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ORIGINAL ARTICLE

Phase I safety and pharmacokinetic study of YM155, a potent selective survivin inhibitor, in combination with erlotinib in patients with EGFR TKI refractory advanced non-small cell lung cancer

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Abstract

Purpose This phase I study was conducted to evaluate the safety and pharmacokinetics of YM155, a potent, selective survivin inhibitor, in combination with erlotinib in patients with EGFR TKI refractory advanced non-small cell lung cancer (NSCLC).

Methods The pimary objectives were to evaluate the safety and tolerability of YM155 at escalating doses (3.6, 4.8, 6.0, and 8.0 mg/m^2/days) administered every 3 weeks as continuous intravenous infusion over 168 h in combination with erlotinib at a fixed dose (150 mg, once a day). Secondary objectives were to assess the pharmacokinetics of YM155, antitumor activity, and the relationship between biomarkers and efficacy. The changes in survivin expression in biopsied tumor pre- and post-YM155 administration and serum cytokine levels were also analyzed.

Results Fifteen patients were treated. The most common YM155-related adverse event was the presence of urine microalbumin, whereas grades 3/4 toxicities were rare. One patient who received 4.8 mg/m^2/days YM155 developed a dose-limiting grade 2 serum creatinine elevation. YM155 exposure in plasma showed dose proportionality across all dose ranges tested. No pharmacokinetic interaction occurred between YM155 and erlotinib. The serum cytokines IL-8, G-CSF, and MIP-1b showed decreasing trends in patients who achieved progression-free survival of ≥ 12 weeks. Durable stable disease for ≥ 24 weeks was observed in two patients.

Conclusion Up to 8.0 mg/m^2/days YM155 administered every 3 weeks in combination with erlotinib exhibited a favorable safety profile and moderate clinical efficacy. These results suggest that inhibiting survivin is a potential therapeutic strategy for select patients with EGFR TKI refractory NSCLC.

Trial registration UMIN000031912 at UMIN Clinical Trials Registry (UMIN-CTR).

Keywords Phase I study · YM155 · Anti-apoptotic agent · Survivin inhibitor · EGFR-mutant NSCLC

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Introduction

Among cancer-related deaths, deaths from lung cancer are the most common worldwide, and approximately 85% of lung cancers are classified as non-small cell lung cancer (NSCLC) [1]. The epidermal growth factor receptor (EGFR) is a transmembrane glycoprotein of the ErbB family of tyrosine kinase receptors. Somatic mutations in the EGFR, which are mostly concentrated in the exon 18–21 region, are major oncogenic drivers. These mutations are present in approximately 30–50% and 10–20% of NSCLC in Asians and Caucasians, respectively [2–5], and activating these mutations in the EGFR kinase domain induces cancer cell growth and survival [6, 7]. Various tyrosine kinase inhibitors (TKIs) targeting the EGFR mutations, such as gefitinib, erlotinib, and afatinib, have been developed as anticancer agents. Osimertinib, one of the third-generation EGFR TKIs, has been approved for treating patients with T790M acquired resistance mutations-confirmed NSCLC [8–11]. Several mechanisms of acquired resistance have been reported, but a large proportion of patients develop a secondary T790M point mutation in the ATP-binding site of *EGFR* exon 20, contributing to approximately 50–60% of resistance in patients. Other resistance mechanisms include alternative pathway activation and histological and phenotypical transformations. Although several acquired resistance mechanisms could be potential and rational therapeutic targets, at the time when this trial was designed, there were no standardized clinical strategies for patients with EGFR TKI refractory NSCLC.

Survivin is a member of the inhibitor of apoptosis protein (IAP) family expressed in multiple human solid and hematological cancers, with limited expression in normal tissues [12]. Survivin plays an important role in cell division and growth via the regulation of mitosis [13–15]. In cancer cells, survivin interferes with apoptosis by inhibiting caspase-dependent and -independent mechanisms [16, 17]. Overexpression of survivin has been associated with increased invasive phenotype and worse clinical prognosis [18, 19]. Based on these findings, survivin is considered a promising therapeutic target. Our previous preclinical studies demonstrated the following: (1) the downregulation of survivin reverses first-generation EGFR TKI resistance in tumor cells in vitro and (2) survivin inhibitor in combination with erlotinib synergistically inhibited the growth of EGFR-mutant NSCLC tumors in vivo [20, 21]. These results suggest that targeting survivin (BIRC5) has the therapeutic potential to overcome EGFR TKI resistance in EGFR-mutant NSCLC [20, 21].

