The Role of a More Invasive Phenotype in Response to MAPK-Directed Therapies in Thyroid Cancer. HM Hicks (Ph.D., GS), VL Espinoza, N Pozdeyev, RE Schweppe, School of Medicine, University of Colorado Anschutz Medical Campus, Aurora, CO.

Advanced papillary thyroid cancer (PTC) and anaplastic thyroid cancer (ATC) are the leading causes of endocrine cancer death. Mutations in the MAP kinase (MAPK) pathway are common in PTC and ATC, especially in *BRAF*. However, therapies targeting the MAPK pathway are not approved for PTC patients, and despite the approved combination of BRAF and MEK inhibition to treat *BRAF*-mutant ATC, these patients often progress. An emerging mechanism of resistance to targeted therapies is an invasive phenotype switch in which cells transition from a proliferative, therapy sensitive population to an invasive, therapy resistant population. Using Matrigel Chamber Invasion assays, we showed that *BRAF*-mutant PTC and ATC cells resistant to BRAFi exhibit an increase in invasion when treated with BRAFi while sensitive cells do not. We further identified an increase in the levels and secretion of fibronectin (FN1) in response to BRAFi treatment in resistant cells. Treatment with either FN1 or conditioned media from BRAFi-treated resistant cells phenocopies BRAFi-treatment by also increasing invasion. However, depletion of FN1 blocks this response. Interestingly, ERK inhibition also mitigates the invasiveness observed in response to BRAFi or FN1 in resistant cells. We further observed that dual BRAF and ERK inhibition slows tumor growth *in vivo* in a BRAFi-resistant patient-derived xenograft model. These data indicate that thyroid cancer cells resistant to BRAF inhibition exhibit a more invasive phenotype characterized by increased FN1 and a pro-invasive secretome. Further, dual inhibition of BRAF and ERK ablates BRAFi-induced invasion and slows tumor growth *in vivo,* providing a potential therapeutic strategy for *BRAF*-mutant thyroid cancer patients.