docetaxel Related Adverse Events Leading to Permanent Discontinuation of Study Drug	5 (10.4)	0	5 (5.1)
YM155 or Docetaxel Related Adverse Events Leading to Permanent Discontinuation of Study Drug	13 (27.1)	9 (17.6)	22 (22.2)

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

AE: adverse event; TEAE: treatment-emergent adverse event was defined as an adverse event observed after starting administration of either study regimen.

† Possible or probable, as assessed by the Investigator, or records where relationship is missing.

Source: Table 12.6.1.1

Table 5 Incidence of Treatment-emergent Adverse Events Occurring in at Least 10% of Patients (Safety Analysis Set)

MedDRA v12.1 System Organ Class Preferred Term	Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 48 (%)	Arm B Docetaxel n = 51 (%)	Total n = 99 (%)
All Systems, Any Adverse Event	**48 (100)**	**51 (100)**	**99 (100)**
Blood and lymphatic system disorders	**42 (87.5)**	**46 (90.2)**	**88 (88.9)**
Neutropenia	40 (83.3)	43 (84.3)	83 (83.8)
Leukopenia	13 (27.1)	17 (33.3)	30 (30.3)
Anaemia	13 (27.1)	6 (11.8)	19 (19.2)
Febrile neutropenia	11 (22.9)	5 (9.8)	16 (16.2)
Lymphopenia	3 (6.3)	6 (11.8)	9 (9.1)
General disorders and administration site conditions	**37 (77.1)**	**34 (66.7)**	**71 (71.7)**
Fatigue	24 (50.0)	21 (41.2)	45 (45.5)
Oedema peripheral	9 (18.8)	12 (23.5)	21 (21.2)
Asthenia	7 (14.6)	8 (15.7)	15 (15.2)
Mucosal inflammation	8 (16.7)	5 (9.8)	13 (13.1)
Pyrexia	8 (16.7)	5 (9.8)	13 (13.1)
Skin and subcutaneous tissue disorders	**34 (70.8)**	**32 (62.7)**	**66 (66.7)**
Alopecia	30 (62.5)	27 (52.9)	57 (57.6)
Nail disorder	6 (12.5)	5 (9.8)	11 (11.1)
Gastrointestinal disorders	**32 (66.7)**	**29 (56.9)**	**61 (61.6)**
Nausea	18 (37.5)	21 (41.2)	39 (39.4)
Diarrhoea	11 (22.9)	10 (19.6)	21 (21.2)
Stomatitis	11 (22.9)	8 (15.7)	19 (19.2)
Constipation	6 (12.5)	8 (15.7)	14 (14.1)
Nervous system disorders	**25 (52.1)**	**26 (51.0)**	**51 (51.5)**
Neuropathy peripheral	7 (14.6)	12 (23.5)	19 (19.2)
Dysgeusia	5 (10.4)	9 (17.6)	14 (14.1)
Headache	8 (16.7)	5 (9.8)	13 (13.1)
Peripheral sensory neuropathy	3 (6.3)	6 (11.8)	9 (9.1)
Musculoskeletal and connective tissue disorders	**20 (41.7)**	**23 (45.1)**	**43 (43.4)**
Arthralgia	8 (16.7)	4 (7.8)	12 (12.1)

Table continued on next page

MedDRA v12.1 System Organ Class Preferred Term	Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 48 (%)	Arm B Docetaxel n = 51 (%)	Total n = 99 (%)
Back pain	9 (18.8)	2 (3.9)	11 (11.1)
Bone pain	4 (8.3)	7 (13.7)	11 (11.1)
Pain in extremity	4 (8.3)	6 (11.8)	10 (10.1)
Myalgia	2 (4.2)	6 (11.8)	8 (8.1)
Infections and infestations	**25 (52.1)**	**17 (33.3)**	**42 (42.4)**
Urinary tract infection	6 (12.5)	5 (9.8)	11 (11.1)
Respiratory, thoracic and mediastinal disorders	**22 (45.8)**	**13 (25.5)**	**35 (35.4)**
Dyspnoea	16 (33.3)	7 (13.7)	23 (23.2)
Cough	6 (12.5)	8 (15.7)	14 (14.1)
Metabolism and nutrition disorders	**15 (31.3)**	**16 (31.4)**	**31 (31.3)**
Decreased appetite	8 (16.7)	9 (17.6)	17 (17.2)
Investigations	**15 (31.3)**	**13 (25.5)**	**28 (28.3)**
Vascular disorders	**11 (22.9)**	**11 (21.6)**	**22 (22.2)**
Cardiac disorders	**10 (20.8)**	**9 (17.6)**	**19 (19.2)**
Injury, poisoning and procedural complications	**11 (22.9)**	**6 (11.8)**	**17 (17.2)**
Psychiatric disorders	**8 (16.7)**	**5 (9.8)**	**13 (13.1)**
Insomnia	6 (12.5)	3 (5.9)	9 (9.1)
Renal and urinary disorders	**8 (16.7)**	**4 (7.8)**	**12 (12.1)**
Eye disorders	**2 (4.2)**	**7 (13.7)**	**9 (9.1)**