YM155 (Sepantronium Bromide) was the first discovered potent, selective small-molecule inhibitor of survivin [22–24]. The mechanism of action of YM155 is mediated via a 2-kb promoter region in the survivin IAP gene, causing survivin downregulation [23, 24]. Preclinical studies demonstrated that YM155 suppresses both survivin protein and mRNA expression in various human tumor cell lines [22, 23]. In the previous phase I studies of YM155 monotherapy, the inhibitor was well tolerated when administered as a continuous intravenous infusion over 7 days. The dose-limiting toxicity (DLT) of YM155 was a reversible elevation in serum creatinine, and the maximum tolerated dose (MTD) was 4.8 mg/m^2/days in the USA and 8.0 mg/m^2/days in Japan. The recommended phase II dose (PP2D) of YM155 was 4.8 mg/m^2/days administered as a continuous intravenous infusion over 168 h [25, 26]. In phase II trials, YM155 showed moderate antitumor activity as monotherapy against castration-resistant prostate cancer, NSCLC, melanoma, and diffuse large B-cell lymphoma [27–31], as well as in combination with other therapeutic agents [32–35].

Based on the potential rationale of overcoming EGFR TKI resistance by targeting survivin, along with the preclinical antitumor activity, this phase I study was conducted to evaluate the safety, pharmacokinetics, and pharmacodynamics of YM155 in combination with erlotinib in patients with EGFR TKI refractory advanced NSCLC.

Materials and methods

Patient eligibility

This study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review board of the study site (Kindai University Hospital, Osaka, Japan). The main eligibility criteria were as follows: (1) patients with histologically confirmed recurrent or metastatic NSCLC with EGFR exon19 deletion or exon21 point mutation who were refractory to prior EGFR TKI therapy; (2) patients > 20 years with an anticipated life expectancy of > 12 weeks; (3) patients with an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2; (4) patients with adequate hematologic, hepatic, and renal functions (serum creatinine ≤ upper limit of normal (ULN), AST, ALT ≤ 2.5 × ULN, T-bilirubin ≤ 1.5 × ULN); and (5) patients with no ECG abnormalities that need treatment. The exclusion criteria were as follows: (1) patients receiving chemotherapy, radiotherapy, or biological therapy 4 weeks (2 weeks for palliative radiotherapy and small-molecule kinase inhibitors) before enrollment; (2) patients with other active cancers, previous history or presence of interstitial lung diseases (ILDs), symptomatic CNS metastasis, a history (within 6 months before study enrollment) or presence of severe cardiovascular or cerebrovascular diseases, severe thrombosis; (3) patients with any of the following medical

complications: clinically severe infections, chronic diarrhea, inflammatory bowel disease, uncontrolled diabetes mellitus, uncontrolled hypertension regardless of appropriate therapy, and (4) positive test for hepatitis B virus antigen and hepatitis C virus antibody or HIV antibody. All patients provided written informed consent, and the study was conducted in accordance with the good clinical practice standards. This study was registered at UMIN Clinical Trials Registry (UMIN-CTR): UMIN000031912.

Study design and evaluation

This was a single-center (in Japan), open-label, non-randomized, phase I study of YM155 in combination with erlotinib in patients with EGFR TKI refractory advanced NSCLC. The primary objectives were to evaluate the safety and tolerability of YM155 in combination with erlotinib and determine the DLT and MTD. The secondary objectives were to (1) evaluate the pharmacokinetics and preliminary efficacy of YM155 in combination with erlotinib and (2) explore biomarkers including survivin expression by immunohistochemistry (IHC) in biopsied tumors if available and serum proteins using the luminex analysis pre- and post-YM155 administration. YM155 at escalating doses (3.6, 4.8, 6.0, and 8.0 mg/m^2/day) was administered by continuous intravenous infusion over 168 h in combination with erlotinib at a fixed dose of 150 mg QD in 21-day treatment cycles until disease progression or intolerable toxicity occurrence. YM155 was administered through an implantable central venous catheter for 168 h via portable syringe pump. Dose escalation was conducted using the 3 + 3 design and the initial 21 days (cycle 1) were regarded as the DLT evaluation period, and three or six patients were enrolled for each dose cohort (total of four cohorts). In the DLT assessment, if none of the three patients or none/one of the six patients had a DLT at a certain dose, that dose was considered to be tolerable. Adverse events were evaluated using the NCI Common Terminology Criteria for AEs (CTCAE), ver. 4.0. A DLT was defined as any of the following adverse events occurring during cycle 1 (the initial 21 days) related to either YM155 or erlotinib: (1) hematological toxicity of ≥ G4 (excluding G4 neutropenia within 5 days); (2) grade 3 or higher anorexia, nausea, vomiting, and diarrhea despite maximal supportive therapy; (3) grade 3 or higher toxicity, with the exception of (1)–(2) as well as transient electrolyte abnormality, and transient laboratory abnormality not requiring treatment and without clinical symptoms; (4) serum creatinine level of ≥ 2.0 mg/d; and (5) toxicity that resulted in the failure to meet the criteria for proceeding to the next cycle, due to unresolved AEs. Efficacy assessment was conducted according to the Response Evaluation Criteria in Solid Tumors (RECIST ver. 1.1), and CT scans were obtained at the baseline, every 6 weeks thereafter, and during cycle 1 on day 21.

