

## Phase I Study of YM155, a Novel Survivin Suppressant, in Patients with Advanced Solid Tumors

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**Abstract Purpose:** YM155, a novel molecular targeted agent, suppresses survivin, a member of the inhibitor of apoptosis protein family that is overexpressed in many tumor types. The aim of this study was to determine the maximum tolerated dose (MTD) and to assess the safety, pharmacokinetics, and antitumor activity of YM155 in patients with advanced refractory solid tumors.

**Experimental Design:** Patients with advanced refractory solid tumors were treated with escalating doses of YM155 administered by continuous i.v. infusion for 168 hours in 21-day cycles.

**Results:** Of the 34 patients enrolled, 33 (median age, 59 years) received at least 1 dose of YM155 (range, 1-19 cycles). The dose levels studied were 1.8, 3.6, 4.8, 6.0, 8.0, and 10.6 mg/m<sup>2</sup>/d. The MTD was determined to be 8.0 mg/m<sup>2</sup>/d, based on a dose-limiting toxicity of increased blood creatinine observed in 2 patients receiving 10.6 mg/m<sup>2</sup>/d. The most common adverse reactions judged to be related to YM155 were urine microalbumin present; fever; injection-site phlebitis; fatigue; and decreased hemoglobin/anemia, blood albumin, and lymphocyte count. The pharmacokinetic profile was almost linear over the dosing range and was similar between cycles 1 and 2. Urinary excretion of YM155 showed no definite difference among doses. Stable disease was achieved in nine patients.

**Conclusions:** YM155 was safely administered to patients with advanced refractory solid tumors by 168-hour continuous i.v. infusion in 21-day cycles. The MTD was determined to be 8.0 mg/m<sup>2</sup>/d. The safety profile, plasma concentrations achieved, and antitumor activity observed merit further studies with this survivin suppressant, alone and in combination regimens.

Survivin, a member of the inhibitor of apoptosis family of proteins, is expressed during embryonic and fetal development, but is undetectable in normal adult human tissues, apart from thymus, placenta, CD34<sup>+</sup> cells, and some cells within the basal crypt layer of the gastrointestinal tract (1-5). *In vitro* studies suggest that survivin inhibits cell death induced via the extrinsic

and intrinsic apoptotic pathways. In addition, survivin may also confer resistance to apoptosis by directly suppressing caspase activity (3). Overexpression of survivin has been shown in a variety of human cancers and is reportedly associated with a poor prognosis (6-13). It has been shown that the suppression of survivin induces tumor cell apoptosis and also enhances the sensitivity to apoptosis induced by existing anticancer drugs and other apoptotic stimuli (4, 14-16).

YM155 is a novel survivin suppressant that is currently in clinical development by Astellas Pharma, Inc. A preclinical study showed that YM155 suppressed both survivin protein and mRNA expression (17). In addition, sensitivity to YM155 was high in various human tumor cell lines such as hormone-refractory prostate cancer (17) and malignant lymphoma.<sup>8</sup> Furthermore, YM155 exerted greater antitumor activity compared with existing anticancer drugs, and YM155 concentrations were higher in tumor tissue than in plasma. In a toxicologic study, short-term exposure at high blood concentrations caused cardiotoxicity in the form of atrioventricular

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## Translational Relevance

Survivin is a member of the inhibitor of apoptosis protein family that is overexpressed in many tumor types, and as such represents an excellent target for anticancer drug development. YM155 is a small molecule that suppresses survivin and has shown anticancer activity in a range of tumor cell lines *in vitro* and human tumor xenografts models *in vivo*. In this phase I study, YM155 was administered to 33 patients with advanced refractory solid tumors. YM155 seemed to be safe and well-tolerated, with a maximum tolerated dose of 8.0 mg/m<sup>2</sup>/d. Stable disease was achieved in nine patients. The position of survivin as an anticancer drug target, together with the safety profile and antitumor activity in heavily pretreated patients with advanced refractory tumors shown in this phase I study, strongly supports the further evaluation of YM155, both as monotherapy and within combination regimens.

block and myocardial degeneration/necrosis, as well as nephrotoxicity, mainly displayed as proximal tubular necrosis and increased serum creatinine. In contrast, long-term exposure at low blood concentrations by 168-hour continuous infusion did not cause cardiotoxicity.<sup>9</sup>

Based on the differential expression of survivin in human malignancies and the negative prognostic role, together with preclinical antitumor activity and encouraging safety data, a phase I study of YM155 in patients with advanced solid tumors was conducted in Japan. The aim of this study was to determine the recommended dose and pharmacokinetic profile of YM155 and to evaluate its safety profile and antitumor effects.

## Patients and Methods

**Study design.** This was an open-label, single-center, nonrandomized, phase I dose-escalation study. The primary objective was to assess the safety of YM155 administered to patients with advanced solid tumors. The secondary objectives included the investigation of the pharmacokinetic profile and tumor activity of YM155. After one cycle, patients could continue further treatment until either an unacceptable toxicity was experienced or disease progression occurred.

**Inclusion and exclusion criteria.** Eligibility criteria for patients enrolled in this study included refractory advanced solid tumors for which no standard therapy existed; histologic or cytologic diagnosis of cancer; at least 20 y of age; life expectancy of at least 12 wk; Eastern Cooperative Oncology Group performance status of <3; and adequate hematopoietic, hepatic, and renal functions (absolute neutrophil count of  $\geq 1.5 \times 10^9/L$ , platelets of  $\geq 100 \times 10^9/L$ , hemoglobin of  $\geq 9$  g/dL, bilirubin within 1.5 $\times$  upper limit of normal, transaminases of  $\leq 2.5\times$  upper limit of normal, and creatinine of  $<1.5 \times$  upper limit of normal). Patients must have discontinued all cancer therapies for at least 4 wk before study entry. Exclusion criteria included primary brain tumor or known central nervous system metastases, and uncontrolled clinically significant disease unrelated to the primary malignancy.

