PM-04. IN SILICO ANALYSIS OF AVAglio AND RTOG 0825 PHASE III CLINICAL TRIALS SUGGESTS SIGNATURES OF PATIENTS TO RECEIVE BENEFIT FROM COMBINED BEVACIZUMAB AND RADIATION THERAPIES

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Despite the growing interest in anti-angiogenic therapies for glioblastoma (GBM), no statistically significant evidence has been found to indicate that bevacizumab in combination with other therapies increases the overall survival of glioblastoma patients. Most recently two phase III trials, AVAglio and RTOG 0825, were concluded considering bevacizumab in the upfront setting in combination with radiation and chemotherapy. Although the aggregate results of these Phase III studies were disappointing, there remains an open question of the potential benefits of this combination therapy for predictable subpopulations of patients. We utilize a mathematical model of GBM growth which incorporates vascular density, hypoxia and necrosis to investigate differential benefits of combination therapy consisting of surgical resection, radiation and bevacizumab. Proliferation and migration rates of the simulated tumors were varied across known growth dynamics observed in human GBMs. The model assumes that the anti-angiogenic therapy normalizes vasculature and thus decreases hypoxia. We assess the differential hypoxic burden left after a gross total resection along with the change in radiation cell kill from re-normalization of the tissue due to treatment with bevacizumab. We found that hypoxic burden and the resulting change in radiation induced cell kill varied dramatically across a range of tumor growth kinetics. Under the assumption of vasculature renormalization leading to decreased hypoxia, we determined that patients undergoing a gross total resection, which is the case for about 50% of the patients enrolled in the AVAglio and RTOG 0825 Phase III trials, would not likely benefit from combination therapy because the majority of the hypoxic burden would have been surgically removed. For patients not undergoing a gross total resection, our results indicate that there is a subpopulation of patients, those with large tumors and high proliferation rates, who would have a dramatic change in the total radiation cell kill when combined with anti-angiogenic therapy.