Published OnlineFirst January 7, 2011; DOI: 10.1158/1535-7163.MCT-10-0994



Molecular Cancer Therapeutics

# *PIK3CA* Mutations in Patients with Advanced Cancers Treated with PI3K/AKT/mTOR Axis Inhibitors

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## Abstract

Preclinical data suggest that *PIK3CA* mutations predict response to PI3K/AKT/mTOR inhibitors. Concomitant *KRAS* or *BRAF* mutations may mediate resistance. Therefore, tumors from patients referred to the phase I program for targeted therapy starting in October 2008 were analyzed for *PIK3CA* mutations using PCR-based DNA sequencing of exons 9 and 20. Consecutive patients with diverse tumor types and *PIK3CA* mutation were treated whenever possible with agents targeting the PI3K/AKT/mTOR pathway. Overall, *PIK3CA* mutations were detected in 25 of 217 patients (11.5%; exon 9, $n = 11$; exon 20, $n = 14$). In tumor types with more than 10 patients tested, *PIK3CA* mutations were most frequent in endometrial (3 of 14, 21%), ovarian (5 of 30, 17%), colorectal (9 of 54, 17%), breast (2 of 14, 14%), cervical (2 of 15, 13%), and squamous cell cancer of the head and neck (1 of 11, 9%). Of the 25 patients with *PIK3CA* mutations, 17 (68%) were treated on a protocol that included a PI3K/AKT/mTOR pathway inhibitor, and 6 (35%) achieved a partial response. In contrast, only 15 of 241 patients (6%) without documented *PIK3CA* mutations treated on the same protocols responded ($P = 0.001$). Of the 17 patients with *PIK3CA* mutations, 6 (35%) had simultaneous *KRAS* or *BRAF* mutations (colorectal, $n = 4$; ovarian, $n = 2$). Colorectal cancer patients with *PIK3CA* and *KRAS* mutations did not respond to therapy, whereas both ovarian cancer patients with *PIK3CA* and *KRAS* or *BRAF* mutations did. In conclusion, *PIK3CA* mutations were detected in 11.5% of patients with diverse solid tumors. The response rate was significantly higher for patients with *PIK3CA* mutations treated with PI3K/AKT/mTOR pathway inhibitors than for those without documented mutations. *Mol Cancer Ther; 10(3); 558–65. ©2011 AACR.*

## Introduction

Recently, major therapeutic advances have been made in tumors with druggable targets (1–4). These include the highly successful use of KIT kinase inhibitors in *KIT* mutation-positive gastrointestinal stromal tumors (GIST), ABL kinase inhibitors in *BCR-ABL*–positive chronic myelogenous leukemia (CML), and *BRAF* inhibitors in *BRAF* mutation-positive melanoma (1, 2, 4). Common solid tumors, such as breast, lung, and colorectal cancer remain difficult to treat, perhaps in part because they are heterogeneous, with each subset of patients having different molecular abnormalities (3). Identifying relevant molecular subtypes within heterogeneous diseases and matching patients with appropriate targeted agents or their combinations is crucial to future therapeutic progress (5).

The phosphatidylinositol 3-kinase (PI3K)/AKT/mTOR signaling pathway is activated in many different cancers (Supplementary Fig. S1; ref. 6). Activation is frequently mediated by mutations in the p110α subunit of *PI3K* called *PIK3CA*, with most mutations (>80%) occurring either in exon 9, which codes for the helical domain, or exon 20, which codes for the kinase domain (Supplementary Fig. S2; ref. 7). Preclinical studies suggested that *PIK3CA* mutations may predict for response to PI3K inhibitors (8).

We investigated the *PIK3CA* mutation status of patients referred to the phase I clinical trials program clinic (known as the Clinical Center for Targeted Therapy). Whenever possible, patients with *PIK3CA* mutations were offered treatment targeting the PI3K/AKT/mTOR pathway, and their clinical outcomes were analyzed.

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**Note:** Supplementary data for this article are available at Molecular Cancer Therapeutics Online (http://mct.aacrjournals.org/).

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**doi:** 10.1158/1535-7163.MCT-10-0994

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## Patients and Methods

### Patients

We investigated the *PIK3CA* mutation status of patients with advanced tumors and available tissue referred to the Department of Investigational Cancer Therapeutics (phase I clinical trials program) at The University of Texas M.D. Anderson Cancer Center starting in October 2008. The registration of patients in the database, pathology assessment, and mutation analysis were done at M.D. Anderson. Eligible patients were those referred for clinical trials of targeted therapeutic agents. The study and all treatments were conducted in accordance with the guidelines of the M.D. Anderson Institutional Review Board.

