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CLINICAL TRIAL

Phase II, multicenter, open-label, randomized study of YM155 plus docetaxel as first-line treatment in patients with HER2-negative metastatic breast cancer

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Abstract The objective of this study was to assess the efficacy and tolerability of YM155, a survivin suppressor, in combination with docetaxel, compared with docetaxel alone in patients with HER2-negative metastatic breast cancer. This phase II, multicenter, open-label, 2-arm study randomized patients (≥18 years) with histologically or cytologically confirmed stage IV HER2-negative metastatic breast cancer and ≥1 measurable lesion, to receive docetaxel alone or docetaxel plus YM155. The primary endpoint was progression-free survival (PFS). Secondary endpoints included objective response rate (ORR), overall survival (OS), duration of response (DOR), clinical benefit rate (CBR), time to response (TTR), biomarker assessment, and analysis of circulating tumor cells. Patients were women diagnosed with HER2-negative breast cancer; most had received prior drug therapies. The median PFS was 8.4 months with YM155 plus docetaxel ($n = 50$) and 10.5 months with docetaxel alone ($n = 51$; HR 1.53; 95 % CI 0.83, 2.83; $P = 0.176$). No statistically significant differences were observed for secondary endpoints, although slightly greater OS (630 vs 601 days; $P = 0.768$), CBR (84.3 vs 82.0 %; $P = 0.855$), DOR, and TTR were observed with docetaxel alone compared with YM155 plus docetaxel, whereas ORR was similar (25.5 vs 26.0). The most common TEAEs observed with YM155 plus docetaxel compared with docetaxel alone were neutropenia (83.3 vs 84.3 %), alopecia (62.5 vs 52.9 %), fatigue (50 vs 41.2 %), and nausea (37.5 vs 41.2 %). Although YM155 is a novel drug that suppresses survivin, YM155 plus docetaxel exhibited no statistically significant differences in endpoints compared with docetaxel alone. The combination regimen was well tolerated.

Keywords YM155 · Survivin · HER2 · Metastatic breast cancer

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Introduction

Breast cancer is the most common potentially fatal form of cancer in women and is the leading cause of death from cancer in women worldwide [1]. It is estimated that there will be approximately 235,000 new cases of invasive breast cancer and more than 40,000 breast cancer deaths in the United States in 2014 [2]. The majority of patients will be diagnosed with early stage disease [3], which is amenable to curative treatment with surgical care and/or radiation [4]; however, 6–10 % of patients will present with metastatic breast cancer [5], and up to 30 % of all patients may ultimately develop metastatic disease [6].

While metastatic breast cancer generally is incurable, systemic therapy can provide meaningful prolongation of survival and palliation of the distressing symptoms of cancer [7, 8]. The choice of systemic therapy is increasingly determined by biological markers predictive of response to targeted therapy. Patients with hormone receptor positive disease will frequently benefit from endocrine therapies [9]. When the nearly inevitable development of resistance to endocrine therapy occurs [10], these patients can still derive benefit from cytotoxic chemotherapy [11]. Patients whose cancer has an alteration (usually an amplification) of the HER2 gene derive substantial benefit from anti-HER2 therapeutics such as trastuzumab given in combination with chemotherapy or endocrine therapy [12].

Approximately 15 % of patients have tumors that do not express the estrogen or progesterone receptors, and do not have altered HER-2 [9]. There are currently no markers predictive of response for patients with these "triple negative" tumors, and conventional cytotoxic chemotherapy remains the standard of care [11]. Unfortunately, prognosis remains poor due to high rates of relapse and chemoresistance in this subset of breast cancer patients [13]. New molecularly targeted systemic therapies for triple negative breast cancers (TNBC) are urgently needed.

One such candidate target molecule is survivin, a member of the "inhibitor of apoptosis protein" family that contributes to increased proliferation and resistance to apoptosis in tumor cells [14]. Overexpression of survivin has been demonstrated in metastatic breast cancer compared with normal breast tissue [15]. A recent meta-analysis found that increased expression of survivin was significantly associated with unfavorable overall survival (OS) in patients with breast cancer [16].

