thal et al. cite also states that CMS payments to participating clinics totaled $20 per beneficiary per month.[2] Similarly, bonus payments from CMS to MSSP ACOs raised Medicare spending by 0.7% in the program's first year, while the ACOs saved Medicare 0.5%, for a net increase in spending of 0.2%.[3]

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: We do not claim overall savings in the three Medicare experiments Marmor and Sullivan reference but rather note savings in comparison with control populations — namely, fee-for-service Medicare beneficiaries. We also note that the cost results are early and modest.

The CMS Office of the Actuary report that Marmor and Sullivan cite reiterates that both the Pioneer ACO program and the MSSP have been shown to produce savings relative to fee-for-service Medicare and that an expansion of the Pioneer ACO program would lead to an overall reduction in Medicare costs.[1] Similarly, although we do not reference the fee of $20 per member per month paid by CMS to the practices that are participating in the Comprehensive Primary Care Initiative in the main text of our article, we clearly state in the Supplementary Appendix, available with the full text of the article at NEJM.org, that the $14 reduction in monthly Medicare expenditures per beneficiary is not enough to yield overall net savings for CMS.

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Since publication of their article, the authors report no further potential conflict of interest.

1. Office of the Actuary, Centers for Medicare and Medicaid Services. Certification of Pioneer Model savings. April 10, 2015 (https://www.cms.gov/Research-Statistics-Data-and-Systems/Research/ActuarialStudies/Downloads/Pioneer-Certification-2015-04-10.pdf).

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

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 PI3Kδ 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