The study was approved by the ethics board of the participating center, and all patients gave written informed consent. The study

was conducted in accordance with the Declaration of Helsinki and the applicable guidelines on good clinical practice.

**Dosage and drug administration.** YM155 was prepared for administration by dilution of an appropriate volume of concentrated stock solution in 5% dextrose in a light- and temperature-controlled environment. The diluted drug was administered via continuous i.v. infusion over 168 h, followed by 14-d observation (1 cycle). This method of administration was selected because toxicity studies using 168-h continuous infusion in dogs showed no cardiotoxicity and time-dependent antitumor activity.<sup>10</sup> A starting dose of 1.8 mg/m<sup>2</sup>/d was chosen on the basis of toxicologic studies in rodents and the data from a U.S. phase I study (18). To avoid renal toxicity with YM155, patients were instructed to take sufficient quantities of water during administration of the drug.

**Toxicity (tolerability and safety evaluation).** The following safety assessments were done for each patient: subjective/objective symptoms, vital signs, laboratory tests, and 12-lead electrocardiogram. Adverse events were graded according to the Common Terminology Criteria for Adverse Events v3.0. Creatinine clearance was determined by the evaluation of fluctuations in urine creatinine and serum creatinine concentrations. A dose-limiting toxicity (DLT) was defined as an adverse drug reaction including nonhematologic toxicities  $\geq$  grade 3, except transient hyperglycemia and anorexia, and serum creatinine increased to  $\geq 2.0$  mg/dL; grade 4 hematologic toxicities, except a decreased neutrophil count of grade 4 ( $<500/\mu L$ ) persisting for 5 d or less; nausea, vomiting, or diarrhea  $\geq$  grade 3 occurring despite prophylaxis after the first episode; and failure to satisfy the criteria for the next cycle within the specified period due to unresolved adverse drug reactions. The maximum tolerated dose (MTD) was defined as the dose that was one level lower than that at which DLT occurred in more than two of six patients.

**Pharmacokinetics.** The pharmacokinetic parameters of YM155 were evaluated during cycles 1 and 2. Venous blood samples, from a site other than the infusion site, were collected in tubes containing heparin sodium immediately before the start of the 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 times thereafter: 168.25, 168.5, 169, 170, 171, 172, 174, 180, 192, and 216 h. Samples were centrifuged immediately, and the resulting plasma was stored at  $-20^\circ C$  before analysis. Urine samples were collected over 216 h after the start of continuous infusion to determine the urinary concentration of YM155 and were stored at  $-20^\circ C$  before analysis.

Concentrations of YM155 were measured by Astellas Europe B.V. EDD using validated liquid chromatography tandem mass spectrometry procedures (18) and following Good Laboratory Practice.

The lower limits of quantitation for YM155 were 0.05 ng/mL in plasma and 1.0 ng/mL in urine. The concentrations are expressed as those of the cationic moiety of YM155.

Pharmacokinetic analysis was done in a model-independent manner using actual values of plasma concentration and actual time from the start of continuous infusion. Values below the lower limits of quantitation were treated as zero.

**Efficacy (tumor assessment).** Evaluations of lesions were done with computed tomography, magnetic resonance imaging, and bone scintigraphy, with tumor markers also evaluated. Assessment of antitumor activity was done in accordance with the Response Evaluation Criteria in Solid Tumors guidelines (19).

## Results

**Patients.** A total of 34 patients were enrolled into 6 dosing cohorts between August 2004 and October 2006; 33 patients received at least 1 cycle of YM155. The demographic and baseline

<sup>9</sup> Unpublished data.

<sup>10</sup> Unpublished data.

**Table 1.** Patient demographics and disease characteristics

Characteristic	No. of patients
Total patients	33
Male/female	23/10
Age, y	
Median (range)	59 (26-81)
<65	25
≥65	8
ECOG performance status	
0	3
1	29
2	1
Tumor type	
NSCLC	7
Esophageal	6
Colorectal	4
Thymic	3
Thyroid	2
MFH	2
Pleural mesothelioma	2
Others*	7 (1 each)
Prior therapy	
Chemotherapy	32 (97.0%)
No. of prior regimens	
1	7
2	10
3	4
≥4	11
Radiation therapy	17 (51.5%)
Cancer-related surgery	19 (57.6%)

Abbreviations: ECOG, Eastern Cooperative Oncology Group; NSCLC, non-small cell lung cancer; MFH, malignant fibrous histiocytoma. \*Others: thymoma, synovial sarcoma, duodenal, double cancer of hypopharynx and thoracic esophageal cancer, paranasal sinus, pancreatic, and esophageal leiomyosarcoma.

patient characteristics are listed in Table 1. The most common malignancies in the 33 patients treated were non-small cell lung cancer (7 patients; 21.2%), esophageal cancer (6 patients; 18.2%), colorectal cancer (4 patients; 12.1%), and thymic can-

cer (3 patients; 9.1%). Thirty-two (97%) of the patients had at least 1 prior chemotherapy. Dose levels studied were 1.8, 3.6, 4.8, 6.0, 8.0, and 10.6 mg/m<sup>2</sup>/d, and patients received 1 to 19 cycles of YM155.

**DLT.** The highest dose of YM155 administered was 10.6 mg/m<sup>2</sup>/d, at which level 2 of 5 treated patients experienced a DLT of increased serum creatinine (accompanied by decreased lymphocyte count in 1 patient). Three of 5 patients in the 10.6 mg/m<sup>2</sup>/d group had their dose reduced to 8.0 mg/m<sup>2</sup>/d from cycle 2 onwards. At the 8.0 mg/m<sup>2</sup>/d dose level, serum creatinine levels remained almost unchanged throughout the study. The MTD was therefore determined to be 8.0 mg/m<sup>2</sup>/d. Additional DLTs were observed in one patient who received YM155 at the 6.0 mg/m<sup>2</sup>/d dose level (grade 3 increased aspartate serum transferase) and in another patient whose dose was reduced to 8.0 mg/m<sup>2</sup>/d (grade 4 anemia).