YM155 is a small molecular suppressor of survivin. Continuous infusion of YM155 significantly reduced tumor size and the incidence of spontaneous metastasis, as well as prolonged survival, in a mouse model of metastatic TNBC [17]. In vitro studies demonstrated that inhibition of apoptosis by survivin required interaction with microtubules [18], providing a powerful rationale for the study of survivin together with anti-microtubule agents such as taxanes. YM155 in combination with the microtubule-targeted agent docetaxel induced greater apoptosis compared with either agent alone, resulting in complete tumor regression in a mouse TNBC xenograft model [19]. The results of a phase I study indicated that YM155 was well tolerated with manageable toxicities in patients with advanced solid tumors, including breast cancer, that were refractory to standard therapy [20]. Additionally, findings from an open-label, single-arm, single-center study of YM155 plus docetaxel in patients with advanced hormone refractory prostate cancer and other tumors showed responses in a few patients with breast cancer, supporting the design and execution of the present study [21].

The objective of the current phase II study was to assess the effects of YM155 in combination with docetaxel compared with docetaxel alone on progression-free survival (PFS) in patients with HER2-negative metastatic breast cancer.

Methods

Study design

This was a phase II, multicenter, open-label, randomized, 2-arm study (NCT01038804) conducted in the United States, Europe, and Russia. Local institutional review boards and independent ethics committees, or both, approved the study protocol and informed consent forms before use. The study was conducted in accordance with the International Conference on Harmonization Guidelines for Good Clinical Practice, the European Clinical Trial Directive, and applicable laws and regulations. Each patient provided written informed consent before study enrollment.

Study population

Inclusion criteria

Patients aged ≥18 years with histologically or cytologically confirmed stage IV HER2-negative metastatic breast cancer and ≥1 measurable lesion (RECIST criteria, version 1.1) were eligible for enrollment. HER2-negative breast cancer was defined as negative fluorescence in situ hybridization (FISH), 0 or 1+ immunohistochemistry (IHC), or IHC 2+ with negative FISH. Patients had an Eastern Cooperative Oncology Group performance status ≤1 at baseline. In general, prior first-line chemotherapy for metastatic breast cancer was not permitted. However, prior cytotoxic therapy was permitted if it was administered in the neoadjuvant or adjuvant setting ≥3 weeks before baseline. Patients with prior docetaxel treatment were eligible if they had no evidence of recurrent disease within 12 months of completing treatment. Prior treatment with a kinase inhibitor or hormonal therapy also was permitted if administered ≥4 and ≥2 weeks, respectively, before baseline, and prior palliative radiation therapy was allowed if completed ≥2 weeks before baseline. For a brief period, the protocol was amended to enroll patients who had previously received first-line chemotherapy, but this was revised back to the original criteria of no prior therapy for metastatic disease based upon preclinical data that suggested that YM155 was a p-glycoprotein substrate.

Exclusion criteria

Patients were excluded if they had hypersensitivity to docetaxel or polysorbate 80; major surgery, open biopsy, or significant traumatic injury within 28 days before baseline or anticipated need for major surgery during the study; neuropathy grade $\geq$2 at baseline; inadequate marrow at baseline; inadequate hepatic function and renal function, or both, at baseline; known brain or leptomeningeal metastasis; known immunodeficiency virus, hepatitis B surface antigen, or hepatitis C antibody; or significant and/or uncontrolled cardiac, renal, hepatic, or other systemic disorders or significant psychological conditions at baseline.

Treatment regimen

One cycle was considered 21 days and was divided into a 7-day treatment period followed by a 14-day (Arm A; YM155 plus docetaxel) or a 20-day (Arm B; docetaxel alone) observation period. YM155 was administered by continuous infusion at a dose of 5 mg/m^2/day for 168 h. The YM155 infusion was initiated on day 1 within 1 h of completion of docetaxel dosing using a portable infusion pump to administer study drug through a dedicated central line, port, or peripherally inserted central catheter. Dose reduction of YM155 to 3.6 mg/m^2/day was permitted at the investigator's discretion in patients with a grade 3 or 4 adverse event (AE), with the exception of weight loss or gain, anorexia, alopecia, and fatigue. Infusion of YM155 and docetaxel was interrupted until the AE resolved to grade $\leq$1 or returned to baseline, and infusion of YM155 could then be restarted at the original dose of 5 mg/m^2/day or reduced to 3.6 mg/m^2/day at the discretion of the investigator.