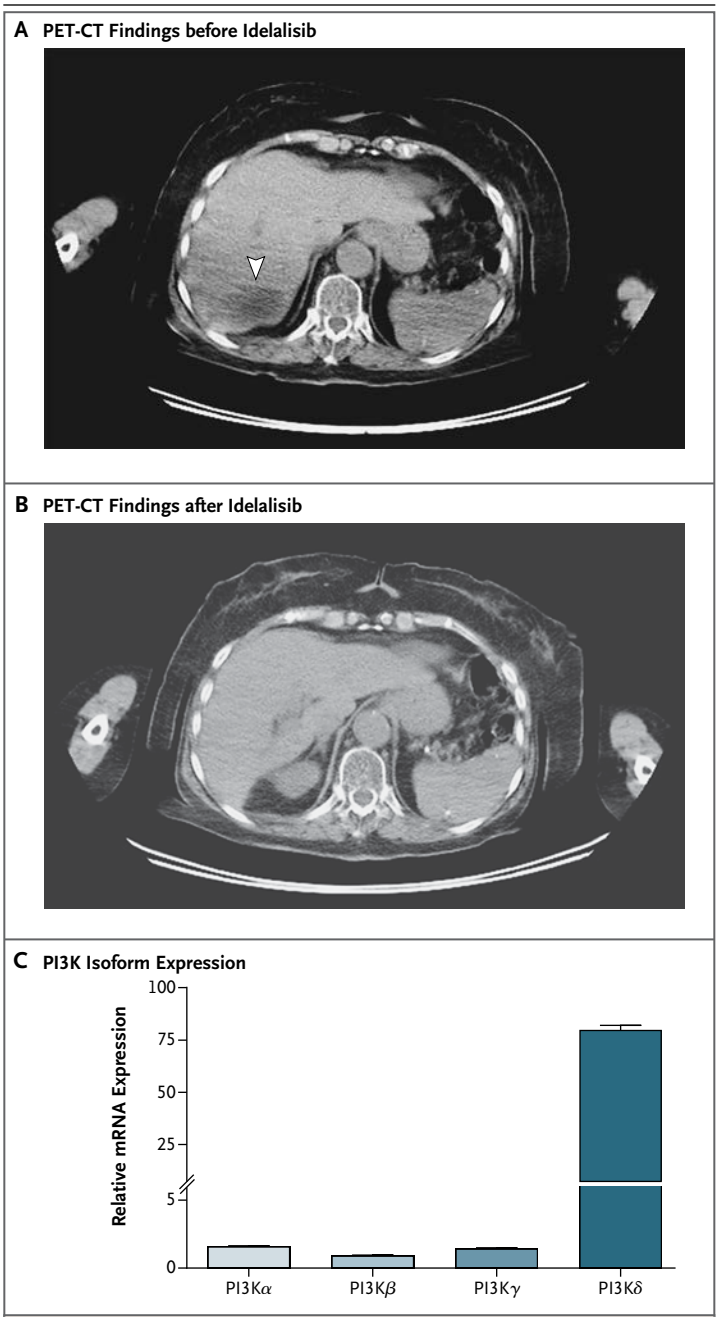

Figure 1. Radiologic Images of the Patient's Liver and Phosphoinositide 3-Kinase (PI3K) Expression in the Patient's Tumor Cells.

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 PI3Kδ (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.

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 PI3Kδ (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 PI3Kδ 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 PI3Kδ inhibitors in solid tumors.[5] Although the cause of high expression of PI3Kδ in Merkel-cell carcinoma is unclear, the efficacy of idelalisib in our patient provides initial clinical evidence that the targeting of PI3Kδ in Merkel-cell carcinoma is warranted.

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Disclosure forms provided by the authors are available with the full text of this letter at NEJM.org.

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CORRECTIONS

First-Line Crizotinib versus Chemotherapy in ALK-Positive Lung Cancer (December 4, 2014;371:2167-77). In the final paragraph of the "Efficacy" subsection of Results (page 2172), the first sentence should have read, "Among patients randomly assigned to crizotinib, 65 of 89 patients with progressive disease (73%) continued to receive crizotinib beyond disease progression for a median of 3.1 months (range, 0.7 to 22.6)," rather than ". . . 74 of 89 patients . . . (83%) . . . for a median of 3.0 months. . . ." In the final paragraph of the "Patient-Reported Outcomes" subsection of Results (page 2174), the penultimate sentence should have ended, " . . . (hazard ratio for worsening of symptoms with crizotinib, 0.59; 95% CI, 0.45 to 0.77; P<0.001 . . .) . . . ," rather than "(. . . 0.62; 95% CI, 0.47 to 0.80; P=0.002 . . .)." These errors also affected the Supplementary Appendix, which has been replaced. The article is correct at NEJM.org.

Crizotinib versus Chemotherapy in Advanced ALK-Positive Lung Cancer (June 20, 2013;368:2385-94). In the first paragraph of the "Patient-Reported Outcomes" subsection of Results (page 2390), the last sentence should have ended, " . . . 4.5 months with crizotinib, as compared with 1.4 months with chemotherapy (hazard ratio with crizotinib, 0.50; 95% CI, 0.37 to 0.66; P<0.001) . . . ," rather than " . . . 5.6 months with crizotinib, . . . (hazard ratio with crizotinib, 0.54; 95% CI, 0.40 to 0.71 . . . ." These errors were also present in Figure 2B (page 2392). The article is correct at NEJM.org.

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A course, entitled "Healing Health Care Disparities through Education: An Interdisciplinary Faculty Development Program," will be offered in Boston, Oct. 16 and 17. It is sponsored by Brigham and Women's Hospital.

Contact Helen M. Shields, Brigham and Womens Hospital, Medical Communications and Gastroenterology, 75 Francis St., Boston, MA 02115; or call (617) 525-9315; or fax (617) 525-8740; or e-mail hmshields@partners.org; or see http://hms.harvard.edu/education/continuing-education.

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The lecture will be held in Boston, Oct. 29. Joann E. Manson, M.D., will present a lecture entitled "Controversies in Primary Prevention: Aspirin, Estrogen, and Vitamin D."

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Contact Franziska Schweikert, CARS Conference Office, Im Gut 15, 79790 Kuessaberg, Germany; or call (49) 7742-922 434; or fax (49) 7742-922 438; or e-mail office@cars-int.org; or see http://www.cars-int.org.

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