Pharmacokinetics

Pharmacokinetic parameters of YM155 were evaluated during cycles 1 and 2. Pharmacokinetic samples were collected immediately before the start of infusion (time 0); at 0.25, 0.5, 1, 2, 3, 4, 6, 12, 24, 48, 72, 96, 120, and 144 h after the start of infusion; at the end of infusion (168 h); and at the following timing: 15 min, 30 min, and 1, 2, 3, 4, 6, 12, 24, and 48 h after the end of infusion. The concentration of YM155 was measured by using liquid chromatography–tandem mass spectrometry procedures according to good laboratory practice (PPD, Richmond, VA, USA). Pharmacokinetic parameters after the first dose were calculated using the non-compartmental analysis with WinNonlin (ver.6.2; Certara G.K., Japan). Pharmacokinetic statistical analyses were performed using SAS System Release 9.2 (SAS Institute Japan Ltd., Tokyo, Japan). The primary pharmacokinetic parameters were area under the concentration–time curve extrapolated to infinity ($AUC_{0-\infty}$), steady-state concentrations (C_{ss}), terminal half-life ($T_{1/2}$), volume of distribution at steady state (V_{ss}), and clearance (CL).

Pharmacodynamics and biomarkers

Serum cytokines were evaluated using the Luminex analysis of serum proteins (Bio-Plex Pro Human Cytokine Panel and Bio-Plex Pro Human Cancer Biomarker Panel; Bio-Rad Laboratories, Inc. Hercules, CA, USA) pre- and post-administration of YM155 in all patients. Blood sample for serum biomarker analysis was collected on days 1 (before administration of YM155), 2, 3, and 4 of cycle 1 and, days 1, 2, and 3 of cycle 2. Changes in serum protein levels including serum cytokines (PDGF-bb, IL-1b, IL-1ra, IL-2, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-10, IL-12(p70), IL-13, IL-15, IL-17, eotaxin, G-CSF, GM-CSF, IFN-g, IP-10, MCP-1(MCAF), MIP-1a, MIP-1b, RANTES, TNF-a, sEGFR, FGF-basic, follistatin, G-CSF, HGF, sHER2/neu, Hu sIL-6Ra, leptin, osteopontin, PECAM-1, PDGF-AB/BB, prolactin, SCF, sTIE-2, sVEGFR-1, sVEGFR-2, angiopoietin-2, and VEGF-A) were evaluated. Changes in survivin expression were detected by immunohistochemistry (IHC) in biopsied tumor samples pre- and post-YM155 administration, if available. The changes in serum cytokine levels before the administration of YM155 were analyzed for their correlation with the best clinical response between the patient groups who showed stable disease (SD) and disease progression (PD).

Results

Patient characteristics

A total of 15 EGFR TKI refractory advanced NSCLC patients received YM155 in combination with erlotinib between January 2013 and July 2015. Three patients were treated with 3.6 mg/m^2/days, six patients with 4.8 mg/m^2/days, three patients with 6.0 mg/m^2/days, and three patients with 8.0 mg/m^2/days YM155. The baseline patient characteristics are summarized in Table 1. The age range was 52.0–84.0 years (median: 65.0 years); the EGFR mutation status of all patients was known (exon 19 del, 6; exon 21 L858R, $n = 8$; exon 18 G719S, $n = 1$, and three patients secondarily developed the exon 20 T790M mutation). The median number of prior systemic chemotherapy regimens was 6 (range, 2 – 10), and the distribution of prior EGFR-TKI regimens is presented in Table 1. On the final cutoff date, all 15 patients discontinued treatment: 1 due to an AE (grade 2 diarrhea that was considered to be related to erlotinib) and 14 due to disease progression.

Table 1 Baseline characteristics of patients

Characteristics	Value
Number of patients	15
Age, year	
Median	65.0
Range	52.0–84.0
Sex	
Male	4
Female	11
ECOG Performance status	
0	3
1	10
2	2
Type of EGFR mutation status	
Exon 19 del	6
Exon 21 L858R	8
Exon 18 G719S	1
Exon 20 T790M	3
Number of prior systemic therapies	
Median	6
Range	2–10
Type of prior EGFR-TKIs	
Gefitinib	9
Erlotinib	9
Afatinib	1
Third-generation EGFR-TKIs (investigational drug setting)	2