**Safety.** All 33 patients treated were included in the safety population. Throughout all treatment cycles, adverse events occurred in 97.0% (32 of 33 patients) and adverse drug reactions in 87.9% (29 of 33 patients) of all patients treated with YM155.

The most common drug-related adverse events (occurring in ≥15% of patients) were urine microalbumin present (12 patients; 36.4%), injection-site phlebitis (12 patients; 36.4%), fever (11 patients; 33.3%), decreased hemoglobin/anemia (9 patients; 27.3%), decreased lymphocyte count (8 patients; 24.2%), decreased blood albumin (8 patients; 24.2%), and fatigue (7 patients; 21.2%; Table 2). In most patients with decreased hemoglobin, reductions in hemoglobin were detected immediately after study drug initiation and were rated grade 1 or 2. The events recovered or remitted without treatment. Injection-site phlebitis was frequently reported in patients receiving infusion of lower doses of YM155 via peripheral veins. Consequently, infusion via a central vein was recommended for doses higher than 4.8 mg/m<sup>2</sup>/d, which prevented the development of phlebitis.

The vast majority of drug-related adverse events (200 of 217, 92.2%) were judged to be grade 1 or 2 in severity. Grade 3 or 4 drug-related adverse events were reported in 8 patients. Grade 3 decreased lymphocyte count occurred in 6 patients, including 1

**Table 2.** Adverse events (≥15% incidence overall) related to YM155

Adverse event/YM155 dose (mg/m <sup>2</sup> /d)	No. of patients experiencing toxicity during first course (all courses)													
	1.8 (n = 3)		3.6 (n = 6)		4.8 (n = 6)		6.0 (n = 7)		8.0 (n = 6)		10.6 (n = 5)		All (n = 33)	
Grade of adverse event	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3	G1/2	G3/4	G1/2	G3/4
Urine microalbumin present	0	0	0(1)	0	1(1)	0	1(1)	0	4(4)	0	5(5)	0	11 (12)	0
Fever	0	0	1(2)	0	0	0	2(3)	0	2(2)	0	4(4)	0	9 (11)	0
Decreased hemoglobin/anemia	0	0	0(1)	0	1(1)	0	1(2)	0	1(1)	0	3(3)	1(1)*	6 (8)	1 (1)
Injection site phlebitis	2(3)	0	2(4)	0	2(2)	0	2(2)	0	0	0	0(1) <sup>†</sup>	0	8 (12) <sup>†</sup>	—
Fatigue	1(1)	0	0(1)	0	0(1)	0	1(1)	0	1(1)	0	2(2)	0	5 (7)	—
Decreased blood albumin	0	0	0	0	1(1)	0	1(1)	0	2(2)	0	4(4)	0	8 (8)	—
Decreased lymphocyte count	0	0	0	1(1)	0	1(1)	1(1)	0	0	1(1)	0	4(4) <sup>‡</sup>	1 (1)	7 (7)
Abnormal liver function test <sup>§</sup>	0(1)	0	0(1)	0	0	0	2(2)	1(1)	0	0	1(1)	0	3 (5)	1 (1)
Increased C-reactive protein	0	0	0	0	0	0	1	0	2	0	2(3) <sup>†</sup>	0	5 (6) <sup>†</sup>	—
Urine protein present	0	0	0	0	0	0	0	0	1	0	4	0	5 (5)	—

NOTE: \* and † are the same patient.

\*Grade 4.

<sup>†</sup>An event after dose reduction to 8.0 mg/m<sup>2</sup>/d in one patient.

<sup>‡</sup>Grade 4 in one patient.

<sup>§</sup>Abnormal liver function test includes increased aspartate, increased alanine serum transaminase, and increased γ-glutamyl transpeptidase.

each at YM155 doses of 3.6, 4.8, and 8.0 mg/m<sup>2</sup>/d and 3 patients at the 10.6 mg/m<sup>2</sup>/d YM155 dose level. A grade 4 decreased lymphocyte count was observed in an additional patient at the 10.6 mg/m<sup>2</sup>/d dose level. Decreases in lymphocyte count were principally noted on day 3, and typically recovered without treatment during study drug administration, and without causing infection that might lead to study discontinuation. The remaining grade 3/4 drug-related adverse events included decreased hemoglobin/anemia [grade 4 in 1 patient in the 10.6 mg/m<sup>2</sup>/d dose level (the same patient in which grade 4

lymphocyte count decreased was observed)] and abnormal liver function test (grade 3 in 1 patient in the 6.0 mg/m<sup>2</sup>/d dose level).

The trial established kidney monitoring parameters for patients treated with YM155. Changes in renal parameters that occurred in 2 patients with a DLT in the 10.6 mg/m<sup>2</sup>/d dose level in cycle 1 are shown in Fig. 1. Both patients had increased urine microalbumin at days 3 to 7, increased urinary protein at days 6 to 8, and increased serum creatinine and blood urea nitrogen at days 8 to 10 when administration