### Tissue samples and mutation analyses

*PIK3CA* mutations were investigated in archival formalin-fixed, paraffin-embedded tissue blocks or material from fine needle aspiration biopsy obtained from diagnostic and/or therapeutic procedures. All histologies were centrally reviewed at M.D. Anderson. *PIK3CA* mutation testing was done in the Clinical Laboratory Improvement Amendment–certified Molecular Diagnostic Laboratory within the Division of Pathology and Laboratory Medicine at M.D. Anderson. DNA was extracted from microdissected paraffin-embedded tumor sections and analyzed using a PCR-based DNA sequencing method for *PIK3CA* mutations in codons [c]532–554 of exon 9 (helical domain) and c1011–1062 of exon 20 (kinase domain), which included the mutation hotspot region of the *PIK3CA* proto-oncogene by Sanger sequencing following amplification of 276 bp and 198 bp amplicons, respectively, utilizing primers designed by the M.D. Anderson Molecular Diagnostic Laboratory. Whenever possible, in addition to *PIK3CA*, mutation analysis was done for *KRAS* and *NRAS* c12, c13, and c61 mutations of exon 2; and *BRAF* c595–600 mutations of exon 15 by pyrosequencing as previously described (9).

### Treatment and evaluation

Consecutive patients with underlying *PIK3CA* mutations were enrolled whenever possible in clinical trials containing inhibitors of the PI3K/AKT/mTOR pathway, particularly protocols with anti–mTORC1 (rapalog)-based regimens or regimens containing PI3K inhibitors. Treatment continued until disease progression or unacceptable toxicity occurred.

Treatment was carried out according to the specific requisites in the treatment protocols selected.

Assessments, including history, physical examination, and laboratory evaluations, were done as specified in each protocol, typically before the initiation of therapy, weekly during the first cycle, and then, at a minimum, at the beginning of each new treatment cycle. Efficacy was assessed from computed tomography scans and/or magnetic resonance imaging at baseline before treatment initiation and then every 2 cycles (6–8 weeks). All radiographs were read in the Department of Radiology at M.D. Anderson and reviewed in the Department of Investigational Cancer Therapeutics tumor measurement clinic. Responses were categorized per RECIST 1.0 criteria and were reported as best response (10). In brief, complete response was defined as the disappearance of all measurable and nonmeasurable disease; partial response (PR) was defined as at least a 30% decrease in the sum of the longest diameter of measurable target lesions; progressive disease (PD) was defined as at least a 20% increase in the sum of the longest diameter of measurable target lesions, or unequivocal progression of a nontarget lesion, or the appearance of a new lesion; and stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR nor sufficient increase to qualify for PD.

### Statistical analysis

Statistical analysis was verified by our statistician (X. Wang). Fisher's exact test was used to assess the association among categorical variables and *PIK3CA* mutation status. The Wilcoxon rank-sum test assessed the association between age and *PIK3CA* mutation status. Time to progression was defined as the time interval from the start of therapy to the first observation of disease progression or death, whichever occurred first. All tests were 2-sided, and $P < 0.05$ was considered statistically significant. All statistical analyses were carried out using SAS 9.1 software (SAS Institute).

## Results

### Patients

A total of 217 patients with advanced tumors were analyzed for the presence of *PIK3CA* mutations. One hundred thirty-one (60%) patients were women and 86 (40%) were men (Table 1). The median age was 56 years (range, 13–91 years). One hundred seventy-six (81%) were Caucasians, 19 (9%) African Americans, 12 (6%) Hispanic, and 10 (4%) Asians. Fifty-four (25%) had colorectal cancer, 30 (14%) ovarian cancer, 18 (8%) melanoma, 14 (6%) breast cancer, 14 (6%) endometrial cancer, 8 (4%) squamous cell cervical cancer, 7 (3%) cervical adenocarcinoma, 8 (4%) soft tissue sarcoma (excluding GIST), and 11 (5%) squamous cell cancer of head and neck. A variety of other tumors made up the rest of the patients (Table 1).

### PIK3CA mutations

*PIK3CA* proto-oncogene mutations were detected in 25 of the 217 patients (11.5%). In 11 patients, a mutation in exon 9 was detected: 8 in c545, 1 in c542, 1 in c546, and 1 in c545/c549. Exon 20 mutations were found in the 14 remaining individuals: 10 in c1047, 3 in c1049, and 1 in c1043 (Table 2). In tumor types with more than 3 patients tested, *PIK3CA* mutations were most frequent in endometrial cancer (3 of 14 patients, 21%).

