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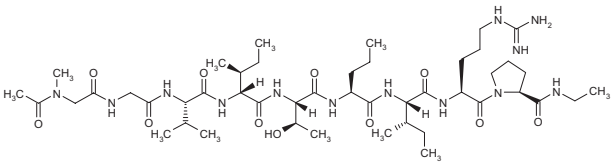
ABT-510

Oncolytic
Angiogenesis Inhibitor

N-Acetyl-*N*-methyl-glycyl-glycyl-L-valyl-D-alloisoleucyl-L-threonyl-L-norvalyl-L-isoleucyl-L-argininyl-L-proline *N*-ethylamide



$C_{46}H_{83}N_{13}O_{11}$
Mol wt: 994.2322

CAS: 251579-55-2

CAS: 251579-56-3 (as monotrifluoroacetate)

EN: 300354

Abstract

Thrombospondin-1 (TSP-1) is secreted by most epithelial cells and acts as a multifunctional inhibitor of angiogenesis. It has direct effects via CD36 on activated endothelial cells, inhibiting migration, inducing apoptosis and inhibiting growth factor mobilization/access to the cell surface; it may also downregulate cell survival pathways. Thus, TSP-1 significantly attenuates tumor progression and metastasis. Although TSP-1 appears to be a potentially effective anticancer agent, it is extremely large, not very abundant and exerts multiple actions, making its use in the clinic impractical. Researchers have therefore developed small peptide mimetics of TSP-1 for use as potent antiangiogenic agents in the treatment of malignancies. The first of two compounds in this novel class of antiangiogenic/proapoptotic agents is ABT-510. ABT-510 exhibited potent proapoptotic activity *in vitro* and suppressed neovascularization in preclinical models. Moreover, clinically, ABT-510 was very well tolerated and therapeutic benefits have been reported against several malignancies. ABT-510 has been or is being evaluated in phase II clinical trials for the treatment of head and neck cancer, non-small cell lung cancer, lymphoma, renal cell carcinoma and soft tissue sarcoma.

Synthesis

ABT-510 is prepared by solid-phase peptide synthesis using an automatic peptide synthesizer (1-3).

Introduction

The growth, invasion and metastasis of solid tumors are dependent on angiogenesis, and antiangiogenic therapy targeting the formation of new blood vessel capillaries in these tumors has become an attractive therapeutic strategy for the treatment of many malignancies, especially when combined with chemotherapy. The process of angiogenesis is regulated by a balance of proangiogenic factors such as vascular endothelial growth factor (VEGF) and endogenous antiangiogenic factors such as thrombospondins (TSPs). Tumors secrete several proangiogenic factors, including VEGF, basic fibroblast growth factor (bFGF) and platelet-derived growth factor (PDGF). These factors activate microvascular endothelial cells to proliferate, migrate and assemble into capillary structures. Moreover, activation of these cells results in the production of antiapoptotic cytokines, thus further ensuring malignant progression (4-8).

TSPs are an endogenous family of extracellular glycoproteins including 5 members that regulate tissue growth and remodeling. TSP-1 in particular is a large multifunctional inhibitor of angiogenesis that is secreted by most epithelial cells and is involved in perivascular matrix organization. TSP-1 exerts direct effects on endothelial cells through CD36 (one of many TSP-1 receptors) to antagonize all functions of activated cells, *i.e.*, migration, apoptosis and growth factor mobilization and access to the surface of endothelial cells. TSP-1/CD36 signaling to induce endothelial cell apoptosis is thought to require fyn, c-Jun *N*-terminal kinase-1 (JNK-1), caspase-3, CD95 (Fas ligand) and p38 mitogen-activated protein kinase (MAPK), and TSP-1 is also suspected of downregulating survival pathways. Hence, TSP-1 significantly attenuates tumor progression and metastasis. On the other hand,

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enhanced tumor growth and metastasis occur in the absence of TSP-1, and studies have shown that TSP-1 expression inversely correlates with lung and breast carcinoma and melanoma progression (9-15).

Theoretically therefore, TSP-1 appears to have the potential to be effective as part of anticancer therapy. Unfortunately, TSP-1 is extremely large, not very abundant and exerts multiple actions, and its direct use in the clinic would thus be impractical. Researchers have therefore focused on developing small peptide mimetics of TSP-1 for use as potent antiangiogenic agents in the treatment of malignancies. The heptapeptide *N*-Ac-Gly-Val-D-Ile-Thr-Arg-Ile-Arg-NHEt was identified as a structurally modified proteolytic fragment derived from the second type 1 repeat of TSP-1. However, although it possessed antiangiogenic activity, the half-life of the agent was too short. This peptide was further optimized, resulting in the design and synthesis of the first compounds in this novel class of angiogenesis inhibitors/apoptosis inducers: ABT-526 and ABT-510. ABT-510 in particular exhibited potent proapoptotic activity *in vitro* and suppressed neovascularization in preclinical models. ABT-510 was therefore chosen for further development as a treatment for malignancies (3, 16).