Docetaxel [22] was administered by intravenous infusion for 1 h on day 1 every 21-day cycle at a dose of 75 mg/m^2 in patients treated with YM155 plus docetaxel and 75 or 100 mg/m^2 in patients treated with docetaxel alone at the discretion of the investigator. Dose reduction of docetaxel to 75 mg/m^2 was permitted at the discretion of the investigator in patients with febrile neutropenia or an absolute neutrophil count <500 cells/mm^3 lasting >1 week and in patients with severe or cumulative cutaneous reactions. In the event that these AEs were ongoing, further dose reduction of docetaxel to 55 mg/m^2 or discontinuation of docetaxel was permitted at the discretion of the investigator. In patients with a grade 3 or 4 AE, with the exception of peripheral neuropathy, weight loss or gain, anorexia, alopecia, and fatigue, docetaxel treatment was interrupted until the AE resolved to grade $\leq$1 or returned to baseline and then could be restarted at 75 for patients receiving 100 mg or 55 mg/m^2 for patients receiving 75 mg/m^2 at the time of the AE. Discontinuation of docetaxel treatment was required in patients with grade 3 or 4 neuropathy.

Retreatment criteria

The following criteria must have been met before a patient began the next cycle of treatment: no evidence of disease progression based on radiological and/or clinical assessments, and any YM155- and/or docetaxel-related toxicity must have either resolved to a grade of $\leq$1 or returned to baseline level.

Assessments

The primary efficacy endpoint was PFS. Subgroup analyses of PFS were performed according to TNBC or hormone receptor positive status. The secondary efficacy endpoints assessed included objective response rate (ORR), OS, duration of response (DOR), clinical benefit rate (CBR), and time to response (TTR). Patients were evaluated by computed tomography, magnetic resonance imaging, or both, every 6 weeks (cycle 1 and 2) within 5 days of the initial docetaxel infusion and every 12 weeks thereafter. Objective tumor assessments were determined using RECIST, version 1.1.

Blood samples were collected from all patients during screening and cycles 1–3 to assess biomarkers, including caspase-cleaved cytokeratin 18 (M30 Apoptosense® ELISA, PEVIVA AB, Broma, Sweden), a tumor apoptosis marker. Blood samples were collected during cycles 1 and 2 for analysis of circulating tumor cells.

Safety and tolerability assessments included AEs and clinical laboratory evaluations.

Statistical analyses

The efficacy analyses were conducted on the full analysis set (FAS) and per protocol (PP) set. The FAS included all patients randomized into the study and was considered the primary analysis set. The PP set included all randomized patients who were administered $\geq$1 dose of their assigned study regimen, had histologically or cytologically proven adenocarcinoma of the breast that was HER2-negative, had no known brain or leptomeningeal metastasis, had no history of other malignancy within 5 years before the first dose of YM155, except for treated basal or squamous cell carcinoma of the skin or in situ cervical cancer, and did not have major protocol deviations.

Demographic data and baseline disease and treatment characteristics were summarized using descriptive statistics. The median PFS, including subgroup analyses of PFS, OS, and DOR were estimated using the Kaplan–Meier method reported with corresponding 95 % CI. PFS and OS were analyzed between treatment arms using a two-sided log-rank test stratified by prior taxane therapy and triple negative status ($\alpha = 0.05$). PFS also was compared

between treatment arms using the hazard ratio, corresponding 95 % CI, and *P* value from the stratified Cox proportional hazards regression model. ORR and CBR were compared between treatment arms using the stratified Cochran-Mantel-Haenszel test, and the difference in response rates and corresponding 95 % CIs were estimated using large sample methods and unpooled variance estimates. The TTR was summarized using descriptive statistics.

Approximately 100 patients (randomized in a 1:1 ratio) stratified by prior taxane therapy and triple negative status (yes or no for both) were required to observe 67 PFS events (progressive disease or death). The sample size had 55 % power to detect a true hazard ratio of 0.60 (median PFS of 10 vs 6 months).

Safety was assessed in all patients who received ≥1 dose of study regimen and summarized using descriptive statistics or frequency distributions, as appropriate.