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**Table 1.** Patients' characteristics and distribution of *PIK3CA* mutations

| Variable | Patients ($n = 217$) | Patients with *PIK3CA* mutations in the category |
|---|---|---|
| Sex | | |
| Male | 86 (40) | 11 (13) |
| Female | 131 (60) | 14 (11) |
| Age, y | | |
| <50 | 66 (30) | 8 (12) |
| 50–70 | 127 (59) | 17 (13) |
| >70 | 24 (11) | 0 (0) |
| Ethnicity | | |
| Caucasian | 176 (81) | 17 (10) |
| African American | 19 (9) | 4 (21) |
| Hispanic | 12 (6) | 1 (8) |
| Asian | 10 (4) | 3 (30) |
| Tumor type | | |
| Colorectal | 54 (25) | 9 (17) |
| Ovarian | 30 (14) | 5 (17) |
| Melanoma | 18 (8) | 0 (0) |
| Breast | 14 (6) | 2 (14) |
| Endometrial | 14 (6) | 3 (21) |
| Cervix | 15 (7) | 2 (13) |
| Soft tissue sarcomas | 8 (4) | 0 (0) |
| Non–small cell lung cancer | 7 (3) | 1 (14) |
| Small-cell lung cancer | 2 (<1) | 0 (0) |
| Head and neck: squamous | 11 (5) | 1 (9) |
| Head and neck: adenoid cystic | 3 (1) | 0 (0) |
| Renal | 4 (2) | 0 (0) |
| Parotid | 4 (2) | 0 (0) |
| Thymoma | 3 (1) | 0 (0) |
| Pancreatic | 3 (1) | 1 (33) |
| Neuroendocrine | 3 (1) | 0 (0) |
| Vulvar: squamous | 2 (<1) | 0 (0) |
| Adrenocortical | 2 (<1) | 0 (0) |
| Small intestine | 1 (<1) | 1 (100) |
| Other cancers | 19 (9) | 0 (0) |

NOTE: All values are given as *n* (%).

Mutations were also present in 5 of 30 patients (17%) with ovarian cancer, 9 of 54 patients (17%) with colorectal cancer, 2 of 14 patients (14%) with breast cancer, 2 of 15 patients (13%) with cervical cancer (both of whom had squamous histology), 1 of 7 patients (14%) with non–small cell lungcarcinoma (NSCLC), and 1 of 11 patients (9%) with squamous cell cancer of head and neck (Table 1). *PIK3CA* mutation status was not significantly associated with age, gender, or race (Fisher's exact test).

### Simultaneous RAS and PIK3CA mutations

Preclinical data suggest that activation of RAS mediates resistance to PI3K inhibitors (8). Therefore, *RAS* mutation status was investigated whenever possible.

*KRAS* mutations in exon 2 were assessed in 130 patients and identified in 33 individuals (25%; Table 3). The presence of *KRAS* mutations was significantly associated with *PIK3CA* mutations ($P = 0.03$; Fisher's exact test). Indeed, 45% of patients (9 of 20) with a *PIK3CA* mutation (who were also tested for a *KRAS* mutation) also had a *KRAS* mutation, whereas only 22% of patients (24 of 110) without a *PIK3CA* mutation (who were also tested for *KRAS*) harbored a *KRAS* mutation. Of the 33 patients with *KRAS* mutations, 9 (27%) had simultaneous *PIK3CA* mutations. In contrast, of the 97 patients without a *KRAS* mutation, only 11 (11%) had a *PIK3CA* mutation ($P = 0.03$). Of the 9 patients with simultaneous *PIK3CA* and *KRAS* mutations, disease distribution was as follows: colorectal cancer, 7; pancreatic cancer, 1; ovarian cancer, 1 (Table 2).

*NRAS* c61 mutations were detected in 2 patients (3%) of the 62 tested. Both patients had melanoma with wild-type *PIK3CA*.

### Simultaneous BRAF and PIK3CA mutations

*BRAF* exon 15 mutations were assessed in 122 patients, of whom 11 (9%) had a c600 mutation (Table 3). *BRAF* mutations were found in 7 patients with melanomas, 3 with colorectal cancer, and 1 with ovarian cancer. Only 1 patient had a simultaneous *PIK3CA* and *BRAF* mutation detected (ovarian cancer; Table 2).

