

## **Antiangiogenic Thrombospondin-I peptides result in regression of naturally occurring cancers in pet dogs.**

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Thrombospondin-1 (TSP-1) is a natural antiangiogenic protein that enhances apoptosis in activated endothelial cells (EC). D-amino acid substituted peptides within the TSP-1(Mal II) sequence inhibit EC function. A related antiangiogenic nonapeptide (ABT526) was found to slow tumor growth in syngeneic and xenograft mouse models. To examine the safety and efficacy of ABT526 antiangiogenic therapy a prospective pre-clinical trial in pet dogs with naturally occurring cancers was undertaken. Eligible cases had histologically confirmed measurable cancers, no cancer therapy within 21 days and no concurrent cancer therapy. The first 26 cases received 12.5 mg BID, SC; subsequent cases received 0.5 mg/kg BID, SC. Treatment was continued until significant progressive disease (SPD). Endpoints included adverse effects, significant disease stabilization and objective responses (PR >50%; CR 100% response) in measurable lesions. Seventy-four cases (carcinomas, lymphomas, sarcomas and others) were entered for study. Over 95% had failed conventional treatments prior to ABT526 monotherapy. Fifty-six dogs received at least 30 days of therapy before SPD (evaluable cases). Treatment was not associated with observable toxicity in any animal, and no disturbance of wound healing was seen in four cases requiring surgery. Unexpected disease stabilization and objective responses were seen in 11/56 and 8/56 evaluable cases, respectively. Relapse after durable objective responses were seen in 8/8 cases.

### Objective responders with ABT526 antiangiogenic therapy

<b>Histology</b>	<b>Clinical Stage</b>	<b>Response</b>
Nasal Carcinoma	T3bN0M0	CR
Cutaneous Lymphoma	Generalized	CR
Nasal Carcinoma	T3bN1M0	PR
NH Lymphoma	IIIb	PR
Soft Tissue Sarcoma	T2bN2N3bM1(lung)	PR
Cutaneous Lymphoma	Generalized	PR
GI adenocarcinoma	TsxN2N1M0	PR
NH Lymphoma	IIIa	PR

Results suggest that ABT526 therapy is well-tolerated, effective, and associated with regression of measurable lesions in naturally occurring cancers. A randomized trial of ABT-526 plus chemotherapy versus chemotherapy alone in canine NH lymphoma is underway.

Objective responders with ABT526 antiangiogenic therapy include (Histology-Clinical Stage-Response): Nasal Carcinoma-T3bN0M0-CR; Cutaneous Lymphoma-Generalized-CR; Nasal Carcinoma-T3bN1M0-PR; NH Lymphoma-IIIb-PR; Soft Tissue

Sarcoma-T2bN2N3bM1(lung)-PR; Cutaneous Lymphoma-Generalized-PR; GI-adenocarcinoma-TsxN2N1M0-PR; NH Lymphoma-IIIa-PR.