ECOG Eastern Cooperative Oncology Group

Safety and tolerability

No DLTs were observed in the initial three patients treated with 3.6 mg/m^2/days YM155. At the 4.8 mg/m^2/days dose, one patient developed dose-limiting grade 2 serum creatinine level increase, accompanied by grade 3 diarrhea, requiring the discontinuation of investigational drug administration. These adverse events were manageable and reversible, although the patient required temporary fluid infusion support. Given the occurrence of this toxicity, three additional patients were entered at this dose (4.8 mg/m^2/days) without further DLT. At both 6.0 and 8.0 mg/m^2/days doses, no additional DLTs were observed, and 8.0 mg/m^2/days YM155 in combination with 150 mg QD erlotinib was determined as the maximum administered dose. All treatment-emergent adverse events that occurred in ≥ 20% of subjects are summarized in Table 2. All patients ($n = 15$) experienced drug-related AEs (mostly grade 1 or 2). The most common AEs related to YM155 in combination with erlotinib treatment were rash, diarrhea, pyrexia, stomatitis, fatigue, elevated serum β-NAG level, anemia, dysgeusia, dry skin, and elevated serum creatinine levels (≥ 20% subjects for each AE). Among these AEs, rash, diarrhea, stomatitis, and dry skin were considered to be related to erlotinib, as common effects of EGFR inhibition. The most common AE considered to be related to YM155 was the asymptomatic and transient presence of urine microalbumin. No drug-related AE greater than grade 4 was observed.

Pharmacokinetics

The pharmacokinetic profiles of all 15 patients were available. The mean plasma concentration of YM155 administered in combination with erlotinib for each dose versus time is shown in Fig. 1 and the descriptive statistics of the pharmacokinetic parameters are summarized in Table 3. The plasma concentrations of YM155 almost reached the steady state approximately 24 h after the infusion start, with the area under the plasma concentration–time curve being increased with the dose. The mean apparent elimination $t_{1/2}$ and total body CL of YM155 tended to be almost constant across the tested dose range. At the dose of 8.0 mg/m^2/days, the geometric mean $t_{1/2}$ and CL were 16.29 h and 36.77 L/h, respectively.

Pharmacodynamics and biomarkers

The IHC analysis of serial tumor biopsied from three patients pre- and post-YM155 administration was conducted. A decrease in survivin expression was observed post-treatment in one case (Fig. 2); however, despite the clinical efficacy, the patient was diagnosed with PD. Furthermore, increased or unchanged expression of survivin was observed in two

Table 2 All Treatment-emergent adverse events ≥ 20% subjects

	YM155 dose level									
	3.6 mg/m²/days		4.8 mg/m²/days		6.0 mg/m²/days		8.0 mg/m²/days		Total	
System organ class	(*n* = 3)		(*n* = 6)		(*n* = 3)		(*n* = 3)		(*n* = 15)	
Preferred term	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)	*n*	(%)
TEAE	3	(100.0)	6	(100.0)	3	(100.0)	3	(100.0)	15	(100.0)
Rash	3	(100.0)	3	(50.0)	1	(33.3)	3	(100.0)	10	(66.7)
Diarrhea	1	(33.3)	3	(50.0)	1	(33.3)	2	(66.7)	7	(46.7)
Pyrexia	0	(0.0)	2	(33.3)	2	(66.7)	3	(100.0)	7	(46.7)
Stomatitis	0	(0.0)	1	(16.7)	2	(66.7)	2	(66.7)	5	(33.3)
Fatigue	1	(33.3)	1	(16.7)	2	(66.7)	1	(33.3)	5	(33.3)
b-NAG elevation	1	(33.3)	1	(16.7)	1	(33.3)	2	(66.7)	5	(33.3)
Anemia	0	(0.0)	1	(16.7)	2	(66.7)	1	(33.3)	4	(26.7)
Dysgeusia	1	(33.3)	1	(16.7)	0	(0.0)	2	(66.7)	4	(26.7)
Dry skin	0	(0.0)	2	(33.3)	0	(0.0)	1	(33.3)	3	(20.0)
Blood creatinine elevation	0	(0.0)	0	(0.0)	1	(33.3)	2	(66.7)	3	(20.0)