### Response in patients with PIK3CA mutations treated with PI3K/AKT/mTOR inhibitors

Of the 25 patients with an underlying *PIK3CA* mutation, 17 were enrolled in clinical trials that included a PI3K/AKT/mTOR inhibitor. These patients were refractory to a median of 4 prior therapies (range, 1–12). Of these patients, 6 had colorectal cancer, 4 had ovarian cancer, 3 had endometrial cancer, 2 had squamous cell cervical cancer, 1 had small intestine cancer, and 1 had breast cancer (Table 2). Sixteen patients received anti–mTORC1-based regimens and 1 patient was treated with an anti–PI3K-based regimen (Table 4; ref. 11). A PR was observed in 6 (35%) patients. Duration of response was 8.9, 17.9+, 25+, 30.6+, 35.3, and 59+ weeks (with the plus sign indicating ongoing response at the time period noted; Figs. 1, 2, 3, and 4). Seven (41%) patients had SD, including 4 (23.5%) patients with prolonged SD lasting for more than 16 weeks. In total, 10 patients (59%) achieved either SD for more than 16 weeks or a PR. Four (23.5%) patients had PD (2 with radiological and 2 with clinical progression). In comparison, patients without documented *PIK3CA* mutations (meaning they had no mutation or tumor tissue was unavailable for testing) treated on the same protocols showed a significantly lower response rate of 6% (15 of 241; $P = 0.001$).

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**Table 2.** Characteristics of 25 patients with *PIK3CA* mutations

| Case no. | Tumor type | Histology | *PIK3CA* mutations | Other mutations | Response (RECIST %) | TTP (weeks)[a] |
|---|---|---|---|---|---|---|
| 1 | Ovarian | Clear cell carcinoma | c1047 | *BRAF* c600 | PR (−34) | 17.9+ |
| 2 | Ovarian | High-grade endometrioid carcinoma | c1047 | None | – | – |
| 3 | Ovarian | Clear cell carcinoma | c1049 | None | SD (−4) | 23.3 |
| 4 | Ovarian | High-grade carcinoma | c542 | None | SD (−6) | 17.9+ |
| 5 | Ovarian | High-grade carcinoma | c546 | *KRAS* c61 | PR (−34) | 30.6+ |
| 6 | Colorectal | Moderately differentiated adenocarcinoma | c1047 | *KRAS* c12 | PD (+87) | 7.9 |
| 7 | Colorectal | Moderately differentiated adenocarcinoma | c545 | *KRAS* c12 | – | – |
| 8 | Colorectal | Moderately differentiated adenocarcinoma | c1049 | *KRAS* c12, c13 | SD (−2) | 6.4+ |
| 9 | Colorectal | Moderately differentiated adenocarcinoma | c1047 | *KRAS* c12 | – | – |
| 10 | Colorectal | Moderately differentiated adenocarcinoma | c545 | *KRAS* c12 | SD (−3) | 5.3 |
| 11 | Colorectal | Moderately differentiated adenocarcinoma | c545 | *KRAS* c12 | SD (+14) | 16.1+ |
| 12 | Colorectal | Moderately differentiated adenocarcinoma | c545 | None | SD (−5) | 11+ |
| 13 | Colorectal | Moderately differentiated adenocarcinoma | c1047 | None | PD[b] | 2.9 |
| 14 | Colorectal | Moderately differentiated adenocarcinoma | c545 | *KRAS* c61 | – | – |
| 15 | Endometrial | High-grade endometrial | c1047 | None | PR (−37) | 35.3 |
| 16 | Endometrial | Endometrial adenocarcinoma, grade 2 | c1047 | None | PR (−60) | 59+ |
| 17 | Endometrial | Endometrial adenocarcinoma, grade 2 | c1049 | None | PD (+46) | 5.6 |
| 18 | Breast | Lobular carcinoma, $ER^+$, $PR^+$, $HER2/neu^-$ | c1047 | None | PR (−37) | 25+ |
| 19 | Breast | Ductal carcinoma, grade 2, $ER^+$, $PR^+$, $HER2/neu^-$ | c1047 | None | - | - |
| 20 | Cervix | Moderately differentiated squamous cell carcinoma | c545 | None | SD (−4) | 19.1 |
| 21 | Cervix | Moderately/poorly differentiated squamous cell carcinoma | c545, c549 | None | PR (−100) | 8.9 |
| 22 | Head & Neck | Poorly differentiated squamous cell carcinoma | c1043 | None | – | – |
| 23 | Lungs | Adenocarcinoma | c545 | None | – | – |
| 24 | Pancreas | Poorly differentiated adenocarcinoma | c545 | *KRAS* c12 | – | – |
| 25 | Small Intestine | Poorly differentiated adenocarcinoma | c1047 | None | PD[b] | 8.1 |

Abbreviations: TTP, time to progression; $ER^+$, estrogen receptor positive; $PR^+$, progesteron receptor positive; $HER2/neu^-$, HER2/neu receptor negative.