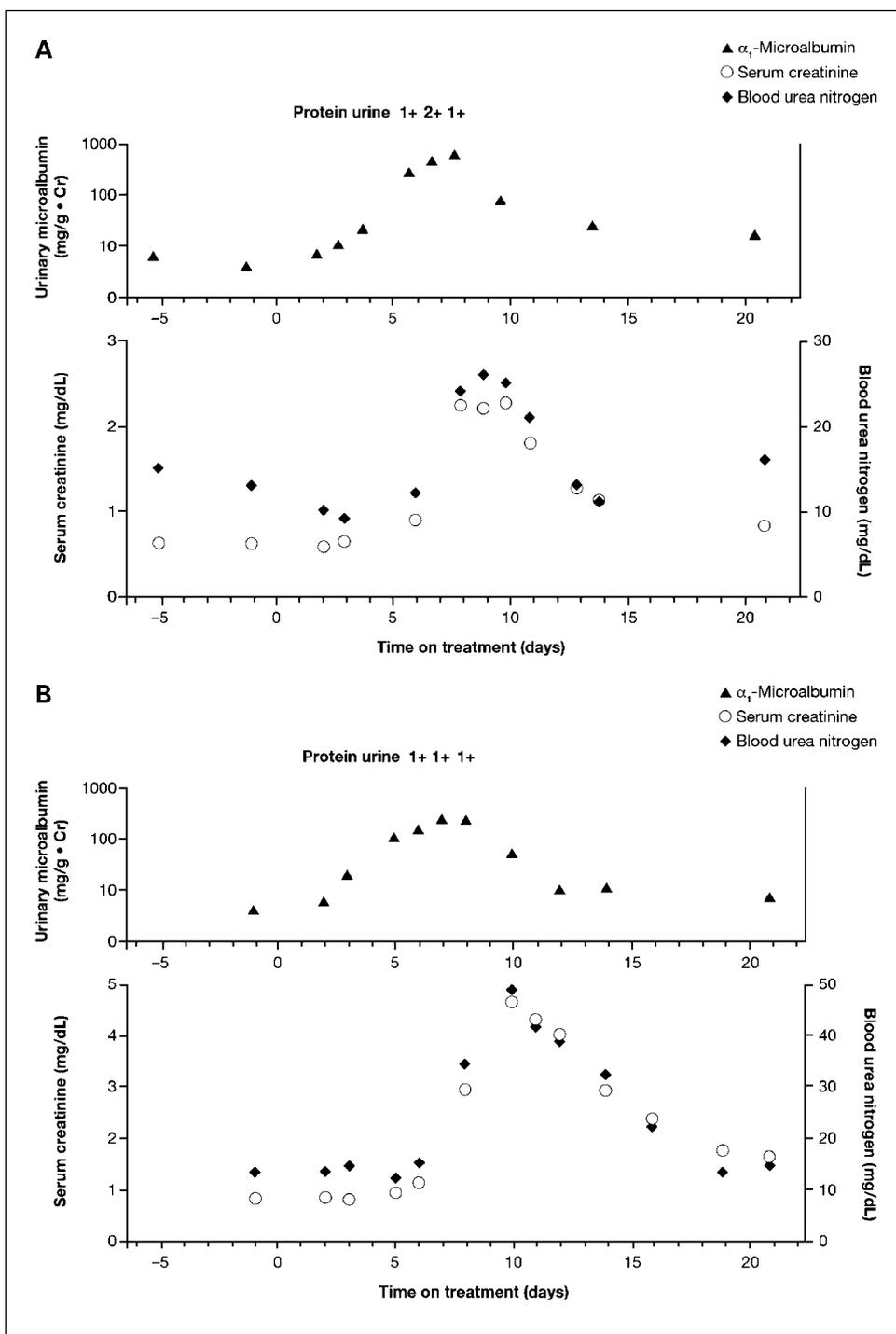
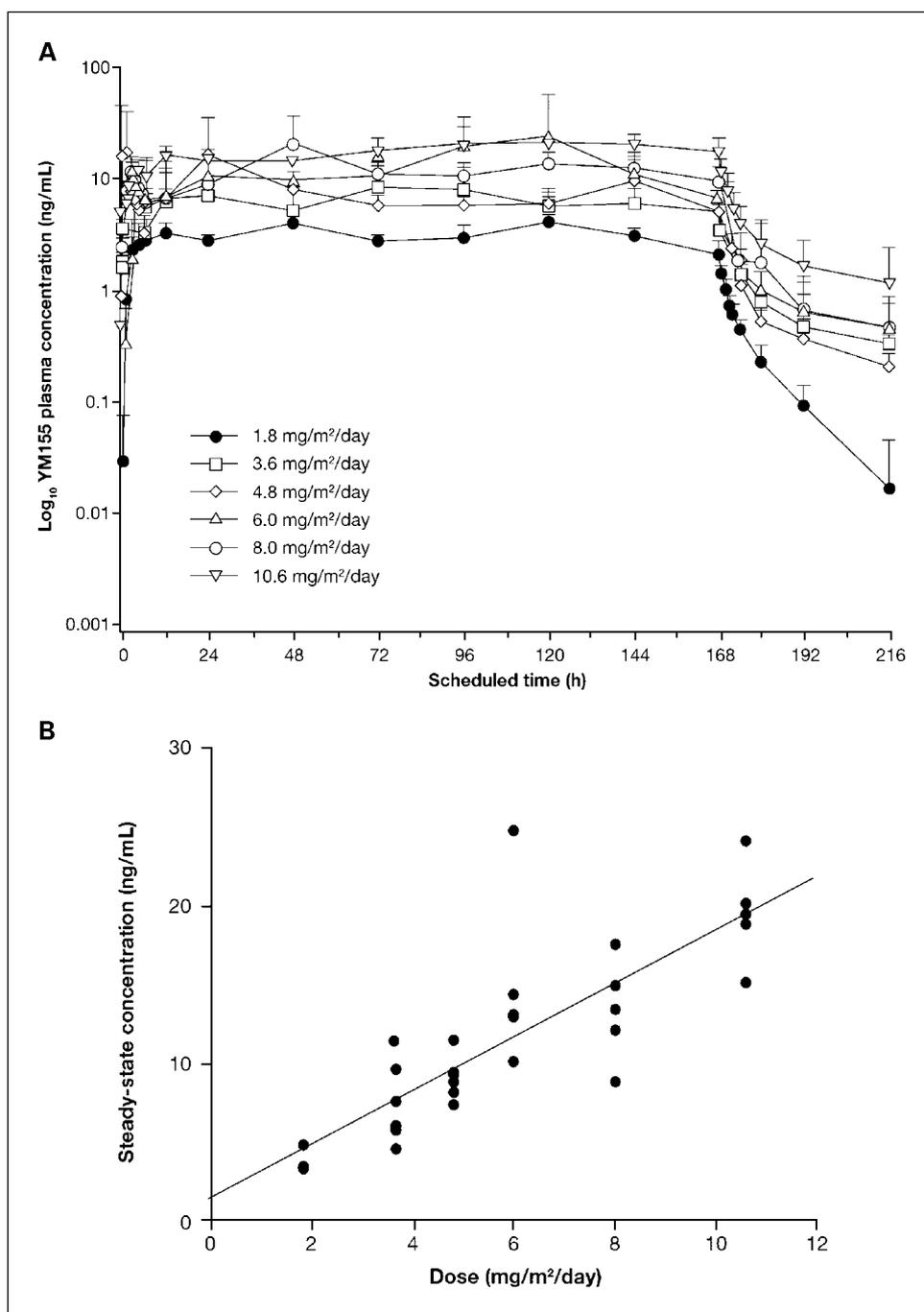


