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Response to Idelalisib in a Patient with Stage IV Merkel-Cell Carcinoma

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To the Editor

Metastatic Merkel-cell carcinoma is often lethal, and there is no effective treatment.¹ Activation of phosphoinositide 3-kinase (PI3K) in Merkel-cell carcinoma is independent of the presence of the Merkel-cell polyomavirus.^{2,3} Idelalisib, a selective PI3K δ inhibitor, has shown remarkable therapeutic efficacy in B-cell hematologic cancers.⁴ Here, we report a complete clinical response induced by idelalisib in a patient with stage IV Merkel-cell carcinoma.

The patient was an 86-year-old white woman with stage IIIB Merkel-cell carcinoma of the right temple that was diagnosed in 2013 and recurred in 2014. She underwent surgery and received radiation therapy in May 2013, and she underwent additional surgery in July 2014. At that time, genomic profiling revealed multiple mutations, including a *PIK3CA* mutation (c.1412C→T). In November 2014, positron-emission tomography and computed tomography (PET-CT) showed a liver lesion (Fig. 1A), and metastatic disease was further confirmed by means of a liver biopsy. The patient was deemed to be a poor candidate for chemotherapy, and she underwent palliative hypofractionated radiation therapy in December 2014.

Previously, we had established a primary Merkel-cell carcinoma cell line derived from tumors in the patient's lymph nodes. Activation of the PI3K pathway was detected both in Merkel-cell polyomavirus-negative tumor tissues and in tumor cells (data not shown). A real-time polymerase-chain-reaction analysis was performed, and the tumor cells showed high expression of PI3K δ (Fig. 1C). On the basis of these laboratory findings, treatment with a standard dose of idelalisib (150 mg twice daily) was initiated on February 6, 2015. One week after the initiation of idelalisib, shrinkage of the liver lesion was visible on PET-CT. Repeat PET-CT performed 3 months later did not show tumor in her liver, suggesting a complete clinical response to idelalisib (Fig. 1B). The patient did not have substantial side effects. She died from congestive heart failure after being hospitalized for pneumonia. At the time of her death, she had no evidence of disease recurrence.

Aberrant activation of the PI3K pathway may be a potential therapeutic target in Merkel-cell carcinoma. Idelalisib is a novel PI3K pathway inhibitor approved by the Food and Drug

Administration for application in B-cell lymphoma. Recent studies suggest that inhibition of PI3K δ not only perturbs B-cell signaling but also shifts the balance from immune tolerance toward effective antitumor immunity by suppressing regulatory T cells and unleashing cytotoxic T cells; this provides a rationale for the evaluation of PI3K δ inhibitors in solid tumors.⁵ Although the cause of high expression of PI3K δ in Merkel-cell carcinoma is unclear, the efficacy of idelalisib in our patient provides initial clinical evidence that the targeting of PI3K δ in Merkel-cell carcinoma is warranted.

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Figure 1. Radiologic Images of the Patient's Liver and Phosphoinositide 3-Kinase (PI3K) Expression in the Patient's Tumor Cells

Positron-emission tomography and computed tomography (PET-CT) show the patient's liver before (Panel A) and after (Panel B) administration of idelalisib. The arrowhead in Panel A shows the liver lesion. Higher expression of PI3K δ (Panel C) relative to other PI3K isoforms was detected in the patient's tumor cells ($P < 0.001$ for all comparisons). The expression of target genes was normalized to housekeeping gene mitochondrial ribosomal protein S2 (*MRPS2*) messenger RNA (mRNA) to determine relative expression. The T bars indicate standard errors.