

# Drug evaluation: STA-4783 – enhancing taxane efficacy by induction of Hsp70

Mathias Gehrmann

## Address

University Hospital Regensburg  
Dept Hematology/Oncology  
Molecular Oncology  
H1 Carreras FoBau  
Franz-Josef-Strauss-Allee 11  
D-93053 Regensburg  
Germany  
Email: mathias.gehrmann@klinik.uni-regensburg.de

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*The apoptosis stimulator STA-4783 acts by inducing expression of heat shock protein (Hsp)70 on tumor cell surfaces and disrupting the cytoskeletal network. Currently in development by Synta Pharmaceuticals for the potential treatment of solid tumors, phase II clinical trials in non-small-cell lung cancer, melanoma and sarcoma have been initiated.*

## Introduction

Heat shock proteins (Hsps) are ubiquitous in all cell types and are known to function as 'chaperones' to promote the proper folding and functionality of cytoplasmic proteins. The upregulation of Hsps is most commonly associated with protection against stress-induced protein aggregation and misfolding. Hsp70 (MW ~ 70 kDa) is the major heat-inducible member of the Hsp family. The expression of Hsp70 on the cell membrane plays a pivotal role in the stimulation of the adaptive and innate immune system. It is well known that tumor-derived peptides bind to Hsp70, which targets them to the cell surface of tumor cells where they are presented to the immune system [509145]. Peptide-independent immune-system stimulation by Hsp70 was also identified by Multhoff and co-workers, who described Hsp70 expression on the surface of tumor cell lines as well as primary tumors [669306]. T-cells, for example, recognize and are activated by Hsp70 [509145]. Similarly, natural killer (NK) cells can be activated by Hsp70 on the plasma membrane of tumor cells, leading to a higher proliferation index, increased cytotoxicity and greater potential to migrate to Hsp70-positive tumor cells [652203], [668389].

The taxane anticancer drugs paclitaxel and docetaxel exert cytotoxic activity by destroying the microtubular network and inhibiting its renewal. By binding tubulin, taxanes stabilize non-functional microtubule bundles, thereby blocking the normal development of the mitotic spindle and subsequent cell division, leading to apoptosis [18753]. Rapidly dividing cancer cells are more susceptible to taxanes than healthy cells because their microtubular network is more active. Treatment with taxanes increases the expression of Hsp70 on the membranes of tumor cells [652205]. Taxanes are commonly used in the first-line treatment of ovarian and breast cancers and as part of multidrug regimens in the treatment of various cancer [484549]. Numerous derivatives of paclitaxel have been tested in attempts to improve on the chemotherapeutic activity of the compound or reduce toxicity [668520], some of which have been approved for clinical use [668520].

**Originator** Synta Pharmaceuticals Corp

**Status** Phase II Clinical

**Indications** Melanoma, Non-small-cell lung cancer, Sarcoma, Solid tumor

**Actions** Actin modulator, Anticancer, Apoptosis stimulator, Hsp70 stimulator, Tubulin modulator

**Technologies** Intravenous formulation

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In a novel approach to improving the efficacy of the taxanes, Synta Pharmaceuticals Corp is developing STA-4783, optimized from a screen of small molecules that enhance the antitumor activity of paclitaxel [531145]. STA-4783 exerts antitumor activity by two mechanisms: induction of Hsp70 on tumor cell surfaces, and interruption of the cytoskeletal network (both actin filaments and microtubuli), leading to cell damage, including the inhibition of intracellular transport routes, inhibition of mitosis and induction of apoptosis [531145]. STA-4783 has been shown to enhance the efficacy of paclitaxel in preclinical models, without additional toxicity [531401], and is being tested in three phase II clinical studies in various cancer types.

## Synthesis and SAR

Synthesis of STA-4783 comprises the reaction of thiobenzoylsulfanyl acetic acid with methyl hydrazine in the presence of sodium hydroxide to give a mixture of thiobenzoic acid *N*-methyl hydrazide and thiobenzoic acid *N'*-methyl hydrazide. Treatment of the *N*-methyl isomer with malonyl chloride in the presence of triethylamine yielded STA-4783. The thiobenzoylsulfanyl acetic acid starting material could be prepared, for example, by treating a thiobenzoylsulfanyl magnesium bromide Grignard reagent with sodium chloroacetate [531145].

## Preclinical development

*In vitro* exposure to STA-4783 (0.1 to 1.0  $\mu$ M for 3 h) strongly induced Hsp70 expression in various human tumor cell lines, including MDA435 [531145], [531401] and MCF7 breast cancer cells, HT29 colon cancer cells [531401] and MDA-MB435 melanoma cells [636051], but not in non-tumor cell lines such as human mammary (HMEC) or renal (HREC) epithelial cells (at 5  $\mu$ M) [531401]. Hsp70 induction was also demonstrated in patient-derived primary melanoma cells following *ex vivo* exposure to STA-4783 [531401].

The marked upregulation of Hsp70 mRNA expression by STA-4783 was accompanied by increased levels of cytoplasmic Hsp70 protein and localization of Hsp70 at the cell membrane [531401]. The immune-cell-recruiting activity

of STA-4783 was also evidenced *in vitro* in MDA-MB435 cells incubated with murine splenic NK effector cells; 36% specific cell lysis was seen following incubation with STA-4783 compared with 12% lysis with vehicle [637030].