Fig. 1. Changes in renal parameters in patients in the 10.6 mg/m<sup>2</sup>/d group with thyroid cancer (A); esophageal cancer (B).

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**Fig. 2.** YM155 plasma concentration. **A**, blood plasma concentrations of YM155 overtime. -h infusion were included; points, mean; bars, SD. **B**, dose versus change in steady-state blood plasma YM155 concentration. A total of 33 patients who completed 168-h infusion during cycle 1 were included.

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had been completed. These changes were also temporally associated with decreased creatinine clearance and recovered after completion of administration. In contrast, changes in other parameters, including *N*-acetyl-D-glucosaminidase and  $\alpha_1$ -microglobulin, were not consistently associated with nephropathy and were not judged to be adverse events of clinical significance.

No other changes in safety variables, including vital signs, were considered to be clinically significant. Although atrial fibrillation on 12-lead electrocardiogram was judged to be an adverse drug reaction to YM155, this was only an asymptomatic finding of grade 1 severity and rapid recovery ensued. There were neither cumulative toxicities due to re-

peated cycles nor late-onset adverse events occurring in cycle 2 and beyond.

Fevers occurred mainly at days 2 to 4, with C-reactive protein increased. Part of them reached grade 2, but recovered during infusion of YM155 by nonsteroidal anti-inflammatory drugs.

**Patient withdrawals.** The majority of study discontinuations were due to disease progression (28 of 33 patients). In addition, 3 patients discontinued at their own request; one as a change of a therapy policy; and one as a result of an adverse event of aggravated superior vena caval syndrome, which was observed at a dose level of 4.8 mg/m<sup>2</sup>/d, but causal relationship with the study drug was ruled out. Importantly, there were no treatment-related deaths.

**Table 3.** Tumors showing stable disease after therapy

YM155 dose (mg/m <sup>2</sup> /d)	Tumor type	No. of completed cycles
1.8	MFH	4
	Thymoma	6
3.6	NSCLC	3
	Synovial sarcoma	4
4.8	NSCLC	3
	Thymic	2
6.0	Thyroid	6
	Esophageal leiomyosarcoma	3
10.6	Thyroid	19

**Pharmacokinetic analysis.** Of the 33 patients who received at least 1 cycle of YM155, 31 provided full blood samples for pharmacokinetic analysis after a single cycle. The mean plasma concentration-time profiles of YM155 by dose after 168-hour infusion are shown in Fig. 2A. Plasma concentrations almost reached steady state about 24 hours after the start of infusion, with the area under the plasma concentration-time curve (from zero to the last quantifiable concentration) increasing with dose up to 10.6 mg/m<sup>2</sup>/d. Mean plasma concentrations declined rapidly in a biphasic manner after the end of infusion. Mean values for an apparent elimination half-life ( $t_{1/2}$ ) and total body clearance of YM155 seemed to be constant across the dose range. Steady-state concentration ( $C_{ss}$ ) increased with dose up to 10.6 mg/m<sup>2</sup>/d (Fig. 2B).

The fraction of dose excreted ( $F_e$ ) in urine ranged from 25% to 42% and showed no relationship with the dose administered.

Although the dosing was based on body surface area, obvious correlation between body surface area and each pharmacokinetic parameter was unclear.<sup>11</sup>

**Efficacy.** External evaluation using computed tomography confirmed that 9 of 33 patients achieved stable disease with YM155 treatment (median duration, 81 days; range, 42-438 days; Table 3). The computed tomography images of two of the nine patients are shown in Fig. 3. One patient, a 47-year-old man with malignant fibrous histiocytoma (1.8 mg/m<sup>2</sup>/d YM155 dose level), showed a 13% reduction in tumor size after cycle 1 (Fig. 3A and B). Another patient, a 56-year-old woman, had papillary cancer of the thyroid. This patient received 10.6 mg/m<sup>2</sup>/d in cycle 1, which was reduced to 8.0 mg/m<sup>2</sup>/d in cycle 2. Computed tomography after cycle 2 showed a 14% reduction in tumor size and disappearance of pleural effusion (Fig. 3C and D). External evaluation confirmed stable disease until 62 weeks.

The degree of unconfirmed response of all patients is displayed in the waterfall plot in Fig. 3E. Response was seen in a dose-independent manner.

## Discussion

There has been much recent interest in the role of survivin as a potential molecular target in the treatment of cancer (20, 21).

This is the result of the differential expression of survivin in human malignancies compared with normal adult tissues, the role of survivin in abrogating apoptosis signaling, and a growing body of promising preclinical data. Clearly, inhibition of survivin may induce tumor regression and, importantly, may increase the effectiveness of current therapies. As a result, YM155 is currently in clinical development as the first survivin suppressant.