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

Source: Table 12.6.1.2

Table 6 Number and Percentage of Related Treatment Emergent Adverse Events Occurring in ≥ 10% of Patients (Safety Analysis Set)

MedDRA v. 12.1 System Organ Class Preferred Term	YM155 5.0 mg/m^2/day + docetaxel (Arm A) n = 48 (%)	Docetaxel (Arm B) n = 51 (%)	Total n = 99 (%)
YM155-related Treatment Emergent Adverse Events			
All Systems, Any Adverse Event	**40 (83.3)**	**0**	**40 (40.4)**
General disorders and administration site conditions	**24 (50.0)**	**0**	**24 (24.2)**
Fatigue	13 (27.1)	0	13 (13.1)
Asthenia	6 (12.5)	0	6 (6.1)
Blood and lymphatic system disorders	**23 (47.9)**	**0**	**23 (23.2)**
Neutropenia	18 (37.5)	0	18 (18.2)
Febrile neutropenia	9 (18.8)	0	9 (9.1)
Anaemia	5 (10.4)	0	5 (5.1)
Leukopenia	5 (10.4)	0	5 (5.1)
Gastrointestinal disorders	**17 (35.4)**	**0**	**17 (17.2)**
Nausea	8 (16.7)	0	8 (8.1)
Stomatitis	5 (10.4)	0	5 (5.1)
Nervous system disorders	**13 (27.1)**	**0**	**13 (13.1)**
Respiratory, thoracic and mediastinal disorders	**10 (20.8)**	**0**	**10 (10.1)**
Skin and subcutaneous tissue disorders	**10 (20.8)**	**0**	**10 (10.1)**
Alopecia	6 (12.5)	0	6 (6.1)
Infections and infestations	**9 (18.8)**	**0**	**9 (9.1)**
Investigations	**9 (18.8)**	**0**	**9 (9.1)**
Metabolism and nutrition disorders	**9 (18.8)**	**0**	**9 (9.1)**
Decreased appetite	6 (12.5)	0	6 (6.1)
Musculoskeletal and connective tissue disorders	**9 (18.8)**	**0**	**9 (9.1)**
Back pain	5 (10.4)	0	5 (5.1)
Cardiac disorders	**7 (14.6)**	**0**	**7 (7.1)**
Docetaxel Related Treatment Emergent Adverse Events			
All Systems, Any Adverse Event	**46 (95.8)**	**51 (100)**	**97 (98.0)**

Table continued on next page

MedDRA v. 12.1 **System Organ Class** Preferred Term	**YM155 5.0 mg/m^2/day + docetaxel (Arm A)** **n = 48 (%)**	**Docetaxel (Arm B)** **n = 51 (%)**	**Total** **n = 99 (%)**
Blood and lymphatic system disorders	**42 (87.5)**	**46 (90.2)**	**88 (88.9)**
Neutropenia	39 (81.3)	43 (84.3)	82 (82.8)
Leukopenia	13 (27.1)	17 (33.3)	30 (30.3)
Anaemia	12 (25.0)	6 (11.8)	18 (18.2)
Febrile neutropenia	11 (22.9)	5 (9.8)	16 (16.2)
Skin and subcutaneous tissue disorders	31 (64.6)	31 (60.8)	62 (62.6)
Alopecia	30 (62.5)	27 (52.9)	57 (57.6)
Nail disorder	6 (12.5)	5 (9.8)	11 (11.1)
General disorders and administration site conditions	**30 (62.5)**	**31 (60.8)**	**61 (61.6)**
Fatigue	23 (47.9)	20 (39.2)	43 (43.4)
Oedema peripheral	6 (12.5)	11 (21.6)	17 (17.2)
Asthenia	6 (12.5)	8 (15.7)	14 (14.1)
Mucosal inflammation	6 (12.5)	5 (9.8)	11 (11.1)
Gastrointestinal disorders	**28 (58.3)**	**28 (54.9)**	**56 (56.6)**
Nausea	17 (35.4)	19 (37.3)	36 (36.4)
Diarrhoea	9 (18.8)	9 (17.6)	18 (18.2)
Stomatitis	10 (20.8)	8 (15.7)	18 (18.2)
Constipation	2 (4.2)	6 (11.8)	8 (8.1)
Nervous system disorders	**19 (39.6)**	**25 (49.0)**	**44 (44.4)**
Neuropathy peripheral	6 (12.5)	12 (23.5)	18 (18.2)
Dysgeusia	5 (10.4)	9 (17.6)	14 (14.1)
Peripheral sensory neuropathy	3 (6.3)	6 (11.8)	9 (9.1)
Musculoskeletal and connective tissue disorders	**14 (29.2)**	**19 (37.3)**	**33 (33.3)**
Bone pain	3 (6.3)	6 (11.8)	9 (9.1)
Metabolism and nutrition disorders	**10 (20.8)**	**12 (23.5)**	**22 (22.2)**
Decreased appetite	7 (14.6)	8 (15.7)	15 (15.2)
Investigations	**11 (22.9)**	**10 (19.6)**	**21 (21.2)**
Respiratory, thoracic and mediastinal disorders	**11 (22.9)**	**6 (11.8)**	**17 (17.2)**
Dyspnoea	6 (12.5)	3 (5.9)	9 (9.1)
Infections and Infestations	**9 (18.8)**	**7 (13.7)**	**16 (16.2)**
Cardiac disorders	**6 (12.5)**	**4 (7.8)**	**10 (10.1)**
Eye Disorders	**1 (2.1)**	**6 (11.8)**	**7 (7.1)**