Immunofluorescence studies demonstrated that STA-4783 significantly disrupts the cytoskeletal network of tumor cells by altering the structure and function of the centrosome. Disruption of both microtubules (required for cell division and transport) and actin microfilaments (which provide mechanical support for the cell, determine cell shape and enable cell motility) led to alterations in cell morphology and ultimately to cell death [668428].

*In vivo*, STA-4783 (repeated doses of 25 to 100 mg/kg) as a single agent showed no antitumor activity in nude mouse xenograft models of human breast cancers (MDA435, MCF7 and ZR-75-1), lung cancer (RER) or lymphoma (U937). However, STA-4783 markedly enhanced the efficacy of paclitaxel in these models, both in terms of tumor regression and extended survival of mice [531401], [532818].

In female CD-1 nude mice bearing established MDA435 ( $5 \times 10^6$  cells) breast cancer xenograft tumors in the mammary fat pads (mean baseline tumor volume of  $\sim 75$  mm<sup>3</sup>; n = 5/group), intravenous treatment with a combination of 5 mg/kg paclitaxel and 100 mg/kg STA-4783 (eight doses on alternate days) reduced mean tumor volume to approximately 60 mm<sup>3</sup> at day 17, compared with greatly increased tumor volumes of approximately 225 mm<sup>3</sup> in mice treated with 5 mg/kg paclitaxel alone or vehicle control. The combination did not increase the toxicity of paclitaxel or promote significant weight change [532818], [604045], [604046], [604047]. In a study in a murine ZR-75-1 breast cancer xenograft model, four weekly doses of paclitaxel (15 or 30 mg/kg), STA-4783 (12.5 or 25 mg/kg), a combination, or vehicle control were administered, and tumor-free survival was assessed at day 55. As previously, tumors grew rapidly in mice receiving either STA-4783 alone or vehicle (0% of mice were tumor-free), and were inhibited moderately by low-dose paclitaxel (10% tumor-free) and more effectively by high-dose paclitaxel (30% tumor-free). In combination, however, the drugs improved the number of mice surviving tumor-free by 2- to 4-fold compared with paclitaxel alone. In animals administered 15 mg/kg paclitaxel with low- and high-dose STA-4783, 40 and 30% survived, respectively. With 30 mg/kg paclitaxel combined with low- and high-dose STA-4783, 60 and 70% of mice survived, respectively [532818].

In mice bearing established U937 lymphoma-cell-derived tumors ( $\sim 0.1$  cm<sup>3</sup> at baseline), treatment with 5 mg/kg paclitaxel inhibited the growth of tumors at day 13 ( $\sim 0.7$  cm<sup>3</sup>) compared with vehicle control of 25 mg/kg STA-4783 alone (1.2 cm<sup>3</sup>). The combination of 5 mg/kg paclitaxel and 25 mg/kg STA-4783, however, caused marked tumor regression and eradicated tumors in many animals by day 13 [532818]. STA-4783 reportedly enhanced the efficacy of paclitaxel in a range of other tumor types including lung, ovarian, uterine and melanoma; however, no details of these studies appear to have been published [604045], [604046], [604047].

In contrast to the *in vitro* finding that STA-4783 enhanced the killing of MDA-MB435 melanoma cells by murine NK cells, *in vivo* treatment of a severe combined immunodeficiency (SCID) mouse MDA-MB435 xenograft model with STA-4783 alone (50 mg/kg three times weekly for 7 weeks) exerted no antitumor activity; treatment actually increased the size of tumors relative to those of control mice ( $\sim 400$  mm<sup>3</sup> compared with  $\sim 350$  mm<sup>3</sup>, respectively). However, STA-4783 (50 mg/kg) in combination with paclitaxel (5 mg/kg) significantly reduced tumor volume to approximately 100 mm<sup>3</sup> compared with approximately 250 mm<sup>3</sup> for paclitaxel alone [636051], [637030], [637039].

Contradictory results were obtained in a T-/B-/NK-cell-deficient SCID-beige mouse MDA-MB435S melanoma xenograft model, however, in which STA-4783 failed to enhance the activity of paclitaxel [636051], [637030], [637039]. At day 45, in mice treated on alternate days with paclitaxel (5 mg/kg) alone or in combination with STA-4783 (25 mg/kg), tumor volumes both grew to approximately 300 mm<sup>3</sup>, compared with approximately 500 mm<sup>3</sup> in vehicle- or STA-4783-treated mice [636051], [637030], [637039]. The lack of cytotoxic enhancement is perhaps a result of the deficit in the Hsp70/immune-mediated mechanism of STA-4783 in this severely immunosuppressed model.

### Metabolism and pharmacokinetics

The pharmacokinetic parameters of STA-4783 have been well studied in rats and dogs [529521], [531145], [531791]. In rats administered a slow bolus dose of 25 mg/kg STA-4783 alone or in combination with 5 mg/kg paclitaxel, area under the curve (AUC) values for STA-4783 were 13.1 and 9.8  $\mu\text{g/ml}\cdot\text{h}$ , respectively, and the half-lives were approximately 40 to 50 min. In dogs, a 10-mg/kg dose of STA-4783 alone or in combination with 4 mg/kg paclitaxel (given as a 3-h intravenous infusion) produced AUC values of 30.0 and 31.7  $\mu\text{g/ml}\cdot\text{h}$ , respectively, and a half-life of approximately 1.2 h in dogs. The pharmacokinetics of STA-4783 in dogs were linear and dose-proportional (10 to 30 mg/kg), and the drug was found to be highly protein-bound ( $> 95\%$  at 2  $\mu\text{l}$  and  $> 88\%$  at 10  $\mu\text{l}$ ). No gender-related differences were observed in either species and STA-4783 had no significant effect on the pharmacokinetics of paclitaxel in terms of total AUC, half-life and clearance [531791].