TEAE treatment-emergent adverse event

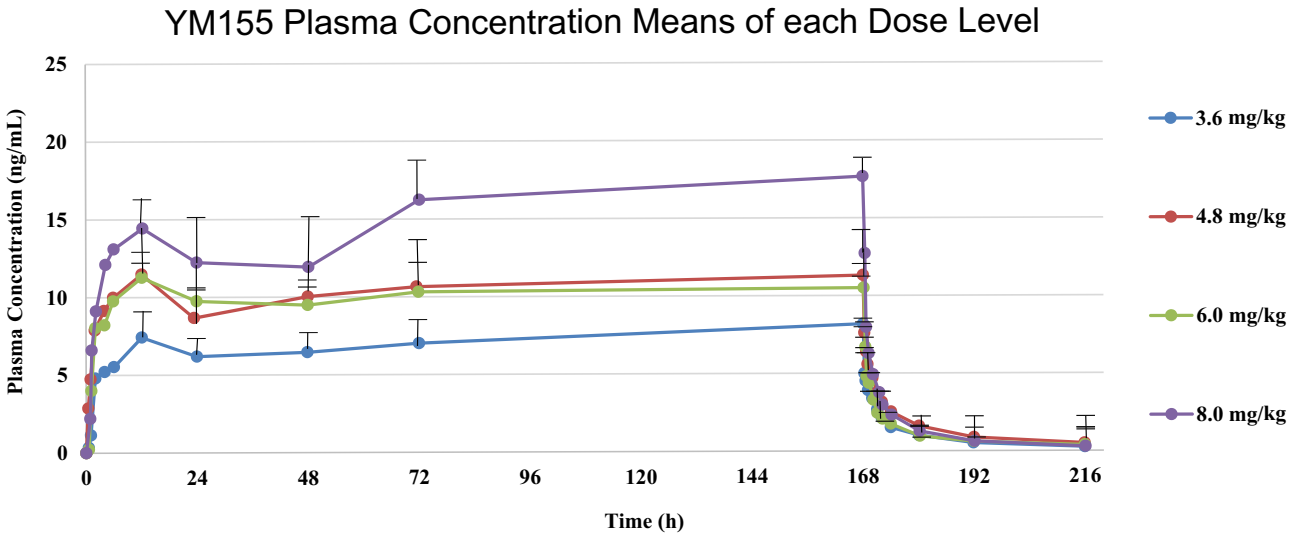

Fig. 1 Mean plasma concentration of YM155 administered in combination with erlotinib for each dose versus time

Table 3 Summary of pharmacokinetic parameters of YM155 administered in combination with erlotinib

Dose of YM155	C_{max}, μg/mL, Mean SD	T_{max}, h, Mean SD	AUC_{0-4}, μg·h/mL, Mean SD	$AUC_{0-\infty}$, μg·h/mL, Mean SD	$t_{1/2}$, h, Mean SD	*V*dss, L, Mean SD	CL, L/h, Mean SD
3.6 mg/m²/days (*n* = 3)	8.18 (0.95)	168.07 (0.12)	1229.30 (176.66)	1236.31 (172.17)	18.17 (6.79)	346.79 (163.67)	31.42 (2.23)
4.8 mg/m²/days (*n* = 6)	11.95 (1.90)	45.98 (61.45)	1821.55 (284.59)	1832.89 (288.56)	17.18 (5.60)	259.62 (159.67)	34.03 (6.67)
6.0 mg/m²/days (*n* = 3)	11.85 (4.29)	52.02 (34.36)	1739.35 (554.87)	1750.96 (567.91)	16.52 (8.76)	186.38 (60.81)	44.49(19.15)
8.0 mg/m²/days (*n* = 3)	18.10 (2.08)	136.03 (55.68)	2615.36 (341.48)	2622.41 (338.99)	16.29 (5.38)	389.24 (171.52)	36.77 (6.03)

C_{max} maximum observed serum concentration, T_{max} time of maximum observed serum concentration, AUC_{0-4} area under the concentration–time curve from day 0 to day 4, $AUC_{0-\infty}$ area under the concentration–time curve from day 0 to infinity, $t_{1/2,}$ elimination half-life, V_{dss} volume of distribution at steady state, *CL* clearance