Results

Baseline demographics and characteristics

Of 119 patients screened, 101 were enrolled and randomized to treatment and 99 received the drug. At baseline, all patients were women diagnosed with HER2-negative metastatic breast cancer, and the majority had received prior drug therapies, principally in the adjuvant or neoadjuvant setting (Table 1).

Table 1 Baseline characteristics (full analysis set)

Characteristic	YM155 + docetaxel ($n = 50$)	Docetaxel ($n = 51$)	Total ($N = 101$)
Sex, *n* (%)			
Female	50 (100)	51 (100)	101 (100)
Median age, years (range)	57.0 (34–79)	55.0 (25–77)	55.0 (25–79)
Race, *n* (%)			
White	47 (94.0)	48 (94.1)	95 (94.1)
Black or African American	1 (2.0)	1 (2.0)	2 (2.0)
Asian	1 (2.0)	0	1 (1.0)
Other	1 (2.0)	2 (3.9)	3 (3.0)
Subtype at diagnosis, *n* (%)			
Ductal	37 (74.0)	33 (64.7)	70 (69.3)
Lobular	4 (8.0)	8 (15.7)	12 (11.9)
Paget's disease and infiltrating	2 (4.0)	0	2 (2.0)
Medullary, NOS	0	1 (2.0)	1 (1.0)
Papillary	0	1 (2.0)	1 (1.0)
Other	7 (14.0)	8 (15.7)	15 (14.9)
Tumor grade, *n* (%)			
Grade 1	1 (2.0)	2 (3.9)	3 (3.0)
Grade 2	24 (48.0)	19 (37.3)	43 (42.6)
Grade 3	15 (30.0)	16 (31.4)	31 (30.7)
Unknown	10 (20.0)	14 (27.5)	24 (23.8)
Tumor receptor status, *n* (%)			
Triple receptor negative[a]	13 (26.0)	12 (23.5)	25 (24.8)
Estrogen receptor status			
Positive	34 (68.0)	35 (68.6)	69 (68.3)
Negative	13 (26.0)	14 (27.5)	27 (26.7)
Unknown	3 (6.0)	2 (3.9)	5 (5.0)
Progesterone receptor status			
Positive	22 (44.0)	33 (64.7)	55 (54.5)
Negative	23 (46.0)	14 (27.5)	37 (36.6)
Unknown	5 (10.0)	4 (7.8)	9 (8.9)
Prior drug therapy, *n* (%)	43 (86.0)	44 (86.3)	87 (86.1)
Prior taxane therapy, *n* (%)	11 (22.0)	9 (17.6)	20 (19.8)

NOS not otherwise specified

[a] HER2, estrogen, and progesterone receptors

Treatment exposure

Patients in the YM155 plus docetaxel group completed a median of 6.0 cycles of YM155 infusion; 4 (8.3 %) patients experienced YM155 dose reduction, and 8 (16.7 %) patients experienced an interruption. In addition, patients in this arm received a median of 6.0 cycles and a cumulative total dose of 679.0 mg of docetaxel infusion; 9 (18.8 %) patients experienced a dose reduction and no patients an interruption.

Patients in the docetaxel arm completed a median of 7.43 cycles and received a median cumulative total dose of 827.5 mg of docetaxel infusion; 12 (23.5 %) patients experienced a dose reduction and no patients experienced an interruption.

Primary and secondary endpoints

The median PFS was 8.4 months in patients treated with YM155 plus docetaxel compared with 10.5 months in patients administered docetaxel alone. This difference was not statistically significant ($P = 0.172$; Table 2). Kaplan–Meier plots of PFS are presented in Fig. 1a. The docetaxel

Table 2 Analysis of primary and secondary efficacy endpoints for the full analysis population

Clinical outcome	YM155 + Docetaxel (FAS, $n = 50$)	Docetaxel (FAS, $n = 51$)	P value
FAS			
Primary efficacy endpoint			
Median (95 % CI) PFS, days	251.0 (172, 333)	315.0 (202, 433)	0.172
HR (95 % CI)	1.53 (0.83, 2.83)		0.176
Secondary efficacy endpoints			
ORR, *n* (%)	13 (26.0)	13 (25.5)	0.987
CBR, *n* (%)	41 (82.0)	43 (84.3)	0.855
Median OS, days	601.0	630.0	0.768
Median DOR, days	231.5	NA*	NA