An autoradiographic distribution study using [<sup>14</sup>C]STA-4783 was conducted in male rats, with imaging performed at 1 and 6 h post-dosing. At 1 h the drug was widely distributed to tissues of the kidney, liver and lungs. Concentrations 20-fold lower than the plasma concentration were detected in the central nervous system after 2 h, but declined to undetectable levels after 6 h [531791]. In excretion studies in rats and dogs, urine samples exhibited high levels of radioactivity, as did the kidney, and rapid renal excretion was also distinguishable. The drug was excreted primarily in the urine ( $\sim 70\%$  of the dose in rats and  $> 60\%$  in dogs) and the remainder was excreted in feces. It was found that 80 to 90% of STA-4783 and its metabolites were eliminated within 48 h after administration [531791]. Six metabolites of STA-4783 were identified in *in vitro* systems; the three main metabolites were common across all organisms tested,

including humans. The characteristic metabolites have exchanges of one or two sulphur atoms (to produce the metabolites STA-5393 and STA-5313, respectively) or hydrolysis of the C-N bond in the hydrazide group of STA-4783 (yielding STA-5370 and STA-5512) [531791].

The pharmacokinetics of STA-4783 in humans have been reported from a phase I study in 13 patients with advanced solid tumors [529521], [531791], [604045], [614009]. Patients were administered STA-4783 (44, 88, 176, 263 or 525 mg/m<sup>2</sup>) in combination with paclitaxel (135 to 175 mg/m<sup>2</sup>) as a 3-h infusion over 3 weeks. The C<sub>max</sub> of STA-4783 was 3.0 ± 0.3 μM at the 88-mg/m<sup>2</sup> dose. STA-4783 was rapidly cleared from plasma with a half-life of 0.85 ± 0.1 h and clearance of 28.4 ± 7.3 l/h/m<sup>2</sup>. The volume of distribution at steady state (Vd<sub>ss</sub>) was comparable to the volume of total body water (20.8 ± 7.2 l/m<sup>2</sup>). The pharmacokinetic parameters for STA-4783 at 44 mg/m<sup>2</sup> were comparable in patients who were co-administered 135 or 175 mg/m<sup>2</sup> paclitaxel. The pharmacokinetic parameters of paclitaxel (175 mg/m<sup>2</sup>) were unaffected by the co-administration of STA-4783: the C<sub>max</sub> for paclitaxel was 4.6 ± 1.0 μM, half-life was 14.6 ± 3.6 h, clearance was 13.3 ± 3.2 l/h/m<sup>2</sup> and Vd<sub>ss</sub> was 86.2 ± 21.1 l/m<sup>2</sup> [614009].

## Toxicity

Preclinical studies in rats, mice and dogs evaluated the toxicity of STA-4783 alone and in combination with paclitaxel [531833]. Preliminary non-good laboratory practice (GLP) studies showed that Sprague Dawley and CD-1 rats both tolerated an intravenous bolus dose of up to 100 mg/kg without mortality. At a dose of 200 mg/kg, 17 and 33% of the respective groups died (1 of 6 and 2 of 6, respectively). The LD<sub>50</sub> values for STA-4783 after an intravenous bolus injection were calculated to be > 200 mg/kg in rats and mice. The LD<sub>50</sub> for dogs could not be determined because the highest tested dose (37.5 mg/kg limited by solubility) was not lethal [531833].

In GLP studies, single intravenous doses of STA-4783 were tolerated at up to 125 mg/kg in rats and 30 mg/kg in dogs. Tests evaluated changes in hematological, gastrointestinal, central and peripheral nervous system, cardiovascular and respiratory, hepatic, renal and dermal systems and examined hypersensitive reactions [531833]. In rats, hematological changes at day 3 of treatment included decreases in platelet, total leukocyte, lymphocyte, neutrophil and/or monocyte counts in animals given paclitaxel alone or in combination with STA-4783. In rats given paclitaxel alone, decreased red blood cell counts, hemoglobin and hematocrit values were seen. Following a single dose of 30 mg/kg STA-4783 in dogs, no treatment-related hematological effects were detectable. Leukopenia (~ 60%), neutropenia (~ 50%), lymphopenia (~ 60%) and thrombopenia (~ 50%) were observed following dosing with paclitaxel (4 mg/kg), and were comparable in dogs receiving paclitaxel (4 mg/kg) plus STA-4783 (10 to 30 mg/kg). These effects (seen at days 4 and 8) were found to be reversible by day 14. No significant gender-based differences were seen in dogs [531833].

No significant differences were detectable in gastrointestinal function following single doses of STA-4783 in rats (50, 75 or 125 mg/kg) or dogs (10, 20 or 30 mg/kg) [531833]. In rats, no significant differences were seen between paclitaxel and the drug combination in terms of inappetence or weight loss. In dogs, a combination of paclitaxel and STA-4783 (combination doses as previously) did not produce any significant differences compared with paclitaxel alone (inappetence, weight loss of up to ~15%, emesis and discolored and mucoid and/or non-formed feces) [531833]. Evaluation of the nervous, cardiovascular and respiratory, hepatic, renal and dermal systems and hypersensitive reactions of both rats and dogs showed no significant differences between response to single administrations of paclitaxel and the combination of paclitaxel with STA-4783 [531833].