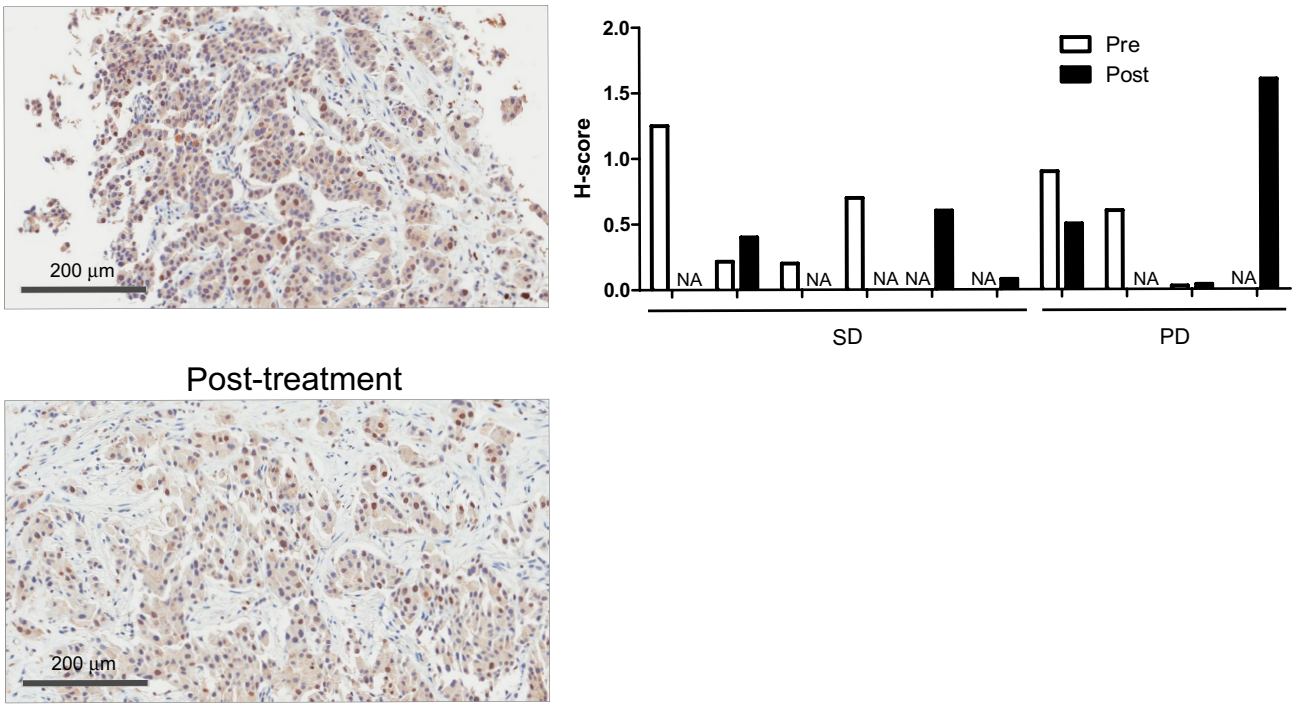

Fig. 2 Changes in survivin expression in serial biopsied tumor pre- and post-YM155 administration evaluated by immunohistochemistry (IHC). Survivin expression decreased in only one patient who experienced disease progression

other patients from whom paired biopsies were obtained. The increased expression of IFN-γ, G-CSF, IL-6, soluble EGFR, and soluble HER2 was observed after the administration of YM155 in the patient groups that showed SD (Fig. 3). The serum cytokine analysis before the administration of YM155 showed a decreasing tendency of IL-8, G-CSF, and MIP-1b in patients who achieved progression-free survival at ≥ 12 weeks (Fig. 3).

Clinical efficacy

Fourteen out of the 15 patients were eligible for overall response assessment using RECIST version 1.1. The best overall response was SD, which was observed in 11 (78.6%) patients. Durable SD for ≥ 24 weeks was observed in two patients (283 days in the YM155 3.6 mg/m^2/days cohort and 264 days in the YM155 6.0 mg/m^2/days cohort). One patient (a 57-year-old female) in the YM155 6.0 mg/m^2/days cohort with EGFR-mutant (exon 19 del) NSCLC refractory to previous sequential administration of gefitinib and an investigational agent of the third-generation T790M-mutant selective EGFR TKI had durable SD lasting ≥ 37 weeks with tumor shrinkage tendency (14% decrease in tumor size at the target lesion). Another patient (a 72-year-old female) in the YM155 3.6 mg/m^2/days cohort with EGFR-mutant (exon 19 del) NSCLC refractory to erlotinib and multiple lines of chemotherapies also showed durable SD lasting ≥ 40 weeks with tumor shrinkage tendency (7% decrease in tumor size at the target lesion). Despite exon 20 T790M mutation was detected by re-biopsy after EGFR TKI failure in this patient, osimertinib was not approved during the time the patient was enrolled.

Discussion

To our knowledge, this phase I study was the first investigational study that combined a potent, selective small-molecule inhibitor of survivin, YM155 (administered for 168 h) with the EGFR TKI erlotinib as a treatment strategy to overcome EGFR TKI resistance by targeting survivin, together with potential preclinical antitumor activity, except for the T790M-mutant selective targeting approach. The clinical efficacy of YM155 was moderate; the best observed response was SD in all cohorts, although two heavily dosed patients achieved durable SD for ≥ 24 weeks.

Moreover, the combination of YM155 and erlotinib was well tolerated, and YM155 up to 8.0 mg/m^2/days ay administered in combination with the standard dose of erlotinib every 3 weeks had a favorable safety profile. At the 4.8 mg/m^2/days dose, one patient developed renal toxicity that was considered to be a DLT (grade 2 serum creatinine