Pharmacological Actions

In competition binding studies performed *in vitro* using human microvascular endothelial cells (HMVEC), ABT-510 displayed saturable binding at 0.20-20 nM and could be concentration-dependently displaced by TSP-1. The K_d value for [^{3}H]-ABT-510 in saturation binding assays was 0.2 nM, which was similar to that of TSP-1. Results suggest that ABT-510 and TSP-1 share a common receptor. ABT-510 inhibited HMVEC migration and tube formation with IC_{50} values of 0.89 ± 0.029 and 5-10 nM, respectively, compared to 0.00035 ± 0.0003 and 0.017-0.021 nM for TSP-1, respectively. ABT-510 also significantly increased apoptosis of primary human umbilical arterial endothelial cells (HUAEC), with an apparent maximum increase of 75% observed. Concentrations of 0.1-100 nM resulted in apoptotic indices (*i.e.*, treated over control) ranging from 1.35 to 1.75 (3).

The antiangiogenic effects of ABT-510 were also demonstrated *in vivo*. ABT-510 (3, 10 and 30 mg/kg/day via s.c. osmotic pump for 7 days) effectively reduced neovascularization in the mouse Matrigel plug model (53% at 30 mg/kg/day). Moreover, ABT-510 (30, 60 and 90 mg/kg/day via s.c. osmotic pump for 2 weeks starting 3 days postinoculation) significantly inhibited tumor growth in the mouse Lewis lung carcinoma model at all doses and inhibited the growth of primary human bladder cancer cells implanted orthotopically in the bladder of immunodeficient mice. Continuous administration of the agent (10 mg/kg/day) decreased rapid flank growth of mouse hemangioma (b.END3) in nude mice by 50% at day 12 and both continuous administration (0.3 mg/kg/day) and bolus injection (3 mg/kg/day) reduced flank growth of implanted human breast tumors (MDA-MB-435) in nude mice by 50%; continuous administration (30 mg/kg/day) also reduced faster growing human breast tumors (MDA-435-LM) by 36% at day 31. Moreover, administration of ABT-510 (0.5 mg/kg s.c. b.i.d.) as monotherapy to pet dogs with different types of histologically confirmed and refractory cancers resulted in stabilization of disease in about 10% and tumor regressions in another 10% (3, 17-19).

The antiangiogenic/antitumor efficacy of ABT-510 (0.1-200 mg/kg/day via s.c. osmotic pump or s.c. bolus injection once or twice daily or every other day) was analyzed from results of experiments using 11 murine tumor models, including orthotopic bladder (253J B-V, EJ-1, HT-1376), flank lung (LX-1, NCI-H460), orthotopic breast (MDA-MB-435), flank breast (MDA-MB-435, MDA-435-LM) and flank colon carcinoma (HC-T15) and melanoma (B16F10), and the corneal micropocket assay. The mean E_{max} (*i.e.*, maximum effect) value for all models was 43% (ranging from 6% in the orthotopic 253J B-V bladder carcinoma model to 90% in the melanoma model). An E_{max} equation could be fitted to data from all models except the flank colon, flank lung and the HT-1376 bladder cancer models. The mean E_{50} (*i.e.*, time to half-maximal effect) value was 1.1 h (ranging from 0.4 h in the bladder 253J B-V model to 1.8 h in the orthotopic breast cancer model) (20).

The antitumor efficacy of ABT-510 was enhanced both *in vitro* and *in vivo* when combined with metronomic low-dose chemotherapy. CD95-dependent apoptosis of endothelial cells induced by ABT-510 was enhanced in the presence of perfosfamide and cisplatin. The ED_{50} of ABT-510 was reduced from approximately 30 nmol/l to about 1 and 3 nmol/l, respectively. In the mouse Matrigel plug model, the slight but significant reduction (1.2-fold) in microvascular density observed with ABT-510 alone (1 mg/kg) was markedly and significantly enhanced in the presence of 2 and 20 mg/kg cyclophosphamide (3.7- and 2.3-fold, respectively) or 4 mg/kg cisplatin (2.8-fold). ABT-510 and cyclophosphamide showed synergy in the syngeneic murine Lewis lung carcinoma model, whereas a combination of ABT-510 and cisplatin resulted in additive effects. Synergy between ABT-510 and cyclophosphamide was also observed in a murine prostate cancer xenograft model. The ABT-510 (240 mg/kg b.i.d.)-induced delay in prostate carcinoma PC-3 tumor growth in nude mice was significantly enhanced in the presence of 1 or 20 mg/kg cyclophosphamide (60% or greater *vs.* approximately 30%) and established tumors were stabilized with combination treatment (21).