## Clinical development

### Phase I

The first phase I study with STA-4783 enrolled patients with advanced solid tumors in a dose-escalation design [545546], [604045], [614009]. The dose level of STA-4783 escalated once a particular dose had been proved safe. In the final data set, STA-4783 had been given over a dose range of 44 to 525 mg/m<sup>2</sup> in combination with paclitaxel (135 to 175 mg/m<sup>2</sup>) to a total of 35 patients, as a 3-h infusion every 3 weeks. Patient tumor types included Kaposi's sarcoma, melanoma, angiosarcoma, esophageal squamous, gallbladder, acinar cell, breast and colon cancers. The median age of patients was 37 years and subjects had received a median of five prior therapies, including paclitaxel, in 40% of cases. Significant induction of Hsp70 was recorded in many patients at 8 h post-dosing, which generally increased with STA-4783 dose, but varied greatly between patients (up to a maximum of 2175% induction over baseline in one patient receiving 350 mg/m<sup>2</sup> STA-4783 and 175 mg/m<sup>2</sup> paclitaxel). No dose-limiting toxicity (DLT) was attributable to STA-4783 and no additional toxicity was recognized compared with paclitaxel alone. No maximum tolerated dose (MTD) was established for STA-4783, although it was considered that the dose-related decreases in paclitaxel clearance might limit the potential for future dose escalation. Indications of clinical activity were seen in some patients, including a subset who had previously been treated with paclitaxel. Stable disease (SD) was seen in 12 patients after two treatment cycles and in three patients after four cycles. Of the ten patients evaluable for response, a partial response (PR) was seen in two patients with Kaposi's sarcoma [604045].

Data from the phase I portions of the two-phase trials are discussed together with the phase II clinical data in the following section.

### Phase II

#### *Non-small-cell lung cancer (NSCLC)*

A phase II clinical trial evaluated STA-4783 in patients with previously untreated advanced (stage IIIB or IV) NSCLC. The two-part design of this trial included an open-label, dose-escalation safety trial in 16 patients that ensured that STA-4783 was well tolerated together with the combination

of paclitaxel and carboplatin (the standard first-line treatment for NSCLC), followed by a larger, randomized, blinded phase II portion [604046], [637030], [668428]. The first portion comprised two cohorts, both of which received the same dose level of carboplatin (AUC = 6) plus either 233 mg/kg STA-4783 and 175 mg/m<sup>2</sup> paclitaxel (n = 7) or 266 mg/kg STA-4783 and 200 mg/m<sup>2</sup> paclitaxel (n = 9), every 3 weeks. At clinical evaluation, PRs were achieved in seven patients, SD was observed in six patients and progressive disease was noted in three patients. Both dose levels were well tolerated, so the higher level was selected for the continuing phase II portion of the trial [604046], [637030].

Data have been presented from 86 patients in the second portion of the study, who were randomized to receive paclitaxel (175 mg/m<sup>2</sup>) and carboplatin (AUC = 6) plus STA-4783 (233 mg/kg) or placebo, as a 3-h infusion every 3 weeks. Patient demographics and disease characteristics were comparable between the two treatment groups. Overall, the patient group receiving STA-4783 failed to show any significant clinical benefit over the standard therapy. In the respective groups the median times to tumor progression (TTP) were 3.3 and 4.6 months, and response rates were 17.5 and 25.0%; the median overall survival time was 8.2 months in both groups. The addition of STA-4783 did not significantly increase the toxicity of paclitaxel/carboplatin. These interim results do not support progression of STA-4783 to phase III clinical trials for the treatment of NSCLC [637030].

#### **Soft tissue sarcomas (STS)**

The ongoing phase II clinical trial in patients with advanced STS also consists of a two-part design [604047], [637039], [668428]. In this study, the phase I portion in 30 patients confirmed initial efficacy (defined as ≥ eight patients having SD at 3 months or ≥ two patients having a PR or better) as well as safety. Patients were administered 213 mg/m<sup>2</sup> STA-4783 plus 80 mg/m<sup>2</sup> paclitaxel as a 1-h weekly infusion for 3 weeks in every 4 weeks. SD occurred in 14 patients (47%), and the trial moved on to the phase II portion. An apparent correlation between NK cell activity and clinical outcome was to be investigated further [604047], [637039].

An additional 54 patients were enrolled to complete the accrual of the study, who received the same dosage as the first study portion. Preliminary data have to date been presented from 79 patients who had received three cycles of treatment. PRs occurred in two patients (3%), SD was seen in 23 patients (29%) and disease had progressed in 43 patients (54%). The median TTP was estimated to be 1.9 months, and non-progression rates at 3 and 6 months were 36 and 12%, respectively. The addition of STA-4783 to the weekly dose of paclitaxel was well tolerated; however, the number of patients that demonstrated partial responses was not encouraging. Owing to the heterogeneity of the disease, subgroup analysis to identify populations with better treatment responses may yield additional avenues for exploration [637039].