In the present study, YM155 was administered by 168-hour continuous infusion to patients with refractory cancer or for whom there were no standard therapies available. The primary end point was an evaluation of the safety of this novel agent. The MTD of YM155 was determined to be 8.0 mg/m<sup>2</sup>/d after the occurrence of a DLT of increased serum creatinine in 2 of 5 patients receiving 10.6 mg/m<sup>2</sup>/d. In addition, most patients receiving this dose of YM155 showed a consistent tendency in the timing of renal abnormal changes. These results were consistent with the expected nephrotoxicity of YM155 following prior preclinical and clinical studies,<sup>12</sup> and further show the renal effects of YM155. None of the events in the present study led to severe renopathy, and renal parameters recovered in all cases. Increased urine microalbumin was observed at first, followed by increased urinary protein, and resulted in increased serum creatinine and blood urea nitrogen. This is indicative of early renal impairment because it occurs at the three highest doses. It was therefore considered that, by careful monitoring of renal parameters and taking appropriate measures in the event of abnormal changes, severe renopathy can be avoided. In addition, at the MTD of 8.0 mg/m<sup>2</sup>/d, minimal changes in creatinine value were found. Increase of urine microalbumin and serum creatinine may suggest that the highest dose of YM155 influenced the glomerulus function. A nonrenal DLT of increased aspartate serum transferase was observed in 1 patient at the 6.0 mg/m<sup>2</sup>/d dose level, which was below the MTD; however, this hepatopathy recovered after withdrawal of YM155. Results from a preclinical study have confirmed that the distribution of <sup>14</sup>C-YM155 is higher in the kidney and liver compared with other organs (15 and 5.2 times higher than in plasma, respectively), suggesting that this might be responsible for the observed renopathy and hepatopathy with YM155.<sup>13</sup>

In a preclinical study, cardiotoxicities were observed at a mean plasma YM155  $C_{ss}$  of 188 ng/mL or higher. However, the mean  $C_{ss}$  in 7-day repeated infusion was 12.8 times the mean  $C_{ss}$  in 168-hour continuous infusion at the same total dose, which did not cause any cardiotoxicity.<sup>14</sup> In this study, even the highest dose of 10.6 mg/m<sup>2</sup>/d produced only a mean  $C_{ss}$  of 19.20 ng/mL, and this did not result in any serious adverse event of cardiotoxicity.

The decreases in hemoglobin/anemia that were frequently observed at the higher doses of YM155 used in this study were typified by a decrease in hemoglobin immediately after the start of study drug administration in almost all patients, given that it is generally not until about 1 to 2 weeks after the start of an anticancer drug that hemoglobin reaches a nadir due to drug-attributable bone marrow suppression. Moreover, hemolysis

<sup>12</sup> Unpublished data.

<sup>13</sup> Unpublished data.

<sup>14</sup> Unpublished data.

<sup>11</sup> Unpublished data.

was unlikely considering that the study drug has a low distribution of ~8% to 11% in blood cells. The cause of the decreases in hemoglobin/anemia therefore remains unidentified. It has been reported that survivin is involved in the regulation of the proliferation of hematopoietic progenitor cells, is essential for steady-state hematopoiesis, and that the high expression of survivin is critical for proper erythroid differentiation (22). Whereas the grade 3 to 4 lymphocytopenia experienced by 7 patients in this study may be indicative of YM155-mediated effects on erythroid and lymphoid differentiation, this must be further evaluated in ongoing and future clinical studies.

Fevers occurred mainly with increase in C-reactive protein, but without significant changes in absolute neutrophil count or leukocytes. The importance of C-reactive protein is under exploration.

In the present study, the majority of study discontinuations were due to disease progression. Indeed, only one patient discontinued because of an adverse event, and this was judged not to be related to YM155. Although the evaluations of the toxicity profile of YM155 remain in the preliminary stages, the data in this study indicate that the adverse reactions observed can be well-controlled by taking due caution and suggest that YM155 has more easily controllable toxicities compared with conventional cytotoxic anticancer drugs.