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MedDRA v. 12.1 System Organ Class Preferred Term	YM155 5.0 mg/m^2/day + docetaxel (Arm A) n = 48 (%)	Docetaxel (Arm B) n = 51 (%)	Total n = 99 (%)
YM155 and Docetaxel Related Treatment Emergent Adverse Events			
All Systems, Any Adverse Event	35 (72.9)	0	35 (35.4)
Blood and lymphatic system disorders	**23 (47.9)**	**0**	**23 (23.2)**
Neutropenia	18 (37.5)	0	18 (18.2)
Febrile neutropenia	9 (18.8)	0	9 (9.1)
Anaemia	5 (10.4)	0	5 (5.1)
Leukopenia	5 (10.4)	0	5 (5.1)
General disorders and administration site conditions	**21 (43.8)**	**0**	**21 (21.2)**
Fatigue	13 (27.1)	0	13 (13.1)
Asthenia	6 (12.5)	0	6 (6.1)
Gastrointestinal disorders	**17 (35.4)**	**0**	**17 (17.2)**
Nausea	7 (14.6)	0	7 (7.1)
Stomatitis	5 (10.4)	0	5 (5.1)
Nervous system disorders	**12 (25.0)**	**0**	**12 (12.1)**
Infections and infestations	**9 (18.8)**	**0**	**9 (9.1)**
Metabolism and nutrition disorders	**9 (18.8)**	**0**	**9 (9.1)**
Decreased appetite	6 (12.5)	0	6 (6.1)
Musculoskeletal and connective tissue disorders	**9 (18.8)**	**0**	**9 (9.1)**
Skin and subcutaneous tissue disorders	**9 (18.8)**	**0**	**9 (9.1)**
Alopecia	6 (12.5)	0	6 (6.1)
Investigations	**8 (16.7)**	**0**	**8 (8.1)**
Respiratory, thoracic and mediastinal disorders	**8 (16.7)**	**0**	**8 (8.1)**
Cardiac disorders	**6 (12.5)**	**0**	**6 (6.1)**
YM155 or Docetaxel Related Treatment Emergent Adverse Events			
All Systems, Any Adverse Event	**47 (97.9)**	**51 (100)**	**98 (99.0)**
Blood and lymphatic system disorders	**42 (87.5)**	**46 (90.2)**	**88 (88.9)**
Neutropenia	39 (81.3)	43 (84.3)	82 (82.8)
Leukopenia	13 (27.1)	17 (33.3)	30 (30.3)
Anaemia	12 (25.0)	6 (11.8)	18 (18.2)
Febrile neutropenia	11 (22.9)	5 (9.8)	16 (16.2)