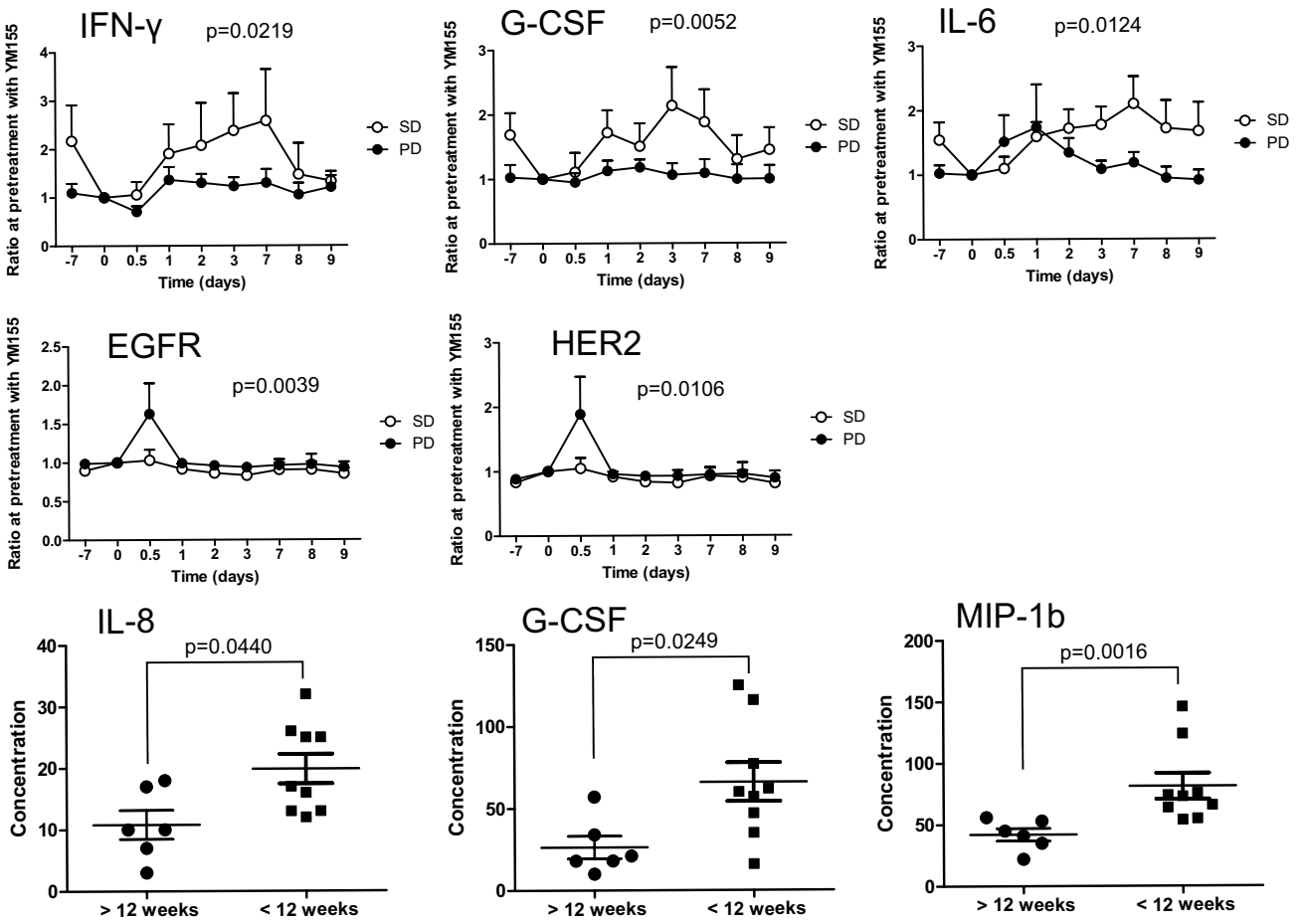

Fig. 3 Changes in serum cytokine expression levels before treatment with YM155, before the administration of erlotinib, before the administration of YM155 (day 0), 12 h after YM155 administration, and on days 1, 2, 3, 7, 8, and 9, were compared for their association with the clinical response between the stable disease (SD) and progressive disease (PD) groups. Association between serum cytokine expression levels and response. The expression levels of IL-8, G-CSF, and MIP-1b (CCL4) before the administration of YM155 in the stable disease (SD) and progressive disease (PD) groups are shown. The AUC was calculated from incremental area on day 0 (before treatment of YM155). An unpaired t test was used to compare the AUC between the SD and PD group. The Mann–Whitney *U* test was used to compare serum protein levels between the SD and PD groups

level elevation). However, this transient AE was completely resolved to the baseline after the termination of YM155 and administration of temporary fluid infusion support. Renal toxicity related to YM155 was manageable by close monitoring of renal parameters including urine microalbumin, urinary protein, and blood creatinine. In a preclinical toxicology study, short-term exposure of YM155 at high blood concentrations caused nephrotoxicity, mainly related to renal proximal tubular necrosis. In contrast, long-term exposure of YM155 at low blood concentrations by 168-h continuous infusion did not cause cardiotoxicity or nephrotoxicity [25]. Based on the safety evaluation and the time-dependent efficacy in preclinical studies, 168 h of continuous intravenous infusion every 3 weeks was selected for clinical trials despite its practical challenges. In this study, 5 out of 15 (33.3%) patients developed elevated serum beta-NAG levels, which were considered to be YM155-related and linked to the cellular injury in the renal proximal tubules. The pharmacokinetic analysis revealed that plasma exposure to YM155 showed dose proportionality across all dose ranges tested. The Css of YM155 when administered in combination with erlotinib was similar to that reported previously [25, 26]. To assess survivin expression by IHC analysis, only three patients were subjected to complete paired biopsies for IHC analysis; thus, the sample size was too small for drawing of any firm conclusions.