Other studies using HMVECs *in vitro* and tumor xenograft models showed that peroxisome proliferator-activated receptor-γ (PPAR-γ) ligands also synergistically enhanced the antiangiogenic and antitumor activity of ABT-510. 15-Deoxy-$\Delta^{12,14}$-prostaglandin J_2 (15d-PGJ_2), troglitazone and rosiglitazone were shown to increase PPAR-γ and CD36 expression in HMVECs and to enhance bFGF-induced HMVEC migration by ABT-510; for example, the ED_{50} value for ABT-510 alone was approximately 10 nM compared to 0.03 nM in the presence of 15d-PGJ2. Similarly, the combination of rosiglita-

zone with a noninhibitory concentration of ABT-510 markedly inhibited HMVEC proliferation by > 75%. Synergistic activity was also observed in the murine Matrigel plug assay *in vivo*, where ABT-510 (1 mg/kg/day)- and rosiglitazone (50 mg/kg/day)-induced reductions in neovascularization were increased with combination treatment (from 39% and 45%, respectively, to approximately 80%). Moreover, troglitazone and 15d-PGJ_2 improved the antitumor activity of ABT-510 in mice bearing TSP-1-negative bladder carcinoma (253J B-V) xenografts. Systemic treatment with ABT-510 (1 mg/kg/day) or troglitazone (50 mg/kg/day) resulted in a 32% and 31% reduction in tumor volume, respectively. In contrast, combination treatment resulted in a 74% reduction in tumor growth; 15d-PGJ_2 also enhanced the antitumor effects of ABT-510 in this model (22).

Pharmacokinetics and Metabolism

The pharmacokinetics of ABT-510 (4.5 mg/kg i.v.) were determined in rats, mice, dogs and monkeys. AUC values obtained for the respective species were 5.3, 1.47, 19.27 and 14.77 μg.h/ml and $t_{1/2}$ values were 0.20, 0.15, 0.80 and 1.20 h; clearance values were 0.86, 3.06, 0.23 and 0.35 l/h/kg, respectively (3).

The absorption, metabolism and excretion of [^{14}C]-ABT-510 (50 mg ABT-510 + 100 μCi) given as a single s.c. bolus injection were determined in 6 healthy male subjects. The agent was well tolerated and rapidly absorbed, with peak plasma levels of total radioactivity observed 1 h postdosing; levels rapidly declined thereafter ($t_{1/2}$ = 1.9 h), such that ABT-510 could not be detected 24 h postdosing. Similar results were obtained for whole-blood radioactivity. However, the whole-blood to plasma ratio obtained (0.6%) strongly indicated that the plasma fraction accounted for most of the total radioactivity. ABT-510 appeared to be completely metabolized by hydrolysis and was excreted renally. The mean recovery of radioactivity was 99% at 96 h postdosing, with the majority found in urine (85% recovered over 96 h). A small amount (13%) of the radioactivity was recovered in feces, indicating some involvement of biliary excretion or secretion across the intestinal wall. The major metabolite detected in urine was the 5-amino cleavage product M1, which accounted for 84% of the total radioactivity. Another metabolite (M2) and intact ABT-510 accounted for only 0.3% of the total radioactivity. M1 and unknown metabolites accounted for 7% and 8%, respectively, of the radioactivity detected in feces (23).

The pharmacokinetics, safety and tolerability of single escalating doses of ABT-510 (10, 50, 75, 100 or 130 mg by s.c. bolus, 100 mg by 24-h s.c. infusion, or 10, 50 or 100 mg by 30-min i.v. infusion; treatment cycle = 28 days) were determined in 43 healthy male subjects participating in a double-blind, placebo-controlled study. The agent was well tolerated, with only mild and transient adverse events reported. Dose-proportional pharmacokinetics were obtained for both s.c. and i.v. dosing. Intersubject variability was low. C_{max} values for the s.c. bolus doses were 240 ± 96, 869 ± 89, 1254 ± 229, 1675 ± 420 and 2574 ± 757 ng/ml, respectively, and AUC values were 369 ± 66, 1988 ± 238, 2920 ± 417, 3798 ± 624 and 3875 ± 698 ng.h/ml, respectively; $t_{1/2}$ values ranged from 0.8 to 1.2 h. Subcutaneous doses were completely bioavailable. Clearance, volume of distribution and $t_{1/2}$ values following i.v. dosing were 35 ± 8 l/h, 44 ± 9 l and 0.9 ± 0.1 h, respectively. The mean steady-state concentration achieved with the s.c. infusion was 150 ng/ml. Plasma M1 exposure was 50% greater than the intact agent and about 78% of the dose was recovered as M1 in urine (24).