#### **Melanoma**

A two-part phase II study is also ongoing in patients with advanced metastatic melanoma [604045], [636051]. Two

cohorts of patients were treated. The first received 80 mg/m<sup>2</sup> paclitaxel plus 106 mg/m<sup>2</sup> STA-4783 (n = 3), weekly for 3 weeks in every 4 weeks, which increased to 213 mg/m<sup>2</sup> STA-4783 in combination the same paclitaxel dose (n = 28) following an initial safety assessment. Efficacy in these patients exceeded criteria for the study to continue enrollment; of 31 evaluable patients, four PRs and 14 SDs were recorded. In the absence of DLTs, the higher dose was used for the phase II trial. The latest data included four PRs and SD in some patients. Patient enrollment was to continue up to the target enrolment of 100 patients [636051] and the trial is expected to be completed in the second quarter of 2006 [642694].

#### **Side effects and contraindications**

The combination of STA-4783 in the phase I study (up to 263 mg/m<sup>2</sup>) with paclitaxel (up to 175 mg/m<sup>2</sup>) was generally well tolerated, with patients experiencing side effects characteristic of paclitaxel treatment. Grade 4 neutropenia occurred in five patients, with no relationship to STA-4783 dose. No DLT attributable to STA-4783 was reached [545546], [604045]. In patients receiving intravenous STA-4783 (213 mg/m<sup>2</sup>) and paclitaxel (80 mg/m<sup>2</sup>) on a weekly basis for 3 weeks every 4 weeks, the noted adverse effects were fatigue, alopecia, nausea, anemia, diarrhea, sensory peripheral neuropathy and headache. It was also concluded that these side effects were comparable to those expected with paclitaxel treatment alone [637039]. Anemia, neutropenia, thrombocytopenia, nausea, vomiting, asthenia, fatigue, anorexia, dehydration, myalgia and alopecia were recorded in NSCLC patients receiving STA-4783 (233 to 266 mg/m<sup>2</sup>) plus paclitaxel (175 to 200 mg/m<sup>2</sup>) and carboplatin (AUC = 6). Side effects with additive STA-4783 were comparable to paclitaxel and carboplatin treatment [637030]. In the melanoma trial, the side effects of STA-4783 (213 mg/m<sup>2</sup>) plus paclitaxel (80 mg/m<sup>2</sup>) for 3 weeks in every 4 were again consistent with those of paclitaxel alone. The most frequent adverse events included alopecia, fatigue, diarrhea, anemia and insomnia [636051].

#### **Patent summary**

The product case for STA-4783 is assigned to SBR Pharmaceuticals Corp and was published as WO-03006428. Three US equivalents have been granted since July 2004. Synta Pharmaceuticals has filed several further applications relating to STA-4783. WO-2004064826 specifically claims the use of the drug in the treatment of multidrug-resistant cancer and WO-2006009940 claims disodium and dipotassium salts of STA-4783. Most recently, WO-2006033913 claimed STA-4783 for the treatment of non-cancerous proliferative disorders such as smooth muscle cell proliferation, systemic sclerosis, liver cirrhosis and restenosis. Drug implants and vascular stents including the drug are also claimed.

#### **Current opinion**

Synta Pharmaceuticals is developing the novel histiobenzoyl compound STA-4783 for anticancer therapy. *In vitro* it has been shown that STA-4783 destroys the intracellular cytoskeletal network and inhibits its new arrangement. In xenograft models in mice and in *in vitro* systems it was shown that the intrinsic antitumor activity of

STA-4783 is low, but that the drug enhances the antitumor activity of paclitaxel dramatically. Besides the effects on the cytoskeletal network, STA-4783 increased the expression of Hsp70 on the cell membranes of tumor cells, but not on healthy cells. This finding is consistent with independent work from other scientists who showed that the disruption of the tubular network caused by treatment with cytostatic drugs, including paclitaxel and vincristine, leads to an increase of the Hsp70 expression both in the cytoplasm and on the membrane [652205]. Elucidation of the tumor-peptide chaperoning and immune-activating mechanisms of Hsp70 led to the hypothesis that the described Hsp70-membrane expression following STA-4783 treatment might be useful for the stimulation of the immune system. Further investigations may be performed to study the effects of STA-4783 treatment on the membrane expression of Hsp70, and an antibody that specifically recognizes membrane-bound Hsp70 on viable tumor cells is now available from Multimmune GmbH.

From the published studies it is not obvious whether the antitumor activity of STA-4783 is based on the destruction of the cytoskeleton or on the stimulation of tumor cell killing initiated by cells from the immune system. As well as the ongoing clinical studies, research groups may further focus

on the biochemical and biological effects of STA-4783 to determine its mode of action in combination with paclitaxel and gain further insight into its immunostimulatory effects. The finding that STA-4783 increases the antitumor activity of paclitaxel may also help to overcome paclitaxel resistance. It is well known that the resistance of single tumor cells against cytostatic drugs, even those as potent as paclitaxel, reduces the clinical outcome or leads to relapse [669313].

In summary, STA-4783 has been shown to damage the cytoskeletal network and inhibit its new arrangement. This effect is accompanied by an increased Hsp70 membrane expression. Although STA-4783 showed little antitumor activity itself, biological and clinical studies show STA-4783 to be a potent enhancer of the antitumor activity of paclitaxel without exacerbating its toxicity. Pharmacokinetic studies have shown that STA-4783 and paclitaxel do not influence each other's pharmacokinetics or excretion, and the results from combination therapy trials show that all noted side effects are equivalent to those for single treatment of the co-administered drugs paclitaxel and carboplatin. Further clinical studies will demonstrate whether STA-4783 has the potential to improve treatment outcomes or to overcome paclitaxel resistance.

