Response and Acquired Resistance to Everolimus in Anaplastic Thyroid Cancer

Nikhil Wagle, M.D., Brian C. Grabiner, Ph.D., Eliezer M. Van Allen, M.D.,
Ali Amin-Mansour, M.S., Amaro Taylor-Weiner, B.S., Mara Rosenberg, B.S.,
Nathanael Gray, Ph.D., Justine A. Barletta, M.D., Yanan Guo, Ph.D.,
Scott J. Swanson, M.D., Daniel T. Ruan, M.D., Glenn J. Hanna, M.D.,
Robert I. Haddad, M.D., Gad Getz, Ph.D., David J. Kwiatkowski, M.D., Ph.D.,
Scott L. Carter, Ph.D., David M. Sabatini, M.D., Ph.D., Pascale A. Jänne, M.D., Ph.D.,
Levi A. Garraway, M.D., Ph.D., and Jochen H. Lorch, M.D.

SUMMARY

Everolimus, an inhibitor of the mammalian target of rapamycin (mTOR), is effective in treating tumors harboring alterations in the mTOR pathway. Mechanisms of resistance to everolimus remain undefined. Resistance developed in a patient with metastatic anaplastic thyroid carcinoma after an extraordinary 18-month response. Whole-exome sequencing of pretreatment and drug-resistant tumors revealed a nonsense mutation in TSC2, a negative regulator of mTOR, suggesting a mechanism for exquisite sensitivity to everolimus. The resistant tumor also harbored a mutation in MTOR that confers resistance to allosteric mTOR inhibition. The mutation remains sensitive to mTOR kinase inhibitors.

A BETTER UNDERSTANDING OF THE MECHANISMS OF SENSITIVITY AND RESISTANCE TO ANTICANCER THERAPIES MAY IMPROVE PATIENT SELECTION AND ALLOW THE DEVELOPMENT OF RATIONAL TREATMENT DESIGNS. ONE APPROACH INVOLVES STUDYING PAIRED BIOPSY SAMPLES OF PRETREATMENT AND DRUG-RESISTANT TUMORS OBTAINED FROM PATIENTS WITH EXQUISITE SENSITIVITY OR UNUSUALLY DURABLE RESPONSES TO THERAPY.

Everolimus is a Food and Drug Administration–approved oral allosteric inhibitor of mTOR. Tumors that exhibit a dependency on the mTOR pathway might have enhanced sensitivity to mTOR inhibition. Inactivating mutations in the tumor-suppressor genes TSC1, TSC2, and STK11 result in mTOR-pathway activation and are targetable by TOR inhibitors in hamartoma syndromes and in malignant perivascular epithelioid-cell tumors. In a phase 2 study of everolimus in urothelial carcinoma, whole-genome sequencing in a patient who had a durable complete remission revealed a somatic TSC1 mutation. We recently identified an additional mechanism of exquisite sensitivity to everolimus in a patient with metastatic urothelial carcinoma: activating mutations in mTOR itself. Although mechanisms of sensitivity to everolimus are beginning to be identified, mechanisms of clinically acquired resistance to everolimus remain unknown.

We identified a patient with metastatic anaplastic thyroid cancer, an aggressive neoplasm associated with a median survival of 5 months, who had exquisite sensitivity to everolimus. The patient, who was enrolled in a phase 2 study of everolimus for thyroid cancer (ClinicalTrials.gov number, NCT00936858), had a near-complete response that lasted for 18 months, followed by progressive disease. Of seven patients with anaplastic thyroid cancer treated with everolimus in this trial to date, this patient was the only one who had a response. To identify potential genomic mechanisms of exquisite sensitivity and acquired resistance to everolimus, we performed whole-exome sequencing on the pretreatment and drug-resistant tumors.