Clinical Studies

The safety, pharmacokinetics and efficacy of ABT-510 (100 mg by 24-h continuous infusion, 100, 200 and 260 mg once daily by s.c. bolus or 50 and 100 mg b.i.d. by s.c. bolus) were examined in a phase I trial in 39 patients with advanced cancer. A total of 144 treatment cycles were administered. The most common toxicities were mild to moderate injection-site reactions and fatigue. Painful skin infiltration at the injection site led to discontinuation of the continuous infusion. Although the maximum tolerated dose (MTD) was not found, the maximum clinically practical dose was identified as 260 mg. ABT-510 was rapidly absorbed. The pharmacokinetics obtained were linear and time-dependent across all doses. Steady-state ABT-510 and M1 concentrations of 242 ± 19 and 273 ± 66 ng/ml, respectively, were achieved on day 22 with the continuous infusion regimen. Following s.c. bolus injections, t_{max} and apparent clearance, apparent volume of distribution and $t_{1/2}$ values obtained for ABT-510 for all dosing regimens were 0.7 ± 0.3 h, 22.5 ± 6.5 l/h, 36.8 ± 10.8 l and 1.1 ± 0.2 h, respectively; values were similar across days 1 and 22. No accumulation was observed with once- or twice-daily dosing. The overall mean $t_{1/2}$ for M1 following s.c. bolus dosing was 2.9 h for all doses and on days 1 and 22. An average of 58 ± 19% and about 1% of the ABT-510 dose was recovered in urine as M1 and the intact compound, respectively. Median serum bFGF was significantly reduced from 14.1 pg/ml at baseline to 3.2 pg/ml after 56 days of treatment. Six patients experienced stable disease lasting for 6 cycles or more (25-27). The results from this and the following studies are summarized in Table I.

ABT-510 (50 or 100 mg b.i.d. s.c. starting on day 2) was combined with gemcitabine (1250 mg/m^2 on days 1 and 8) and cisplatin (80 mg/m^2 on day 1) every 3 weeks in an extension study in 13 patients with advanced solid tumors who had participated in the above study. The most common adverse events reported were consistent with the toxicity profile for gemcitabine/cisplatin in the absence of ABT-510. After 15 days of combination treatment, 1 case of hemoptysis possibly related to treatment developed in a patient with non-small cell lung cancer (NSCLC). No drug interactions were observed for gemcitabine and its dFdU metabolite and ABT-510. Of the 12 evaluable patients, 2 partial responses were obtained in a patient with melanoma and another with NSCLC (28).

Table I: Clinical studies of ABT-510 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Cancer	Open	ABT-510, 100 mg s.c. over 24 h (n=4) ABT-510, 100 mg s.c. o.d. (n=6) ABT-510, 200 mg s.c. o.d. (n=7) ABT-510, 260 mg s.c. o.d. (n=6) ABT-510, 50 mg s.c. b.i.d. (n=6) ABT-510, 100 mg s.c. b.i.d. (n=10)	39	Subcutaneous ABT-510 was well tolerated and showed efficacy in stabilizing disease in patients with advanced solid tumors	25-27
Cancer	Open	ABT-510, 50 mg s.c. b.i.d. on d 2-21 + Gemcitabine, 1250 mg/m2 i.v. on d 1 & 8 + Cisplatin, 80 mg/m2 i.v. on d 1 1x/3 wks (n=7) ABT-510, 100 mg s.c. b.i.d. on d 2-21 + Gemcitabine, 1250 mg/m2 i.v. on d 1 & 8 + Cisplatin, 80 mg/m2 i.v. on d 1 1x/3 wks (n=6)	13	A regimen combining ABT-510, gemcitabine and cisplatin was well tolerated and induced a partial response in 2 of 12 evaluable patients with advanced solid tumors	28
Cancer	Open	ABT-510, 20 mg s.c. o.d. (n=6) ABT-510, 10 mg s.c. b.i.d. (n=6) ABT-510, 50 mg s.c. o.d. (n=6) ABT-510, 25 mg s.c. b.i.d. (n=6) ABT-510, 100 mg s.c. o.d. (n=6) ABT-510, 50 mg s.c. b.i.d. (n=6)	36	ABT-510 showed evidence of antitumor activity in patients with cancer. No significant toxicity was found when the drug was given at doses of 20-100 mg/day	29
Cancer, kidney (renal cell carcinoma)	Randomized	ABT-510, 10 mg s.c. b.i.d. ABT-510, 100 mg s.c. b.i.d.	103	ABT-510 was well tolerated and resulted in a 6-month progression-free rate of 24.6% in patients with advanced renal cell carcinoma	30
Cancer, soft tissue	Randomized	ABT-510, 20 mg s.c. o.d. ABT-510, 100 mg s.c. b.i.d.		ABT-510 showed a very good safety profile and resulted in a 6-month progression-free rate of 34-35% in patients with advanced soft tissue sarcoma	31