## Development history

Developer	Country	Status	Indication	Date	Reference
Synta Pharmaceuticals Corp	US	Phase II	Non-small-cell lung cancer	22-NOV-04	572028
Synta Pharmaceuticals Corp	US	Phase II	Sarcoma	22-NOV-04	572028
Synta Pharmaceuticals Corp	US	Phase II	Melanoma	22-NOV-05	572028

## Literature classifications

### Chemistry

Study type	Result	Reference
Synthesis.	The synthesis of STA-4783 comprises the reaction of thiobenzoylsulfanyl acetic acid with methyl hydrazine in the presence of sodium hydroxide to give a mixture of thiobenzoic acid <i>N</i> -methyl hydrazide and thiobenzoic acid <i>N'</i> -methyl hydrazide. Treatment of the <i>N</i> -methyl isomer with malonyl chloride in the presence of triethylamine yielded STA-4783.	531145

### Biology

Study type	Effect studied	Model	Result	Reference
<i>In vitro</i>	Activity.	Tumor and other cell lines incubated with STA-4783 (0.1 to 5.0 $\mu$ M) for 3 h.	Exposure to STA-4783 strongly induced Hsp70 expression in MDA435 and MCF7 breast cancer cells, HT29 colon cancer cells, MDA-MB435 melanoma cell lines and patient-derived primary melanoma cells (at 0.1 $\mu$ M), but not in non-tumor HMEC or HREC cells (at 5 $\mu$ M).	531401
<i>In vitro</i>	Activity.	STA-4783-treated MDA-MB435 cells incubated with murine splenic NK effector cells.	Specific cell lysis was seen in 36% of STA-4783-treated cells compared with 12% of vehicle-treated cells.	637030
<i>In vivo</i>	Efficacy and safety.	Female CD-1 nude mice bearing established MDA435 ( $5 \times 10^6$ cells) breast cancer xenograft tumors treated with 5 mg/kg paclitaxel and 100 mg/kg STA-4783 (eight doses on alternate days).	Intravenous treatment with the combination reduced mean tumor volume to $\sim 60$ mm <sup>3</sup> at day 17, compared with greatly increased tumor volumes of $\sim 225$ mm <sup>3</sup> in mice treated with 5 mg/kg paclitaxel alone or control. The combination did not increase the toxicity of paclitaxel or promote significant weight change.	532818
<i>In vivo</i>	Activity.	T-/B-/NK-cell-deficient SCID-beige mouse MDA-MB435S melanoma xenograft model treated with paclitaxel (5 mg/kg) alone or in combination with STA-4783 (25 mg/kg).	STA-4783 failed to enhance the activity of paclitaxel. At day 45, in mice treated on alternate days with paclitaxel alone or in combination with STA-4783, tumor volumes both grew to $\sim 300$ mm <sup>3</sup> , compared with $\sim 500$ mm <sup>3</sup> in vehicle- or STA-4783-treated mice.	637030

**Metabolism**

Study type	Effect studied	Model	Result	Reference
<i>In vivo</i>	Pharmacokinetics.	Rats administered a slow bolus dose of 25 mg/kg STA-4783 alone in combination with 5 mg/kg paclitaxel. Dogs given a 10-mg/kg dose of STA-4783 alone or in combination with 4 mg/kg paclitaxel as a 3-h intravenous infusion.	In rats, AUC values for STA-4783 without and with paclitaxel were 13.1 and 9.8 $\mu\text{g/ml}\cdot\text{h}$ , respectively, and the half-lives were approximately 40 to 50 min. In dogs, AUC values for STA-4783 without and with paclitaxel were 30.0 and 31.7 $\mu\text{g/ml}\cdot\text{h}$ , respectively, and the compound showed a half-life of $\sim 1.2$ h. The pharmacokinetics of STA-4783 in dogs were linear and dose-proportional (10 to 30 mg/kg), and the drug was found to be highly protein-bound ( $> 95\%$ at 2 $\mu\text{l}$ and $> 88\%$ at 10 $\mu\text{l}$ ). STA-4783 had no significant effect on the pharmacokinetics of paclitaxel in terms of total AUC, half-life and clearance.	531791
<i>In vitro</i>	Metabolism.	Cellular metabolic systems.	Six metabolites of STA-4783 were identified, the three main species of which were common across all organisms studied, including humans. The characteristic metabolites have exchanges of one or two sulphur atoms or hydrolysis of a C-N bond of the hydrazide group of STA-4783.	531791
<i>In vivo</i>	Human pharmacokinetics.	A phase I study in 13 patients with advanced solid tumors administered STA-4783 (44, 88, 176, 263 or 525 $\text{mg/m}^2$ ) in combination with paclitaxel (135 to 175 $\text{mg/m}^2$ ) as a 3 h-infusion over 3 weeks.	STA-4783 was rapidly cleared from plasma with a half-life of $0.85 \pm 0.1$ h and clearance of $28.4 \pm 7.3$ $\text{l/h/m}^2$ . The $V_{d_{ss}}$ was comparable to the volume of total body water ( $20.8 \pm 7.2$ $\text{l/m}^2$ ). The pharmacokinetic parameters for STA-4783 at 44 $\text{mg/m}^2$ were similar in those who received 135 or 175 $\text{mg/m}^2$ paclitaxel. The $C_{max}$ of STA-4783 was $3.0 \pm 0.3$ $\mu\text{M}$ at the 88- $\text{mg/m}^2$ dose. The pharmacokinetic parameters of paclitaxel (175 $\text{mg/m}^2$ ) were unaffected by the co-administration of STA-4783.	614009