CBR clinical benefit rate, *DOR* duration of response, *FAS* full analysis set, *NA* not available, *ORR* objective response rate, *OS* overall survival, *PFS* progression-free survival

* At the time of data cutoff, median DOR had not been reached

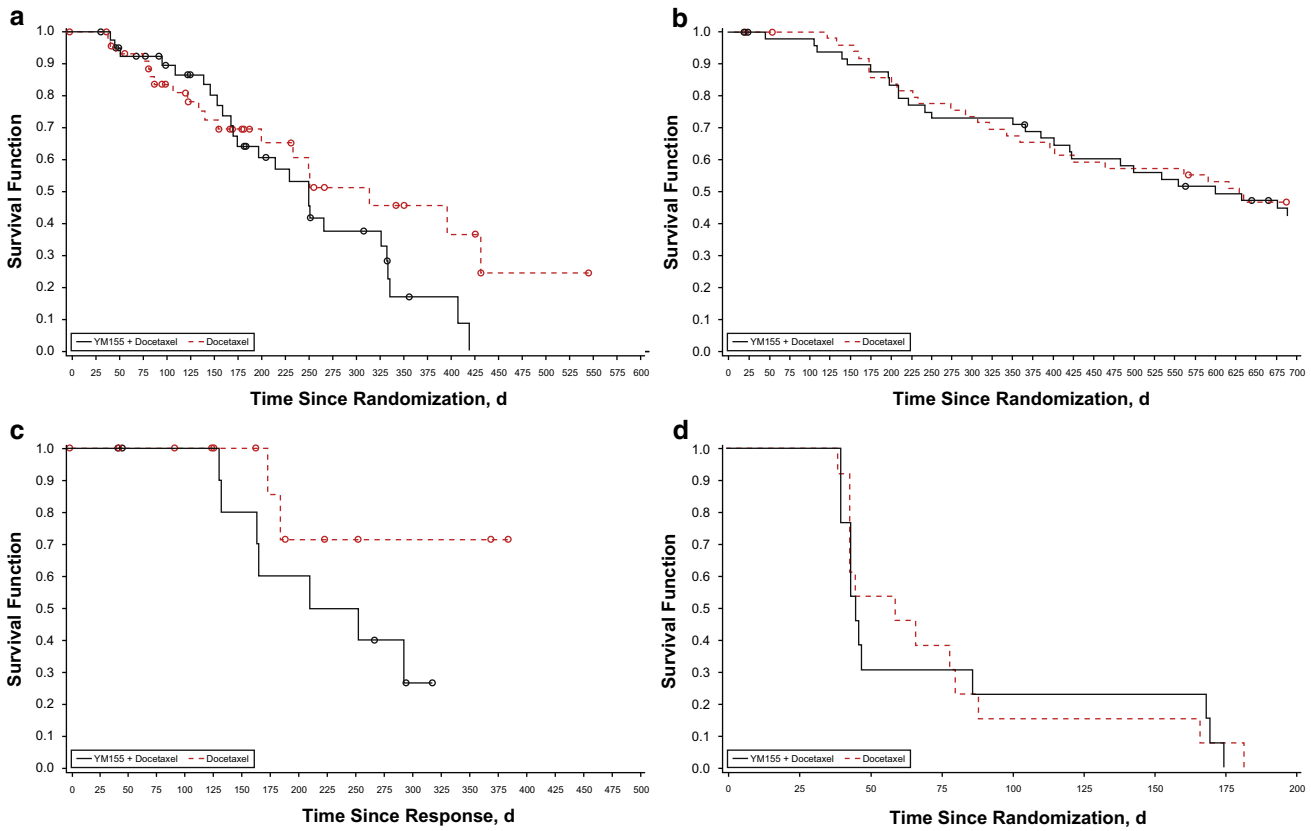

Fig. 1 Kaplan-Meier plots of **a** progression-free survival, **b** overall survival, **c** duration of response, and **d** time to response in the full analysis population

Table 3 Treatment-emergent adverse events occurring in ≥10 % in either treatment arm (safety analysis population)