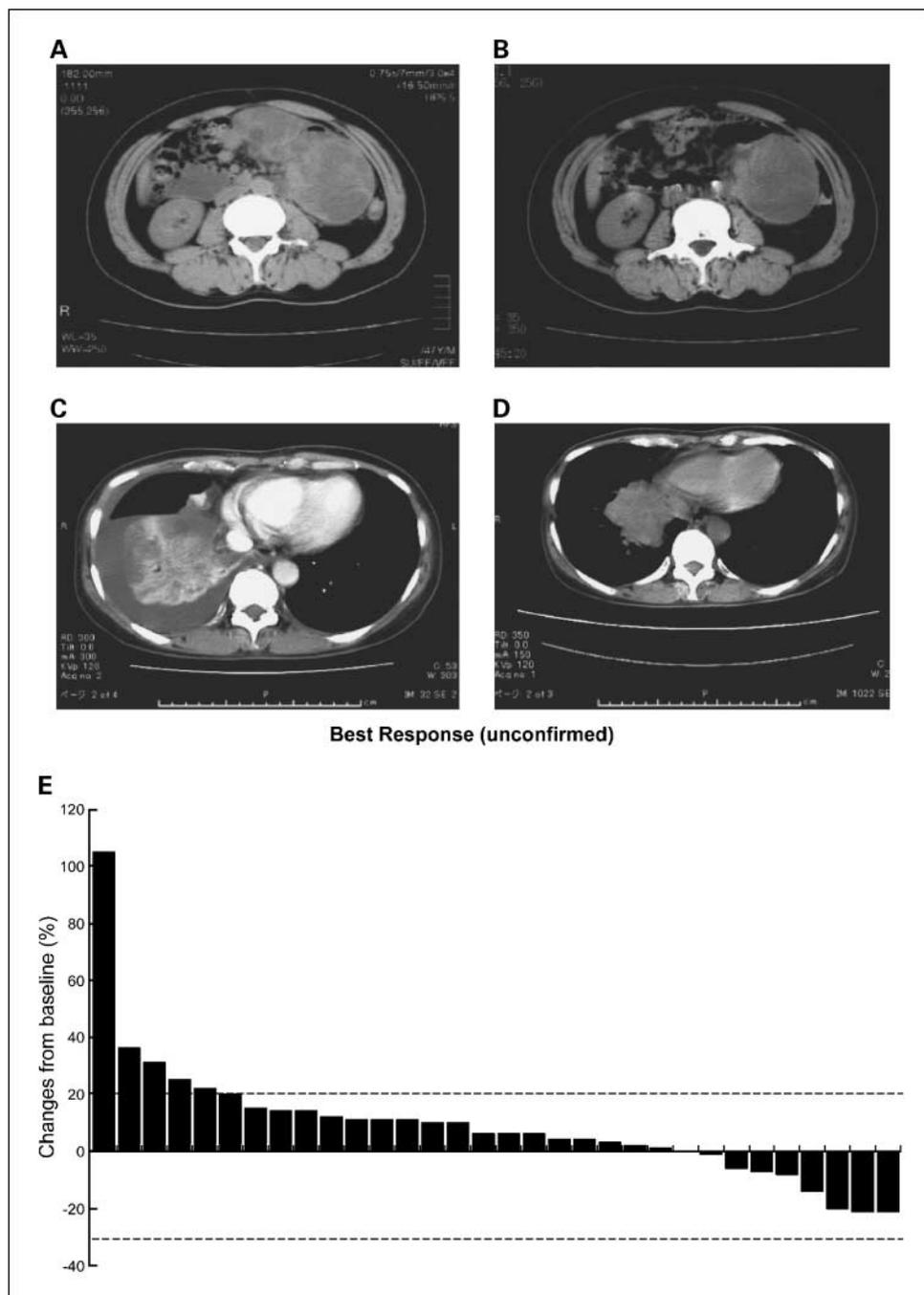


Fig. 3. Computed tomography images of a patient with malignant fibrous histiocytoma before treatment (A) and after (B).

Both  $t_{1/2}$  and clearance seemed to be constant across the dose range. In addition,  $C_{ss}$  increased almost dose-proportionally (Fig. 2B), indicating the linear pharmacokinetics of YM155 over the dose range of 1.8 to 10.6 mg/m<sup>2</sup>/d. Low concentrations of the study drug remained in systemic circulation for 48 hours after the end of infusion; however, plasma concentrations decreased to below 0.5 ng/mL before the start of cycle 2. Pharmacokinetic parameters in cycle 2 (data not shown) were similar to those in cycle 1, suggesting that there is no accumulation of study drug. We need more samples to explore the details including correlation between body surface area and pharmacokinetic parameters.

The  $A_e\%$  in urine was estimated as 25% to 42% at a dose range of 1.8 to 10.6 mg/m<sup>2</sup>/d, suggesting that urinary excretion is a principal route for the elimination of YM155. This result is well-supported by *in vitro* studies indicating that minimal metabolism of YM155 occurred in human hepatocytes (23).

The MTD of YM155 in the current study was determined to be 8.0 mg/m<sup>2</sup>/d, after the occurrence of a DLT of increased serum creatinine in 2 of 5 patients receiving 10.6 mg/m<sup>2</sup>/d. In contrast, in an earlier U.S. phase I trial done using the same design as the present Japanese study, the MTD was determined as 4.8 mg/m<sup>2</sup>/d, after the occurrence of renal DLTs in 2 patients who received 6.0 mg/m<sup>2</sup>/d (18). These DLTs were all reversible. The difference in the MTD between the U.S. and Japanese studies has been investigated by the evaluation of patient demographics, in particular baseline renal function (serum creatinine level) and prior treatment affecting renal function (history of platinum treatment), as well as hydration and pharmacokinetics of the patients with DLT. Serum creatinine levels were 1.1 and 1.4 mg/dL (reference range, 0.6-1.4 mg/dL) in the U.S. patients and 0.59 mg/dL (reference range, 0.5-1.0) and 0.81 mg/dL (reference range, 0.7-1.3 mg/dL) in the Japanese patients. Although these levels were toward the higher end of the reference range in the U.S. patients compared with those in the Japanese patients, any differences observed may be a result of two different testing facilities. Both U.S. patients had a history of platinum treatment, whereas only one of the two Japanese patients did. Furthermore, a comparison of patients receiving 6.0 mg/m<sup>2</sup>/d of YM155 revealed that mean baseline serum creatinine levels were lower in Japanese patients than in U.S. patients. Whereas it is difficult to directly compare renal function between the two patient populations, these data do suggest that renal function may have been decreased in the U.S. patients. An additional factor to consider is body surface area. The body surface area of the U.S. patients with a DLT was 2.11 and 2.05 m<sup>2</sup>

compared with 1.44 and 1.65 m<sup>2</sup> for the Japanese patients. This is suggestive of a smaller total dose of YM155. There were no essential differences between U.S. and Japanese patients in terms of the time course of plasma drug concentrations and pharmacokinetic parameters, suggesting that the difference in the MTD is unlikely to be attributable to the difference in the pharmacokinetics or exposure level.

In the present study, external evaluation showed that stable disease was achieved in nine patients. It should be noted that this prolongation of stable disease was achieved in heavily pretreated patients and response was seen also at the lowest dose. Indeed, one third of the patients had previously received four or more chemotherapy regimens. Such provocative antitumor activity in refractory solid tumors confirms the previously reported activity in the U.S. phase I trial. In the U.S. study, a partial response was achieved in 3 of 5 patients with non-Hodgkin's lymphoma and a PSA response, and a 50% reduction in 2 patients with hormone-refractory prostate cancer. Furthermore, a minor reduction (23% reduction) in tumor size was noted in one patient with non-small cell lung cancer (18). The results from both studies suggest that YM155 has promising antitumor activity against various tumor types.