**Clinical**

Effect studied	Model used	Result	Reference
Safety and efficacy.	Phase I study in 34 patients with advanced solid tumors. STA-4783 (44 to 525 $\text{mg/m}^2$ ) was given in combination with paclitaxel (135 to 175 $\text{mg/m}^2$ ) as a 3-h infusion every 3 weeks.	Significant induction of Hsp70 was recorded in many patients at 8 h. No DLT was attributable to STA-4783 and no MTD was established. SD was seen in 12 patients after two cycles and three patients after four cycles. PRs were seen in two patients with Kaposi's sarcoma.	604045
Safety and efficacy.	Phase II, two-part study in 86 NSCLC patients randomized to receive paclitaxel (175 $\text{mg/m}^2$ ) and carboplatin (AUC = 6) plus STA-4783 (233 mg/kg) or placebo, as a 3-h infusion every 3 weeks.	STA-4783 showed no clinical benefit over the standard therapy. Respective TTPs were 3.3 and 4.6 months, response rates were 17.5 and 25.0%; the overall survival time was 8.2 months in both groups. The addition of STA-4783 did not significantly increase the toxicity of paclitaxel/carboplatin.	637030
Safety and efficacy.	Phase II, two-part study in 84 STS patients randomized to receive 213 $\text{mg/m}^2$ STA-4783 plus 80 $\text{mg/m}^2$ paclitaxel as a 1-h weekly infusion for 3 weeks in every 4 weeks.	Interim data showed PRs in two (3%), SD in 23 (29%) and progressive disease in 43 patients (54%). The median TTP was estimated to be 1.9 months, and non-progression rates at 3 and 6 months were 36 and 12%, respectively. The weekly dose of STA-4783 plus paclitaxel was well tolerated.	637039
Safety and efficacy.	Phase II, two-part study in patients with advanced metastatic melanoma (enrollment complete up to 100) treated with 213 $\text{mg/m}^2$ STA-4783 in combination with 80 $\text{mg/m}^2$ paclitaxel	Of 31 evaluable patients following part one of the trial, four PRs and 14 SDs were recorded. The latest data included four PRs and SD in some patients. The side effects of STA-4783 were consistent with those of paclitaxel alone.	636051

**Associated patent**

Title Taxol enhancer compounds.

Assignee SBR Pharmaceuticals Corp

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**References**

18753 Studies with RP 56976 (taxotere): A semisynthetic analogue of Taxol Ringel I, Horwitz SB *J NAT CANCER INST* 1991 **83** 4 288-291

484549 The current status of docetaxel in solid tumors. An MD Anderson Cancer Center review. Hong WK *ONCOLOGY-NY* 2002 **16** 6 Suppl 6 9-15

509145 Heat shock protein-peptide complexes, reconstituted *in vitro*, elicit peptide-specific cytotoxic T lymphocyte response and tumor immunity. Blachere NE, Li Z, Chandawarkar RY, Suto R, Jaikaria NS, Basu S, Udono H, Srivastava PK *J EXP MED* 1997 **186** 8 1315-1322