[a]+ denotes not progressing at the time of analysis.

[b]Clinical progression.

**Table 3.** *PIK3CA*, *RAS* (*K*- or *N*-), and *BRAF* mutations

| Oncogene | Mutated (%) | Total tested |
|---|---|---|
| *PIK3CA* mutations | 25 (11.5) | 217 |
| *KRAS* mutations | 33 (25) | 130 |
| *NRAS* mutations | 2 (3) | 62 |
| *BRAF* mutations | 11 (9) | 122 |
| *RAS* or *BRAF* mutations | 46 (31) | 145 |
| *KRAS* mutations in mutated *PIK3CA* | 9 (45) | 20 |
| *RAS* or *BRAF* mutations in mutated *PIK3CA* | 10 (50) | 20 |

Fisher's exact test was used to assess the associations among response (PR, SD, or PD) and other patient characteristics, such as age, gender, race, number of prior therapies (>3 prior therapies vs $\leq$ 3 therapies), type of *PIK3CA* mutation (exon 9 vs exon 20), and *KRAS* mutation. None of these variables was significantly associated with response.

## Discussion

We determined that mutations in exon 9 or exon 20 of the *PIK3CA* proto-oncogene were present in 25 of 217 patients (11.5%) with diverse tumor types, with the incidence being highest (9%–21%) in patients with endometrial, ovarian, colorectal, breast, cervical cancer, NSCLC, and squamous cell cancer of head and neck. Although the

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**Table 4.** Therapeutic regimens used to treat patients with *PIK3CA* mutations

| Regimen | Mechanism of action | Patients (case no.[a]) | % | Reference |
|---|---|---|---|---|
| Temsirolimus | mTORC1 inhibitor | 5 (4, 10, 11, 15, 17) | 29 | NCT00877773 |
| Temsirolimus, bevacizumab | mTORC1 inhibitor, anti-VEGF monoclonal antibody | 2 (8, 13) | 12 | NCT00610493 |
| Temsirolimus, liposomal doxorubicin, bevacizumab | mTORC1 inhibitor, anti-VEGF monoclonal antibody, topo II alpha inhibitor | 8 (1, 3, 5, 12, 16, 18, 20, 21) | 47 | NCT00761644 |
| Temsirolimus, topotecan, bortezomib | mTORC1 inhibitor, topoisomerase I inhibitor, proteasome inhibitor | 1 (25) | 6 | NCT00770731 |
| XL147, carboplatin, paclitaxel | PI3K inhibtor, alkylating agent, microtubule stabilizing agent | 1 (6) | 6 | Wheler and colleagues (11) |

NOTE: NCT, clinicaltrials.gov identifier.
[a]Case numbers are depicted in Table 2.

number of patients in each tumor type is limited in our study, previous reports have also documented *PIK3CA* mutations in these tumor types with an incidence as follows: 23% to 36% of endometrial cancers (12, 13), 14% to 32% of colon cancers (12, 14, 15), 4% to 12% of ovarian cancers (16–18), 18% to 40% of breast cancers usually associated with expression of hormone receptors or HER2/neu (12, 16, 17, 19), 8% to 14% of cervical squamous cell cancers (12, 20), and in 11% to 33% of squamous cell cancers of the head and neck (12, 21).