In conclusion, YM155 was administered safely in this study to patients with advanced refractory solid tumors by 168-hour continuous infusion in 21-day cycles. The MTD in this patient population was determined to be 8.0 mg/m<sup>2</sup>/d. This potential for clinical efficacy is supported by the stable responses in advanced refractory tumors achieved in this study with YM155 treatment, in addition to the antitumor activity shown in the U.S. phase I study. On the basis of the potential shown by these promising results, further randomized clinical studies of YM155 are warranted, both in the monotherapy setting and in combination regimens with established therapies.

### Disclosure of Potential Conflicts of Interest

Toru Kakahara, Yumiko Aoyama, and Yohko Hashimoto are employees of Astellas Pharma, Inc.

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### References

- Ambrosini G, Adida C, Altieri DC. A novel anti-apoptosis gene, survivin, expressed in cancer and lymphoma. *Nat Med* 1997;3:917-21.
- Rothe M, Pan MG, Henzel WJ, Ayres TM, Goeddel DV. The TNFR2-TRAF signaling complex contains two novel proteins related to baculoviral inhibitor of apoptosis proteins. *Cell* 1995;83:1243-52.
- Roy N, Deveraux QL, Takahashi R, Salvesen GS, Reed JC. The c-IAP-1 and c-IAP-2 proteins are direct inhibitors of specific caspases. *EMBO J* 1997;16:6914-25.
- Tamm I, Wang Y, Sausville E, et al. IAP-family protein survivin inhibits caspase activity and apoptosis induced by Fas (CD95), Bax, caspases, and anticancer drugs. *Cancer Res* 1998;58:5315-20.
- O'Connor DS, Grossman D, Plescia J, et al. Regulation of apoptosis at cell division by p34cdc2 phosphorylation of survivin. *Proc Natl Acad Sci U S A* 2000;97:13103-7.
- LaCasse EC, Baird S, Korneluk RG, MacKenzie AE. The inhibitor of apoptosis (IAPs) and their emerging role in cancer. *Oncogene* 1998;17:3247-59.
- Jäättelä M. Escaping cell death: survival protein in cancer. *Exp Cell Res* 1999;248:30-43.
- Lu CD, Altieri DC, Tanigawa N. Expression of a novel anti-apoptosis gene, survivin, correlated with tumor cell apoptosis and p53 accumulation in gastric carcinomas. *Cancer Res* 1998;58:1808-12.
- Adida C, Berbebi D, Peuchmaur M, Reyes-Mugica M, Altieri DC. Anti-apoptosis gene, survivin, and prognosis of neuroblastoma. *Lancet* 1998;351:882-3.
- Islam A, Kageyama H, Takada N, et al. High expression of Survivin, mapped to 17q25, is significantly associated with poor prognostic factors and promotes cell survival in human neuroblastoma. *Oncogene* 2000;19:617-23.
- Sarela AI, Macadam RC, Farmery SM, Markham AF, Guillou PJ. Expression of the antiapoptosis gene, survivin, predicts death from recurrent colorectal carcinoma. *Gut* 2000;46:645-50.
- Monzo M, Rosell R, Felip E, et al. A novel anti-apoptosis gene: reexpression of survivin messenger RNA as a prognosis marker in non-small-cell lung cancers. *J Clin Oncol* 1999;17:2100-4.
- Tanaka K, Iwamoto S, Gon G, Nohara T, Iwamoto

- M, Tanigawa N. Expression of survivin and its relationship to loss of apoptosis in breast carcinomas. *Clin Cancer Res* 2000;6:127-34.
14. Yamamoto T, Tanigawa N. The role of survivin as a new target of diagnosis and treatment in human cancer. *Med Electron Microsc* 2001;34:207-12.
15. Giodini A, Kallio MJ, Wall NR, et al. Regulation of microtubule stability and mitotic progression by survivin. *Cancer Res* 2002;62:2462-7.
16. Mesri M, Morales-Ruiz M, Ackermann EJ, et al. Suppression of vascular endothelial growth factor-mediated endothelial cell protection by survivin targeting. *Am J Pathol* 2001;158:1757-65.
17. Nakahara T, Masahiro T. YM155, a novel small-molecule survivin suppressant, induces regression of established human hormone-refractory prostate tumor xenografts. *Cancer Res* 2007;67:8014-21.
18. Tolcher AW, Mita A, Lewis L, et al. Phase I and pharmacokinetic study of YM155, a small molecule inhibitor of survivin. *J Clin Oncol* 2008;26:5198-203.
19. Therasse P, Arbut SG, Eisenhauer EA, et al. New guidelines to evaluate the response to treatment in solid tumors. *J Natl Cancer Inst* 2000;92:205-16.
20. Pennati M, Folini M, Zaffaroni N. Targeting survivin in cancer therapy. *Expert Opin Ther Targets* 2008;14:463-76.
21. Altieri DC. Survivin, cancer networks and pathway-directed drug discovery. *Nat Rev Cancer* 2008;8:61-70.
22. Leung CG, Xu Y, Mularski B, Liu H, Gurbuxani S, Crispino JD. Requirements for survivin in terminal differentiation of erythroid cells and maintenance of hematopoietic stem and progenitor cells. *J Exp Med* 2007;204:1603-11.
23. Sohda K, Suzuki K, Nakamura E, et al. Metabolism of YM155 monobromide, a novel survivin suppressant: *in vitro* species comparison and identification of metabolites in rats. The Proceeding of 8th International ISSX meeting 2007 (Sendai Japan). *Drug Metab Rev* 39:235.