- 529521 **American Association of Cancer Research 95th Annual Meeting – overnight report (part IV), Orlando, FL, USA** Kibble A *IDDB MEETING REPORT* 2004 March 27-31
- 531145 **Synthesis and biological activities of STA-4783: A novel small molecule Taxol enhancer.** Sun L, Chen S, Koya K, Xia Z, Tatsuta N, Korbut T, Du Z, Liang G, Zhou D, Ono M *ACS MEETING* 2004 **227** Abs MEDI 111
- 531401 **STA-4783, a novel HSP70 inducer, enhances the anti-cancer activity of paclitaxel without increasing toxicity in preclinical studies.** Koya K, Sun L, Chen S, Tatsuta N, Korbut T, Zhou D, Liang G, Wu Y, Du Z, Xia Z-Q, Dahl TA, Barsoum J, Ono M, Chen LB *PROC AM ASSOC CANCER RES* 2004 **45** Abs 1504
- 531791 **A novel HSP-70 inducer STA-4783 enhances the anticancer activity of paclitaxel without altering paclitaxel pharmacokinetics. Preclinical pharmacokinetics, distribution and excretion study of STA-4783.** Tatsuta N, Liang G, Wang Q, Press R, Zavorskas PA, Sayyarpour F, McKeon ME, Kitayama E, Zhou D, Dahl TA, Mendenhall S, Sun L, Xie Z, Ono M, Koya K *PROC AM ASSOC CANCER RES* 2004 **45** Abs 2125
- 531833 **Pre-clinical toxicology evaluation of STA-4783 alone or combination with paclitaxel in rats, mice, and dogs.** Zhou D, McKeon ME, Dahl TA, Kitayama E, Tastuta N, Sun L, Ono M, Li L, Barsoum J, Mendenhall S, Koya K *PROC AM ASSOC CANCER RES* 2004 **45** Abs 2112
- 532818 **American Association for Cancer Research – 95th Annual Meeting (part X), Orlando, FL, USA** Kar S *IDDB MEETING REPORT* 2004 March 27-31
- 545546 **STA-4783, a novel HSP inducer, enhances paclitaxel activity. Preclinical to clinical modeling** Salgia R, Berkenblit A, Dezube B, Dahl TA, Koya K *PROC AM SOC CLIN ONCOL* 2004 **23** Abs 3124
- 572028 **Synta raises \$80 million.** Synta Pharmaceuticals Corp *PRESS RELEASE* 2004 November 22
- 601884 **Synta Pharmaceuticals presents preliminary data at ASCO for STA-4783 in patients with non-small cell lung cancer and soft tissue sarcoma.** Synta Pharmaceuticals Corp *PRESS RELEASE* 2005 May 17
- 604045 **STA-4783 in combination with paclitaxel induces heat shock protein 70 (hsp70) in a phase 1 trial.** Berkenblit A, Supko J, Ryan DP, Seiden MV, Nagai M, Bertin J, Dahl T, Dezube B, Eder JP *PROC AM SOC CLIN ONCOL* 2005 **24** Abs 2011
- 604046 **A phase 1/2 study of STA-4783 in combination with paclitaxel and carboplatin in chemo-naïve advanced non-small cell lung cancer (NSCLC).** Jacobs M, Weber R, Hainsworth J, Schwartzberg L, Strauss J, Tatsuta N, Du Z, McLeod M, Dahl T, Salgia R *PROC AM SOC CLIN ONCOL* 2005 **24** Abs 7106
- 604047 **Phase 1/2 study of STA-4783, a novel heat shock protein 70 (hsp70) inducer, in combination with paclitaxel in patients with soft tissue sarcomas (STS).** Sherman ML, Ryan C, Blackstein M, Mendelson D, Agarwala S, Dooley W, Dahl T, Demitri GD *PROC AM SOC CLIN ONCOL* 2005 **24** Abs 9069
- 614009 **A phase I study of STA-4783, an inducer of heat shock protein 70, combined with paclitaxel in patients with advanced solid tumors.** Berkenblit A, Supko JG, Eder JP, Proper J, Royer ES, Dahl TA, Dezube BJ *CLIN CANCER RES* 2003 **9** 16 Pt 2 6131S
- 636051 **A 2-stage, randomized, blinded phase 2 study of STA-4783 in combination with paclitaxel in patients with advanced metastatic melanoma** Powderly J, Khan K, Urba W, Richards JM, Hurwitz C, McLeod M, Dahl TA, Sherman MS *CLIN CANCER RES* 2005 **11** 23 suppl Abs C95
- 637030 **Results of a phase 2 study of STA-4783 in combination with paclitaxel and carboplatin in patients with previously untreated advanced non-small cell lung cancer (NSCLC)** Hainsworth J, Weber R, Jacobs M, Fehrenbacher L, Schwartzberg L, Kalman L, Mills G, Dooley W, McLeod M, Dahl TA, Sherman MS, Salgia R *CLIN CANCER RES* 2005 **11** 23 suppl Abs B112
- 637039 **Preliminary results of a phase 2 study of the novel heat shock protein 70 (hsp70) inducer STA-4783 in combination with paclitaxel in patients with soft tissue sarcomas.** Baker LH, Ryan C, Agarwala S, Cranmer L, Blackstein M, D'Amato G, Mendelson D, Hurwitz C, McLeod M, Dahl T, Sherman MS, Demetri G *CLIN CANCER RES* **11** 23 suppl Abs B108
- 642694 **Synta discontinues STA-5326 development for psoriasis.** Synta Pharmaceuticals Corp *PRESS RELEASE* 2005 December 23
- 652203 **Heat shock protein 72 on tumor cells: A recognition structure for natural killer cells.** Multhoff G, Botzler C, Jennen L, Schmidt J, Ellwart J, Issels R *J IMMUNOL* 1997 **158** 9 4341-4350
- 652205 **Effects of antineoplastic agents on cytoplasmic and membrane-bound heat shock protein 70 (Hsp70) levels.** Gehrman M, Pfister K, Hutzler P, Gastpar R, Margulis B, Multhoff G *BIOL CHEM* 2002 **383** 11 1715-1725
- 668389 **A stress-inducible 72-kDa heat-shock protein (HSP72) is expressed on the surface of human tumor cells, but not on normal cells.** Multhoff G, Botzler C, Wiesnet M, Muller E, Meier T, Wilmanns W, Issels RD *INT J CANCER* 1995 **61** 2 272-279
- 668428 **Product: STA-4783.** Synta Pharmaceuticals Corp *COMPANY WORLD WIDE WEB SITE* 2006 May 19 <http://www.syntapharma.com>
- 668520 **Update on tubulin-binding agents.** Attard G, Greystoke A, Kaye S, De Bono J *PATHOL BIOL* 2006 **54** 2 72-84
- 669306 **Heat shock protein 70 (Hsp70) stimulates proliferation and cytolytic activity of natural killer cells.** Multhoff G, Mizzen L, Winchester CC, Milner CM, Wenk S, Eissner G, Kampinga HH, Laumbacher B, Johnson J *EXP HEMATOL* 1999 **27** 11 1627-36
- 669313 **Mechanisms of Taxol resistance related to microtubules.** Orr GA, Verdier-Pinard P, McDaid H, Horwitz SB *ONCOGENE* 2003 **22** 47 7280-95