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MedDRA v. 12.1 System Organ Class Preferred Term	YM155 5.0 mg/m^2/day + docetaxel (Arm A) n = 48 (%)	Docetaxel (Arm B) n = 51 (%)	Total n = 99 (%)
General disorders and administration site conditions	**33 (68.8)**	**31 (60.8)**	**64 (64.6)**
Fatigue	23 (47.9)	20 (39.2)	43 (43.4)
Oedema peripheral	6 (12.5)	11 (21.6)	17 (17.2)
Asthenia	6 (12.5)	8 (15.7)	14 (14.1)
Mucosal inflammation	7 (14.6)	5 (9.8)	12 (12.1)
Skin and subcutaneous tissue disorders	**32 (66.7)**	**31 (60.8)**	**63 (63.6)**
Alopecia	30 (62.5)	27 (52.9)	57 (57.6)
Nail disorder	6 (12.5)	5 (9.8)	11 (11.1)
Gastrointestinal disorders	**28 (58.3)**	**28 (54.9)**	**56 (56.6)**
Nausea	17 (35.4)	19 (37.3)	36 (36.4)
Diarrhoea	9 (18.8)	9 (17.6)	18 (18.2)
Stomatitis	10 (20.8)	8 (15.7)	18 (18.2)
Constipation	2 (4.2)	6 (11.8)	8 (8.1)
Nervous system disorders	**20 (41.7)**	**25 (49.0)**	**45 (45.5)**
Neuropathy peripheral	7 (14.6)	12 (23.5)	19 (19.2)
Dysgeusia	5 (10.4)	9 (17.6)	14 (14.1)
Peripheral sensory neuropathy	3 (6.3)	6 (11.8)	9 (9.1)
Musculoskeletal and connective tissue disorders	**14 (29.2)**	**19 (37.3)**	**33 (33.3)**
Bone pain	3 (6.3)	6 (11.8)	9 (9.1)
Back pain	6 (12.5)	0	6 (6.1)
Investigations	**12 (25.0)**	**10 (19.6)**	**22 (22.2)**
Metabolism and nutrition disorders	**10 (20.8)**	**12 (23.5)**	**22 (22.2)**
Decreased appetite	7 (14.6)	8 (15.7)	15 (15.2)
Respiratory, thoracic and mediastinal disorders	**13 (27.1)**	**6 (11.8)**	**19 (19.2)**
Dyspnoea	7 (14.6)	3 (5.9)	10 (10.1)
Infections and infestations	**9 (18.8)**	**7 (13.7)**	**16 (16.2)**
Cardiac disorders	**7 (14.6)**	**4 (7.8)**	**11 (11.1)**
Vascular disorders	**5 (10.4)**	**4 (7.8)**	**9 (9.1)**
Psychiatric disorders	**5 (10.4)**	**3 (5.9)**	**8 (8.1)**
Eye disorders	**1 (2.1)**	**6 (11.8)**	**7 (7.1)**

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF). Within a system organ class, a patient may have reported more than one type of adverse event. A treatment-emergent adverse event was defined as an adverse event observed after starting administration of either study regimen.

Source: Tables 12.6.1.3.1 (YM155 alone), 12.6.1.3.2 (docetaxel alone), 12.6.1.3.3 (YM155 and docetaxel), 12.6.1.3.4 (YM155 or docetaxel).

Table 7 Incidence of Serious Treatment-emergent Adverse Events Other than Death by Relationship to Study Drug Regimen (Safety Analysis Set)

	Number (%) of Patients with Serious Treatment-emergent Adverse Events		
MedDRA (v12.1) System Organ Class Preferred Term	**Total n = 99 (%)**	**Arm A YM155 5.0 mg/m^2/day and Docetaxel n = 48 (%)**	**Arm B Docetaxel n = 51 (%)**
All Systems, Any Adverse Event	**42 (42.4)**	**25 (52.1)**	**17 (33.3)**
Blood and lymphatic system disorders	**22 (22.2)**	**14 (29.2)**	**8 (15.7)**
Febrile neutropenia	14 (14.1)	10 (20.8)	4 (7.8)
Neutropenia	9 (9.1)	5 (10.4)	4 (7.8)
Leukopenia	2 (2.0)	0	2 (3.9)
Anaemia	1 (1.0)	1 (2.1)	0
Platelet disorder	1 (1.0)	1 (2.1)	0
Infections and infestations	**14 (14.1)**	**7 (14.6)**	**7 (13.7)**
Pneumonia	5 (5.1)	3 (6.3)	2 (3.9)
Urinary tract infection	3 (3.0)	1 (2.1)	2 (3.9)
Cellulitis	2 (2.0)	1 (2.1)	1 (2.0)
Herpes zoster	2(2.0)	1 (2.1)	1 (2.0)
Arthritis infective	1 (1.0)	0	1 (2.0)
Bronchitis	1 (1.0)	0	1 (2.0)
Catheter sepsis	1 (1.0)	1 (2.1)	0
Central line infection	1 (1.0)	1 (2.1)	0
Clostridium difficile colitis	1 (1.0)	1 (2.1)	0
Infection	1 (1.0)	1 (2.1)	0
Sepsis	1 (1.0)	1 (2.1)	0
Septic shock	1 (1.0)	1 (2.1)	0
Skin infection	1 (1.0)	0	1 (2.0)
Wound infection	1 (1.0)	0	1 (2.0)
Respiratory, thoracic and mediastinal disorders	**9 (9.1)**	**6 (12.5)**	**3 (5.9)**
Pleural effusion	4 (4.0)	2 (4.2)	2 (3.9)
Pulmonary embolism	3 (3.0)	2 (4.2)	1 (2.0)
Dyspnoea	1 (1.0)	0	1 (2.0)
Dyspnoea exertional	1 (1.0)	1 (2.1)	0
Pleurisy	1 (1.0)	0	1 (2.0)
Respiratory failure	1 (1.0)	1 (2.1)	0