Previous preclinical observations have shown that activation of the RAS/RAF/MEK pathway mediates resistance to PI3K inhibitors in *PIK3CA*-mutant tumors (8). Therefore, we examined our patients for coexistence

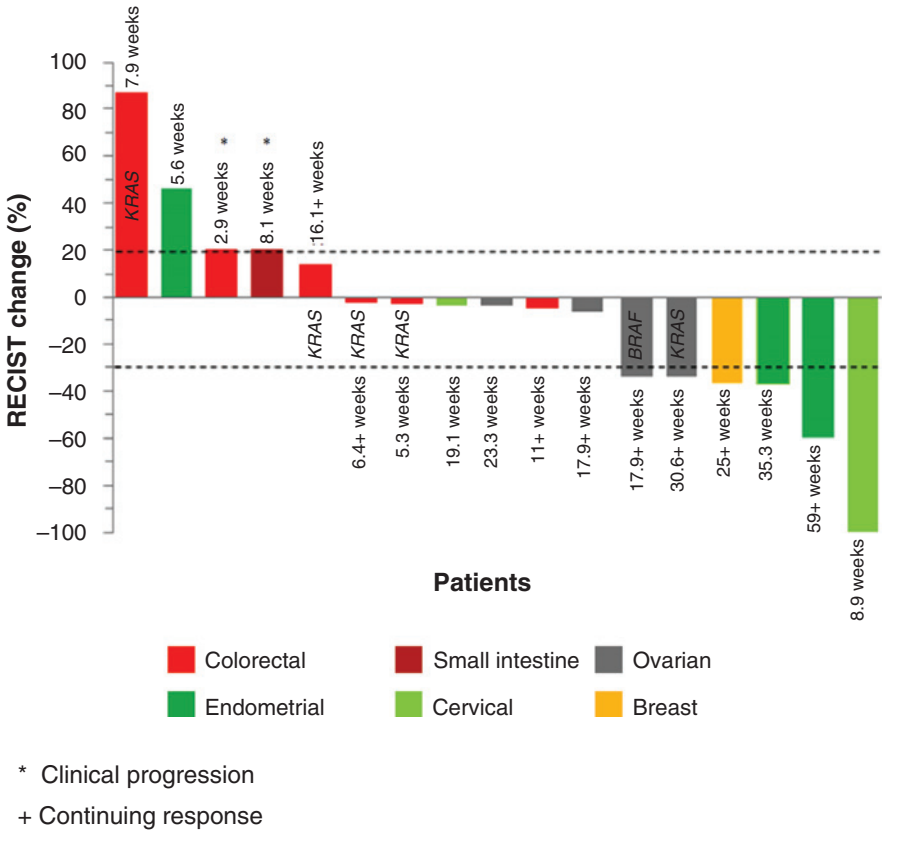


**Figure 1.** Waterfall plot of patients with *PIK3CA* mutations treated with PI3K/AKT/mTOR inhibitors. Six PRs (5 confirmed) and 6 minor responses less than PR were observed. The overall response rate was 35%. The best response was complete resolution of all measurable disease with persistence of nonmeasurable disease in a patient with squamous cell cervical carcinoma treated with an mTOR-based regimen. Four patients with colorectal cancer and 1 patient with ovarian cancer had simultaneous *KRAS* mutations. One patient with ovarian cancer had a simultaneous *BRAF* mutation.

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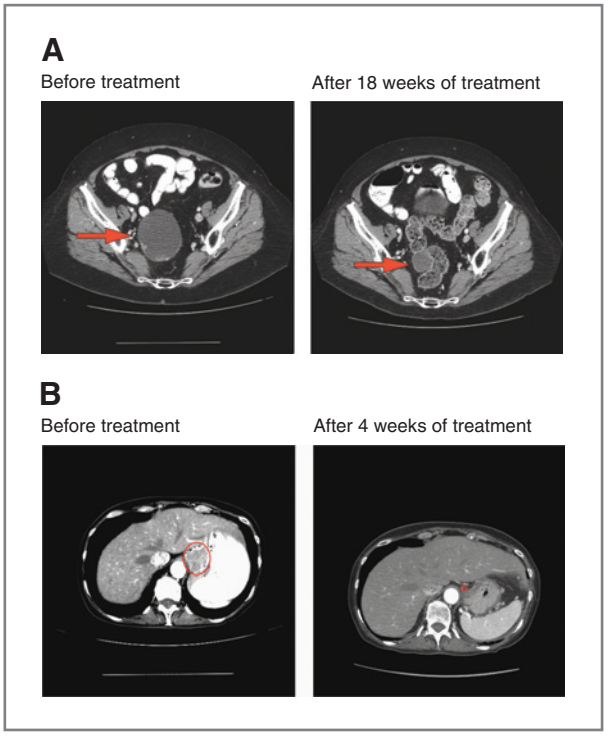


Figure 2. Computed tomography scans of responding patients. A, patient with endometrial cancer demonstrating partial response in pelvic mass. B, patient with squamous cell cervical cancer demonstrating partial response in gastrohepatic metastasis. Arrows or circles, locations of metastases