Parameter, *n* (%)	YM155 + docetaxel (*n* = 48)	Docetaxel (*n* = 51)
Hematologic		
Neutropenia	40 (83.3)	43 (84.3)
Leukopenia	13 (27.1)	17 (33.3)
Anemia	13 (27.1)	6 (11.8)
Febrile neutropenia	11 (22.9)	5 (9.8)
Lymphopenia	3 (6.3)	6 (11.8)
Nonhematologic		
Alopecia	30 (62.5)	27 (52.9)
Fatigue	24 (50.0)	21 (41.2)
Nausea	18 (37.5)	21 (41.2)
Dyspnea	16 (33.3)	7 (13.7)
Diarrhea	11 (22.9)	10 (19.6)
Edema peripheral	9 (18.8)	12 (23.5)
Neuropathy peripheral	7 (14.6)	12 (23.5)
Stomatitis	11 (22.9)	8 (15.7)
Decreased appetite	8 (16.7)	9 (17.6)
Asthenia	7 (14.6)	8 (15.7)
Constipation	6 (12.5)	8 (15.7)
Cough	6 (12.5)	8 (15.7)
Dysgeusia	5 (10.4)	9 (17.6)
Headache	8 (16.7)	5 (9.8)
Mucosal inflammation	8 (16.7)	5 (9.8)
Pyrexia	8 (16.7)	5 (9.8)
Arthralgia	8 (16.7)	4 (7.9)
Back pain	9 (18.8)	2 (3.9)
Bone pain	4 (8.3)	7 (13.7)
Nail disorder	6 (12.5)	5 (9.8)
Urinary tract infection	6 (12.5)	5 (9.8)
Pain in extremity	4 (8.3)	6 (11.8)
Insomnia	6 (12.5)	3 (5.9)
Peripheral sensory neuropathy	3 (6.3)	6 (11.8)
Myalgia	2 (4.2)	6 (11.8)
Oropharyngeal pain	5 (10.4)	0

arm demonstrated slightly better secondary endpoints compared with the YM155 plus docetaxel arm, but no statistically significant differences between the treatment arms were observed (Table 2; Fig. 1b–d). In addition, median PFS, OS, and DOR values were similar between the FAS and PP populations, with no significant differences between treatment arms for the PP population (data not shown).

Biomarker analyses for the presence of caspase-cleaved cytokeratin 18, a specific marker for epithelial cell apoptosis, suggested a slightly higher percentage of tumor apoptosis with YM155 plus docetaxel (31.4 %) compared with docetaxel alone (18.3 %). Circulating tumor cells were very low and no differences could be shown between

Table 4 Treatment-emergent grade ≥3 adverse events (safety analysis population)

Parameter, *n* (%)	YM155 + Docetaxel (*n* = 48)	Docetaxel (*n* = 51)
Grade 3		
Neutropenia	19 (39.6)	12 (23.5)
Leukopenia	6 (12.5)	8 (15.7)
Febrile neutropenia	8 (16.7)	4 (7.8)
Lymphophenia	3 (6.3)	4 (7.8)
Dyspnea	3 (6.3)	1 (2.0)
Pneumonia	2 (4.2)	2 (3.9)
Central line infection	2 (4.2)	1 (2.0)
Palmar-plantar erythrodysasthesia syndrome	1 (2.1)	2 (3.9)
Deep vein thrombosis	2 (4.2)	0
Pleural effusion	2 (4.2)	0
Increased alanine aminotransferase	0	2 (3.9)
Peripheal neuropathy	0	2 (3.9)
Anemia	1 (2.1)	1 (2.0)
Asthenia	1 (2.1)	1 (2.0)
Atrial fibrillation	1 (2.1)	1 (2.0)
Bone pain	1 (2.1)	1 (2.0)
Catheter-related infection	1 (2.1)	1 (2.0)
Cellulitis	1 (2.1)	1 (2.0)
Dehydration	1 (2.1)	1 (2.0)
Decreased white blood cell count	1 (2.1)	1 (2.0)
Syncope	1 (2.1)	1 (2.0)
Atrial thrombosis	1 (2.1)	0
Clostridium difficile colitis	1 (2.1)	0
Decreased appetite	1 (2.1)	0
Diarrhea	1 (2.1)	0
Electrocardiogram T wave inversion	1 (2.1)	0
Excoriation	1 (2.1)	0
Hypoalbuminemia	1 (2.1)	0
Hypotension	1 (2.1)	0
Increased gamma-glutamyltransferase	1 (2.1)	0
Mucosal inflammation	1 (2.1)	0
Nail disorder	1 (2.1)	0
Pericarditis	1 (2.1)	0
Platelet disorder	1 (2.1)	0
Polyneuropathy	1 (2.1)	0
Pulmonary embolism	1 (2.1)	0
Respiratory failure	1 (2.1)	0
Stomatitis	1 (2.1)	0
Superior vena cava occlusion	1 (2.1)	0
Thrombosis	1 (2.1)	0
Vascular access complication	1 (2.1)	0
Back pain	0	1 (2.0)