The safety and efficacy of ABT-510 administered as an s.c. bolus (20, 50 or 100 mg/day once or twice daily) were demonstrated in a randomized, open-label phase IB trial in 36 patients with advanced cancer (baseline ECOG performance score [PS] = 0 or 1; cancer types = colorectal, sarcoma, breast, lung, melanoma and other). The majority (90%) of adverse events reported were grade 1 or 2, and the most frequent adverse events possibly related to ABT-510 included injection-site reactions (70%), asthenia (33%), headache (15%) and nausea (11%). Two cases of grade 3 nausea were reported in addition to 1 case each of dyspnea, bone pain, constipation, vomiting, chills and tremors, which were considered possibly ABT-510-related. C_{max} and AUC values from 20 patients were linear and proportional to dose. No accumulation of ABT-510 was detected and plasma concentrations of 100 ng/ml or greater were observed for over 3 h/day. Thirty-four patients were evaluable for response. A partial response was obtained in a patient with soft tissue sarcoma receiving 20 mg once daily. Stable disease was achieved in 14 and 5 patients at week 8 and 16, respectively, and prolonged stable disease (> 24 weeks) was obtained in 1 patient with NSCLC (50 mg once daily) and 1 patient with soft tissue sarcoma (10 mg b.i.d.) (29).

A randomized phase II study was conducted in patients with previously untreated advanced renal cell carcinoma (baseline ECOG PS = 0 or 1) to determine the efficacy of ABT-510 (10 or 100 mg b.i.d. s.c.). Of the 103 patients enrolled, 42 remained active at the time of reporting and preliminary data were obtained from 88. Treatment was well tolerated. A total of 314 adverse events were reported, of which 32 were serious; 7 serious adverse events were possibly or probably related to ABT-510 and included 2 bleeding events (hemoptysis, gastrointestinal hemorrhage) and 1 case of deep vein thrombosis. Other serious adverse events possibly or probably related to the agent were dehydration, cardiogenic pulmonary edema, cardiomyopathy and gastrointestinal ulcer. However, the most frequent adverse events were injection-site reactions, asthenia and pain. The 6-month progression-free rate was 24.6%, with 1 confirmed partial response. ABT-510 was concluded to provide no real improvement when compared to historical controls. However, due to its excellent safety profile, examination of ABT-510 in combination with other antiangiogenic or targeted agents was recommended (30).

The efficacy and safety of ABT-510 (20 mg once daily or 100 mg b.i.d. s.c.) were demonstrated in a randomized phase II study conducted in 88 patients with locally advanced or metastatic soft tissue sarcoma (baseline ECOG PS = 0 or 1). Nineteen patients were still active at the time of reporting. Treatment was very well tolerated. The most common adverse event was injection-site reaction. Analysis of circulating endothelial cells (CECs) at baseline, 4 weeks and then every 8 weeks revealed a possible correlation between CEC concentration and duration of therapy. Preliminary data from 57 previously treated and 25 previously untreated patients indicated 6-

month progression-free rates of 34.4% and 35%, respectively. No confirmed partial responses were reported. However, the progression-free rate exceeded the rate reported for other agents in soft tissue sarcoma by 14%. From these results, it was suggested that ABT-510 continue to undergo evaluation as a treatment for soft tissue sarcoma as monotherapy or in combination with other agents (31).

ABT-510 was granted orphan drug designation by the FDA for soft tissue sarcoma and is presently undergoing phase II development as a potential treatment for various cancers, including head and neck cancer, NSCLC, lymphoma, renal cell carcinoma and soft tissue sarcoma (32-38).

Source

Abbott Laboratories (US).

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