

**A randomized placebo-controlled clinical trial of the anti-angiogenic thrombospondin-mimetic peptide ABT-526 plus Lomustine chemotherapy versus Lomustine chemotherapy alone in pet dogs with relapsed non-Hodgkin's lymphoma.**

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Background:

Thrombospondin-1 (TSP-1) is a natural antiangiogenic protein that enhances apoptosis of activated endothelial cells (EC). A modified nonapeptide from thrombospondin-1, ABT-526, has been found to be active in mouse cancer models and in dogs with naturally occurring cancers.

Methods:

To assess the safety and efficacy of ABT-526 when given in combination with Lomustine chemotherapy, 94 pet dogs with naturally occurring non-Hodgkin's lymphoma (NHL), in their first relapse, were entered to a prospective randomized placebo controlled double-blinded clinical trial. Dogs were randomly assigned to receive ABT-526 plus Lomustine versus placebo plus Lomustine. Response rate, duration of response, time to progression, and incidence of toxicoses were compared between groups.

Results:

No significant ABT-526 specific toxicities were seen. Lomustine associated dose-limiting toxicities, including neutropenia, thrombocytopenia, gastroenteritis, and elevated alanine transaminase, were similar between treatment groups. No significant difference in the objective response rate was seen between treatment groups [ABT-526+Lomustine = 23/49 (47%) vs placebo+Lomustine = 23/37 (62%);  $P>0.25$ ]. However, the median response duration was significantly greater in patients receiving ABT-526 plus Lomustine compared to placebo plus Lomustine (35 days vs 15 days;  $P=0.05$ ). The time to progression for responding cases was also significantly greater in patients receiving ABT-526 plus Lomustine compared to placebo plus Lomustine (41 days vs 21 days;  $P=0.047$ ).

Conclusions:

The significant activity of ABT-526 demonstrated in this preclinical trial appears to be associated with the maintenance of Lomustine induced treatment responses. Further studies of ABT-526, in this relevant naturally occurring model of NHL, are warranted and may be used to define biomarkers that predict responsiveness to antiangiogenic therapy and evaluate the activity of ABT-526 in combination with conventional and novel treatment agents.