Table 4 continued

Parameter, *n* (%)	YM155 + Docetaxel (*n* = 48)	Docetaxel (*n* = 51)
Bronchitis	0	1 (2.0)
Catheter site infection	0	1 (2.0)
Cerebral infarction	0	1 (2.0)
Decreased neutrophil count	0	1 (2.0)
Fatigue	0	1 (2.0)
Fluid retention	0	1 (2.0)
Herpes zoster	0	1 (2.0)
Hydronephrosis	0	1 (2.0)
Hyponatremia	0	1 (2.0)
Hypophosphatemia	0	1 (2.0)
Increased blood glucose	0	1 (2.0)
Infective arthritis	0	1 (2.0)
Neck pain	0	1 (2.0)
Pain in extremity	0	1 (2.0)
Paresthesia	0	1 (2.0)
Pelvic pain	0	1 (2.0)
Peripheral edema	0	1 (2.0)
Pleurisy	0	1 (2.0)
Pyrexia	0	1 (2.0)
Rash	0	1 (2.0)
Wound infection	0	1 (2.0)
Grade 4		
Neutropenia	21 (43.8)	30 (58.8)
Leukopenia	5 (10.4)	4 (7.8)
Febrile neutropenia	2 (4.2)	1 (2.0)
Decreased neutrophil count	1 (2.1)	1 (2.0)
Decreased white blood cell count	1 (2.1)	1 (2.0)
Pulmonary embolism	1 (2.1)	1 (2.0)
Catheter sepsis	1 (2.1)	0
Fatigue	1 (2.1)	0
Increased blood creatinine	1 (2.1)	0
Infection	1 (2.1)	0
Metastases to central nervous system	0	1 (2.0)
Sepsis	1 (2.1)	0
Septic shock	1 (2.1)	0
Thoracic vertebral fracture	1 (2.1)	0
Grade 5		
Breast cancer	1 (2.1)	0
Cerebrovascular accident	1 (2.1)	0

the two treatment arms. However, for both analyses, the sample sizes were very small and no statistical correlations could be made.

Table 5 Most common serious adverse events regardless of causality occurring in ≥5 % of patients (safety analysis population)

SAE, *n* (%)	YM155 + docetaxel (*n* = 48)	Docetaxel (*n* = 51)	Total (*N* = 99)
Any SAE	25 (52.1)	17 (33.3)	42 (42.4)
Hematologic			
Febrile neutropenia	10 (20.8)	4 (7.8)	14 (14.1)
Neutropenia	5 (10.4)	4 (7.8)	9 (9.1)
Nonhematologic			
Pneumonia	3 (6.3)	2 (3.9)	5 (5.1)

SAE serious adverse event

Safety and tolerability

All patients in the safety analysis population ($n = 99$) experienced ≥1 TEAE (Table 3). The most common TEAEs in both treatment groups were neutropenia, alopecia, fatigue, and nausea. Most TEAEs were grade 3 or 4, and the events reported in the YM155 plus docetaxel arm were judged more often to be possibly or probably related to study drug, whereas none of the events in the docetaxel alone arm were judged to be possibly or probably related (Tables 3, 4).