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MedDRA (v12.1) System Organ Class Preferred Term	Number (%) of Patients with Serious Treatment-emergent Adverse Events		
	Total n = 99 (%)	**Arm A YM155 5.0 mg/m^2/day and Docetaxel** n = 48 (%)	**Arm B Docetaxel** n = 51 (%)
Cardiac disorders	**5 (5.1)**	**4 (8.3)**	**1 (2.0)**
Atrial fibrillation	3 (3.0)	2 (4.2)	1 (2.0)
Atrial thrombosis	1 (1.0)	1 (2.1)	0
Pericarditis	1 (1.0)	1 (2.1)	0
Tachycardia	1 (1.0)	1 (2.1)	0
General disorders and administration site conditions	**5 (5.1)**	**4 (8.3)**	**1 (2.0)**
Pyrexia	2 (2.0)	1 (2.1)	1 (2.0)
Asthenia	1 (1.0)	1 (2.1)	0
Fatigue	1 (1.0)	1 (2.1)	0
Malaise	1 (1.0)	1 (2.1)	0
Gastrointestinal disorders	**4 (4.0)**	**4 (8.3)**	**0**
Abdominal pain	1 (1.0)	1 (2.1)	0
Diarrhoea	1 (1.0)	1 (2.1)	0
Nausea	1 (1.0)	1 (2.1)	0
Stomatitis	1 (1.0)	1 (2.1)	0
Musculoskeletal and connective tissue disorders	**3 (3.0)**	**2 (4.2)**	**1 (2.0)**
Arthralgia	1 (1.0)	0	1 (2.0)
Back pain	1 (1.0)	1 (2.1)	0
Musculoskeletal chest pain	1 (1.0)	1 (2.1)	0
Neoplasms benign, malignant and unspecified (including cysts and polyps)	**3 (3.0)**	**1 (2.1)**	**2 (3.9)**
Breast cancer	1 (1.0)	1 (2.1)	0
Metastases to central nervous system	1 (1.0)	0	1 (2.0)
Metastases to spine	1 (1.0)	0	1 (2.0)
Vascular disorders	**3 (3.0)**	**3 (6.3)**	**0**
Deep vein thrombosis	2 (2.0)	2 (4.2)	0
Hypotension	1 (1.0)	1 (2.1)	0
Superior vena caval occlusion	1 (1.0)	1 (2.1)	0

Table continued on next page

MedDRA (v12.1) System Organ Class Preferred Term	Number (%) of Patients with Serious Treatment-emergent Adverse Events		
	Total	Arm A YM155 5.0 mg/m^2/day and Docetaxel	Arm B Docetaxel
	n = 99 (%)	n = 48 (%)	n = 51 (%)
Metabolism and nutrition disorders	**2 (2.0)**	**2 (4.2)**	**0**
Decreased appetite	1 (1.0)	1 (2.1)	0
Dehydration	1 (1.0)	1 (2.1)	0
Nervous system disorders	**2 (2.0)**	**2 (4.2)**	**0**
Cerebrovascular accident	1 (1.0)	1 (2.1)	0
Dizziness	1 (1.0)	1 (2.1)	0
Investigations	**1 (1.0)**	**1 (2.1)**	**0**
Blood creatinine increased	1 (1.0)	1 (2.1)	0
Blood urea increased	1 (1.0)	1 (2.1)	0
Renal and urinary disorders	**1 (1.0)**	**0**	**1 (2.0)**
Hydronephrosis	1 (1.0)	0	1 (2.0)

All patients who received at least 1 dose of study drug (Safety Analysis Set, SAF).

A serious treatment-emergent adverse event was defined as any AE that met the criteria for serious in accordance with protocol Section 5.6.2 and ICH E6 Section 1.50.

Source: Table 12.6.1.7