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## Bevacizumab as an anti-VEGF strategy in lymphoma

Bevacizumab is a monoclonal antibody directed against vascular endothelial growth factor (VEGF), a potent inducer of angiogenesis that stimulates endothelial cell proliferation and increases microvessel permeability. The role of angiogenesis has been less clear in lymphoma than in solid tumors, in part related to the heterogeneity of disease and technical issues. In addition to VEGF effects on angiogenesis and the integrity of tumor vasculature, autocrine VEGF-receptor (VEGF-R)-mediated signaling may play a role in lymphoma. Microvessel density, a measure of angiogenesis, is highest in peripheral T-cell lymphomas (PTCL), followed by diffuse large B-cell (DLBCL) and intra-follicular follicular lymphoma (FL). Bevacizumab had minimal single agent activity in recurrent DLBCL despite expression of VEGF and VEGF-R, but was found to be safe in combination with R-CHOP in a small feasibility trial. Phase 2 and 3 trials with the RB-CHOP combination are ongoing. Of interest, combined VEGF and VEGF-R expression was associated with a favorable prognosis in

DLBCL, suggesting an autocrine survival or proliferation pathway susceptible to chemotherapy. Although supportive of an anti-VEGF strategy, these data are also compatible with an internal loop that requires a permeable small molecule inhibitor of VEGF-R rather than a recombinant protein acting as an extracellular VEGF sink. Based on strong preclinical data and case reports of the efficacy of bevacizumab in angioimmunoblastic lymphoma, a phase 2 trial of bevacizumab-CHOP is in progress in PTCL. Data in FL related to angiogenesis are unclear. Two groups have reported less favorable FL outcome, including a higher risk of FL transformation to DLBCL in cases with higher vessel density. In another study increased vascularity was favorable, although this may relate to the use of interferon, which can inhibit angiogenesis. In conclusion, based on multiple lines of support, ongoing clinical trials employing bevacizumab will inform on the impact of this treatment in subsets of lymphoma. Biologic correlates will be critical to the interpretation of these studies.