The most common drug-related TEAEs in the YM155 plus docetaxel arm were neutropenia ($n = 18$ [37.5 %]), fatigue ($n = 13$ [27.1 %]), and febrile neutropenia ($n = 9$ [18.8 %]). A total of 14 (29.2 %) patients administered YM155 plus docetaxel and 9 (17.6 %) patients administered docetaxel alone experienced a TEAE leading to study discontinuation. TEAEs leading to study discontinuation that occurred in ≥2 patients in a treatment arm were febrile neutropenia and leukopenia (each $n = 2$ [4.2 %]) in patients administered YM155 plus docetaxel and fluid retention, palmar-plantar erythrodysesthesia syndrome, and peripheral neuropathy (each $n = 2$ [3.9 %]) in patients administered docetaxel alone.

Serious AEs (SAEs) were experienced by 25 (52.1 %) patients administered YM155 plus docetaxel and 17 (33.3 %) administered docetaxel alone (Table 5). SAEs that occurred in ≥5 % of patients in either treatment group included febrile neutropenia, neutropenia, and pneumonia (Table 5). A total of 56 (56.6 %) patients died during the study; 28 (58.3 %) patients were treated with YM155 plus docetaxel and 28 (54.9 %) patients received docetaxel alone. Most of the deaths (87.5 %) were attributed to breast cancer. In patients administered YM155 plus docetaxel, two deaths were attributed to hepatic failure, one to a cerebrovascular accident, one to general state degradation, and the cause of death in one patient was unknown. In patients who received docetaxel alone, one death was attributed to sepsis; in one

patient, the cause of death was unknown. None of the deaths were related to the study medications.

Three patients discontinued treatment due to abnormalities in laboratory values (increased gamma-glutamyltransferase, increased blood urea nitrogen and blood creatinine, and platelet disorder/thrombopathy); all of these abnormalities were considered possibly or probably related to YM155. Other laboratory findings were generally not clinically significant. No cardiac safety signals were detected during the study.

Discussion

Findings from this study of patients with HER2-negative metastatic breast cancer treated with YM155 in combination with docetaxel exhibited no statistically significant differences in the primary endpoint of PFS or secondary endpoints compared with patients administered docetaxel alone. The combination of YM155 plus docetaxel was well tolerated. The most common drug-related TEAEs in the YM155 plus docetaxel arm were expected and included neutropenia, fatigue, and febrile neutropenia. Renal failure was reported in a previous study with YM155 and was considered to be related to YM155 [23]. In the present study, one patient in the combination arm discontinued with elevated blood urea nitrogen and creatinine levels that were deemed related to study drug; these events resolved 11 and 25 days following onset, respectively.

YM155 was administered as a continuous intravenous infusion for 168 h in a 21-day cycle. Preclinical data suggest that bolus infusion may increase the risk for renal and/or cardiovascular toxicity. Although continuous infusion is more time-consuming and may be less convenient, the need for continuous infusion did not affect recruitment in the present study, and patients experienced no difficulty with drug administration over a long period of time.

An urgent unmet need for additional therapeutic options in patients with TNBC exists because of their high risk of relapse and poor long-term prognosis [24, 25]. A positive outcome was expected from this study because YM155 is a novel drug that suppresses survivin at both the mRNA and protein levels [26]; survivin is a protein that is associated with decreased apoptosis and has been shown to be more highly expressed in metastatic breast cancer compared with normal breast tissue [27]. YM155 is also highly distributed to tumor tissues relative to normal plasma [26]. Although these preclinical data provide a good rationale for evaluating YM155 in breast cancer, findings from the present study demonstrated that YM155 plus docetaxel exhibited no statistically significant differences in PFS, ORR, OS, DOR, or CBR compared with patients administered docetaxel alone.

However, this study also had some limitations, including the lack of formal pharmacokinetic interaction analysis between YM155 and docetaxel. In addition, the limited amount of biomarker data available leaves open the question of whether there is a patient population more likely to benefit from the combination of YM155 with docetaxel. Improved availability and use of biomarkers could help identify patients with TNBC or other types of cancer who might benefit from specific inhibition of survivin. Although development of YM155 in patients with TNBC is not proceeding, further research into drugs effective at targeting the survivin pathway is warranted.

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Conflict of interest Michael R. Clemens has received research funding from Astellas. Oleg A. Gladkov, Elaina Gartner, and Vladimir Vladimirov have nothing to disclose. John Crown consulted for Astellas and received honoraria from Sanofi. Anne Keating, Fei Jie, and Joyce Steinberg are Astellas employees.

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