A preclinical study showed that the suppression of survivin expression is associated with a potential decrease in angiogenesis. Hence, VEGF and IL8 levels were measured in this study. The changes in several serum cytokines, including IL8 and VEGF, between the baseline and cycle 2 were compared for their association with the clinical

response between two patient populations, depending on the achievement of at least SD, but there was no correlation among any of these potential biomarkers, or the changes in their levels and clinical efficacy outcome. The serum cytokine analysis showed a decreasing tendency of IL-8, G-CSF, and MIP-1b (CCL4) in patients who showed progression-free survival at ≥ 12 weeks. This result was consistent with previous reports that several cytokines and chemokines levels correlate with the tumor burden in preclinical models and the prognostic significance in patients with advanced cancer, including NSCLC [36–38]. The limitations of our study were the relatively small-sample size used in a phase 1 study along with the lack of monitoring the serum level of the caspase-3 cleavage product of cytokeratin 18 and the survivin mRNA expression level in peripheral blood mononuclear cells. In terms of other limitations, the exon 20 T790M mutation status from the time of progression to the first- or second-generation EGFR TKI was not available for all 15 patients enrolled in this phase I study. However, one patient in the YM155 6.0 mg/m^2/days cohort with EGFR-mutant (exon 19 del) NSCLC who was refractory to previous sequential therapy of gefitinib and an investigational agent of the third-generation T790M-mutant selective EGFR TKI showed durable SD lasting ≥ 37 weeks with tumor shrinkage tendency. Our results suggest that inhibiting survivin expression via the EGFR pathway is a potential therapeutic option in selected patients with previous EGFR TKI refractory NSCLC.

In summary, YM155, in combination with EGFR TKI erlotinib, was well tolerated and showed moderate clinical activity. Establishing ideal predictive biomarkers for clinical efficacy of novel apoptosis-inducing agents and apoptotic pathway-targeted therapies, including survivin inhibition for the treatment of advanced cancers, remains a significant challenge. Overcoming EGFR TKI resistance by utilizing new investigational drug combinations targeting IAP within cancer apoptotic pathways in cancer patients may be a potential therapeutic strategy. Further investigations to clarify the complex signaling interactions are required to overcome EGFR TKI resistance by targeting a programmed cell death pathway.

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Compliance with ethical standards

Conflict of interest Toshio Shimizu reports research grants from Novartis, Eli Lilly, Daiichi-Sankyo, Bristol-Myers Squibb, Eisai, AbbVie, AstraZeneca, Takeda Oncology, Incyte, Chordia Therapeutics, 3D-Medicine, Symbio Pharmaceuticals, PharmaMar, Five Prime, and Astellas Pharma outside the submitted work; and reports advisor role at Takeda Pharmaceutical Co., Ltd. Kazuhiko Nakagawa reports research grants from MSD KK, AstraZeneca, ICON Japan, Astellas, Takeda, Novartis, Eli Lilly, Quintiles Inc., Bristol Myers Squibb, CMIC Shift Zero K.K., Taiho Pharmaceutical, Eisai, Parexel International Corp., Nippon Boehringer Ingelheim, Ono Pharmaceutical, Kissei Pharmaceutical, IQVIA, Pfizer, A2 Healthcare Corp, Kyowa Hakko Kirin, EPS Corporation, Abbvie, Chugai Pharmaceutical, Daiichi-Sankyo, SymBio Pharmaceuticals, Bayer, and Merck Serono outside the submitted work; and reports consulting or advisor role at Astellas Pharma Inc. and Takeda Pharmaceutical Co., Ltd. Isamu Okamoto reports grants from Boehringer Ingelheim, during the study; grants and personal fees from AstraZeneca, Taiho Pharmaceutical, Boehringer Ingelheim, Ono Pharmaceutical, MSD Oncology, Lilly, Bristol-Myers Squibb, and Chugai Pharma; grants from Astellas Pharma, Novartis, and AbbVie; personal fees from Pfizer, outside the submitted work. Masayuki Takeda received honoraria from Novartis Pharma, Chugai Pharma, ONO Pharmaceutical, and Boehringer Ingelheim. Maiko Morishita is an employee of Astellas Pharma. The remaining authors have no potential conflicts of interest to report.

Ethics approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Consent to participate Informed consent was obtained from all individual participants included in the study.

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