In patients with HER2+ breast cancer, metastasis to the brain is a major clinical challenge. To discover targeted therapies, Ni, Ramkissoon, Xie, and colleagues developed orthotopic patient-derived xenografts (PDX) of HER2+ breast cancer brain metastases (BCBM) from 5 patients with BCBMs. An initial PDX exhibited resistance to the HER2 inhibitor lapatinib, and PTEN loss, which occurs in many BCBMs and is expected to activate PI3K signaling. However, there was no response to lapatinib plus the PI3K inhibitor BKM120. Akt and mTOR are downstream of PI3K, and although BKM120 plus lapatinib reduced AKT phosphorylation, phosphorylation of the mTOR effector S6RP was unchanged. In breast cancer, mTOR activity has been shown to mediate PI3K inhibitor resistance, which can be overcome by mTORC1 inhibition. However, it is not known if mTORC1 inhibition is effective in brain metastases, which are often refractory to systemic treatment. Combined inhibition of PI3K with BKM120 and mTORC1 with RAD001 resulted in tumor regression, whereas the single agents had little effect. Combination therapy with BKM120 and RAD001 induced durable tumor regression in 3 of 5 PDXs, with mice remaining healthy after treatment cessation. While single-agent therapy with BKM120 or RAD001 reduced mTORC1 signaling, combined therapy completely inhibited mTORC1 and also reduced proliferation and enhanced apoptosis. Transcriptome analysis of BCBMs from mice showed that responding tumors exhibited increased expression of AKT/mTORC1-dependent genes. Moreover, whereas the responding BCBMs had a nonsynonymous somatic mutation rate of approximately 7–8 per Mb, nonresponding BCBMs exhibited approximately 60–70 mutations per Mb, including mutations in multiple DNA-repair genes. This suggests that hypermutated genomes and genomic instability promoted resistance. Altogether, these findings suggest clinical evaluation of BKM120 and RAD001, a combination already under clinical investigation in solid tumors, is warranted in patients with HER2+ BCBMs. Further, this study demonstrates the utility of brain metastasis PDX models for identification of targeted therapies.

Clinical Trials

Immune checkpoint blockade with anti-PD-1 antibodies including nivolumab and pembrolizumab has achieved durable response in patients with solid tumors and Hodgkin lymphoma. However, nivolumab has not yet been tested across hematologic malignancies that express PD-1/PD-L1. Lesokhin and colleagues performed a phase I, open-label, cohort-expansion study to determine the safety and efficacy of nivolumab in B-cell lymphoma, T-cell lymphoma, and multiple myeloma. A total of 81 patients with refractory or relapsed lymphoma were enrolled: 10 with follicular lymphoma, 11 with diffuse large B-cell lymphoma, 10 with other B-cell lymphomas, 13 with mycosis fungoides, 5 with peripheral T-cell lymphoma, 5 with other T-cell lymphomas, and 27 with multiple myeloma. The primary objective was to evaluate safety, and secondary objectives included evaluation of antitumor activity. Objective responses were achieved in 40% of patients with follicular lymphoma, 36% of patients with diffuse large B-cell lymphoma, 15% of patients with mycosis fungoides, and 40% of patients with peripheral T-cell lymphoma. Response durations ranged from 6 weeks to more than 81 weeks. A total of 4 complete responses were observed, 2 in patients with diffuse large B-cell lymphoma, 1 in a patient with follicular lymphoma, and 1 in a patient with multiple myeloma after radiotherapy. However, responses were not observed in other patients with multiple myeloma. Nivolumab was well tolerated; 65% of patients experienced drug-related adverse events, which were largely grade 1 or 2, although 15% of patients discontinued treatment due to drug-related adverse events. One patient with small lymphocytic B-cell lymphoma died of pneumonitis. Taken together, the results of this study indicate that nivolumab has a favorable safety profile and antitumor activity in non-Hodgkin lymphoma, and prompted continued evaluation of nivolumab in relapsed or refractory follicular lymphoma and diffuse large B-cell lymphoma in ongoing phase II trials.

Dual PI3K/mTORC1 Targeting Suppresses HER2+ Brain Metastasis Xenografts

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