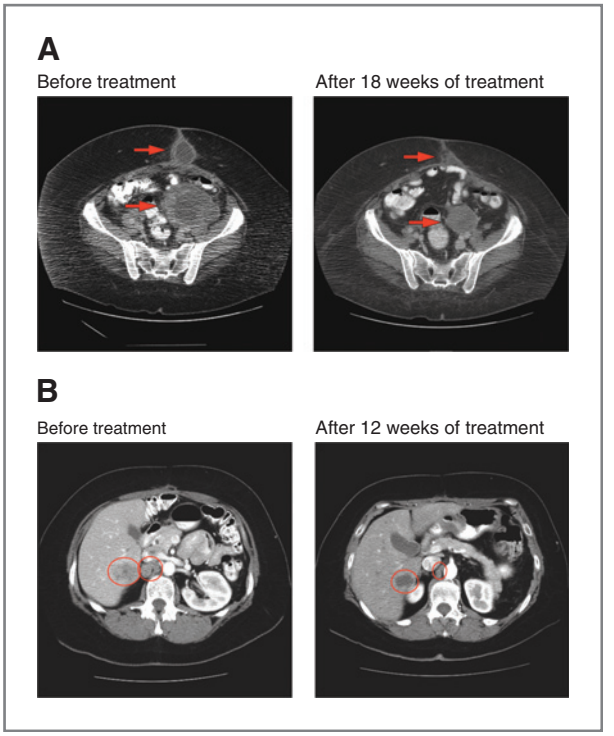


Figure 4. Computed tomography scans of responding patients. A, patient with ovarian cancer demonstrating partial response in pelvic and subcutaneous metastases. B, patient with ovarian cancer demonstrating partial response in liver and aortocaval metastases. Arrows or circles, locations of metastases.

of *PIK3CA* mutations with *RAS* (*K*- or *N*-) or *BRAF* mutations. Forty-five percent of patients (9 of 20) with a *PIK3CA* mutation (who were also tested for a *KRAS* mutation) also had a *KRAS* mutation, whereas only 22% of patients (24 of 110) without a *PIK3CA* mutation (who were also tested for *KRAS*) harbored a *KRAS* mutation. Of the 33 patients with *KRAS* mutations, 9 (27%) had simultaneous *PIK3CA* mutations. In contrast, of the 97 patients without *KRAS* mutation, only 11 (11%) had a *PIK3CA* mutation ($P = 0.03$). These results suggest that these

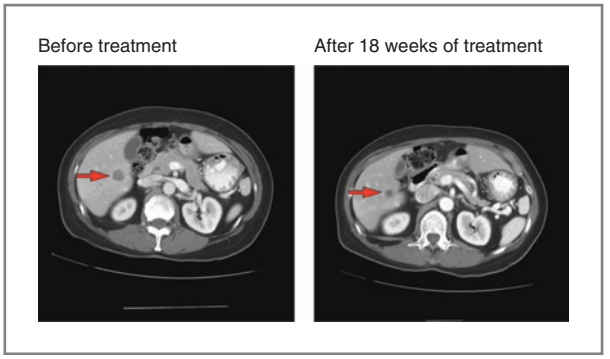


Figure 3. Computed tomography scans of responding patients. Patient with endometrial cancer demonstrating partial response in liver metastases. Arrows, locations of metastases.

mutations (*PIK3CA* and *RAS*) commonly coexist. We also observed that 7 of 9 patients (78%) with colorectal cancer who harbored a *PIK3CA* mutation also had a *KRAS* mutation. This rate of dual mutations is similar to that in a previously reported study that showed mutant *KRAS* in 56% of patients with colorectal cancer and a *PIK3CA* mutations (14). In 1 of 5 patients with *PIK3CA*-mutant ovarian cancer, we detected a simultaneous *KRAS* mutation and, in another, a simultaneous *BRAF* mutation. In contrast, a study from the Middle East showed no coexistence of mutated *KRAS* or *BRAF* mutations with *PIK3CA* mutations in ovarian cancer, though the incidence of *PIK3CA* mutations in the population studied was quite low (4%; ref. 18).

Whenever possible, our patients with *PIK3CA* mutations were entered on trials utilizing targeted inhibitors of the PI3K/AKT/mTOR pathway. Their overall response rate on these trials was 35%. Responses were seen in patients with cervical, endometrial, ovarian cancer, and breast cancer (Fig. 1). In contrast, of the 241 patients without documented *PIK3CA* mutations treated on the same protocols, only 15 (6%) responded ($P = 0.001$). The latter response rate is similar to the 4% to 11% response rate reported by our group and others when patients are treated on phase I trials without molecular selection (22–24). It should be noted that it is conceivable that some of the small group of patients without *PIK3CA*

Published OnlineFirst January 7, 2011; DOI: 10.1158/1535-7163.MCT-10-0994



mutations who responded to PI3K/AKT/mTOR axis inhibitors had other aberrations in *PIK3CA* not detected by our assay or had other abnormalities such as PTEN loss, that are known to activate *PIK3CA* (6). Indeed, we have previously shown that PTEN loss can be detected in approximately 20% of patients in the phase I setting (25).

Consistent with our data, clinical trials with therapies directed against well-defined targets have shown improved results when patients are selected for the presence of those targets, even in the phase I setting (where patients tend to be heavily pretreated and refractory/resistant to multiple conventional drugs), though mostly these trials have reported results in a disease-specific setting. Examples include imatinib mesylate (a KIT and BCR-ABL kinase inhibitor), which showed response rates of more than 50% in patients with GIST (a disorder characterized by *KIT* kinase mutations) or *BCR-ABL*–positive CML (1, 26). More recently, patients with NSCLC and an underlying *EML4-ALK* fusion also showed a response rate more than 50% after treatment with the ALK inhibitor crizotinib, as did patients with metastatic malignant melanoma who had an underlying *BRAF* mutation and responded to the BRAF inhibitor PLX4032 (4, 27). In contrast, epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors were initially tested in an unselected patient population and had only modest activity (28). Subsequent bench to the bedside forays showed that anti-EGFR tyrosine kinase inhibitors are far more effective in patients with lung cancer and an underlying EGFR mutations (29).

One question that arises is whether or not the detection of additional mutations that might confer resistance would provide more predictive information. In this regard, our patients with colorectal cancer and a simultaneous *KRAS* mutation did not respond to PI3K/AKT/mTOR axis therapy, which is in agreement with preclinical data suggesting that *KRAS* activation mediates resistance to PI3K inhibitors (8). In contrast, 2 patients with ovarian cancer and simultaneously occurring *KRAS* or *BRAF* mutations achieved a PR with PI3K/AKT/mTOR axis inhibitors, thus suggesting that such resistance is not absolute or that *RAS*- or *RAF*-mutant colorectal cancers behave differently than *RAS*- or *RAF*-mutant ovarian cancers.

In conclusion, mutations in *PIK3CA* occur in a subset of patients with several common cancers. In this study, the response rate for patients with heavily pretreated, diverse, advanced cancers and *PIK3CA* mutations who were given PI3K/AKT/mTOR axis inhibitors was significantly more than that for patients without documented *PIK3CA* mutations treated on the same trials. The latter observation is consistent with data that show low response rates on traditional phase I trials, in which molecular testing is not used. One hypothesis that could be generated from these data is that selecting *PIK3CA*-mutant patients for treatment with PI3K/AKT/mTOR axis inhibitors may predict response independent of underlying histology. Patients with colorectal cancer and concomitant presence of *KRAS* and *PIK3CA* mutations did not respond, consistent with previous experiments indicating that the RAS/RAF/MEK pathway serves as a driver of resistance to PI3K inhibitors. Because the number of patients in our series was small and no randomization occurred, these data must be interpreted cautiously. However, it seems that screening for *PIK3CA* (and *RAS* or *RAF*) mutations warrants further investigation in the application of targeted PI3K/AKT/mTOR inhibitors to the clinic.

## Disclosure of Potential Conflict of Interest

No potential conflicts of interest were disclosed.

## Acknowledgment

We thank Ms. Joann Aaron for scientific review and editing of this article.

## Grant Support

This study was supported in part by Grant RR024148 from the National Center for Research Resources, a component of the NIH Roadmap for Medical Research (http://nihroadmap.nih.gov/clinicalresearch/overview-translational.asp).

Received November 3, 2010; revised December 30, 2010; accepted January 1, 2011; published OnlineFirst January 7, 2011.

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Published OnlineFirst January 7, 2011; DOI: 10.1158/1535-7163.MCT-10-0994



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Published OnlineFirst January 7, 2011; DOI: 10.1158/1535-7163.MCT-10-0994



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*Mol Cancer Ther* 2011;10:558-565. Published OnlineFirst January 7, 2011.