Targeting the PI3K/AKT/mTOR pathway in lung cancer

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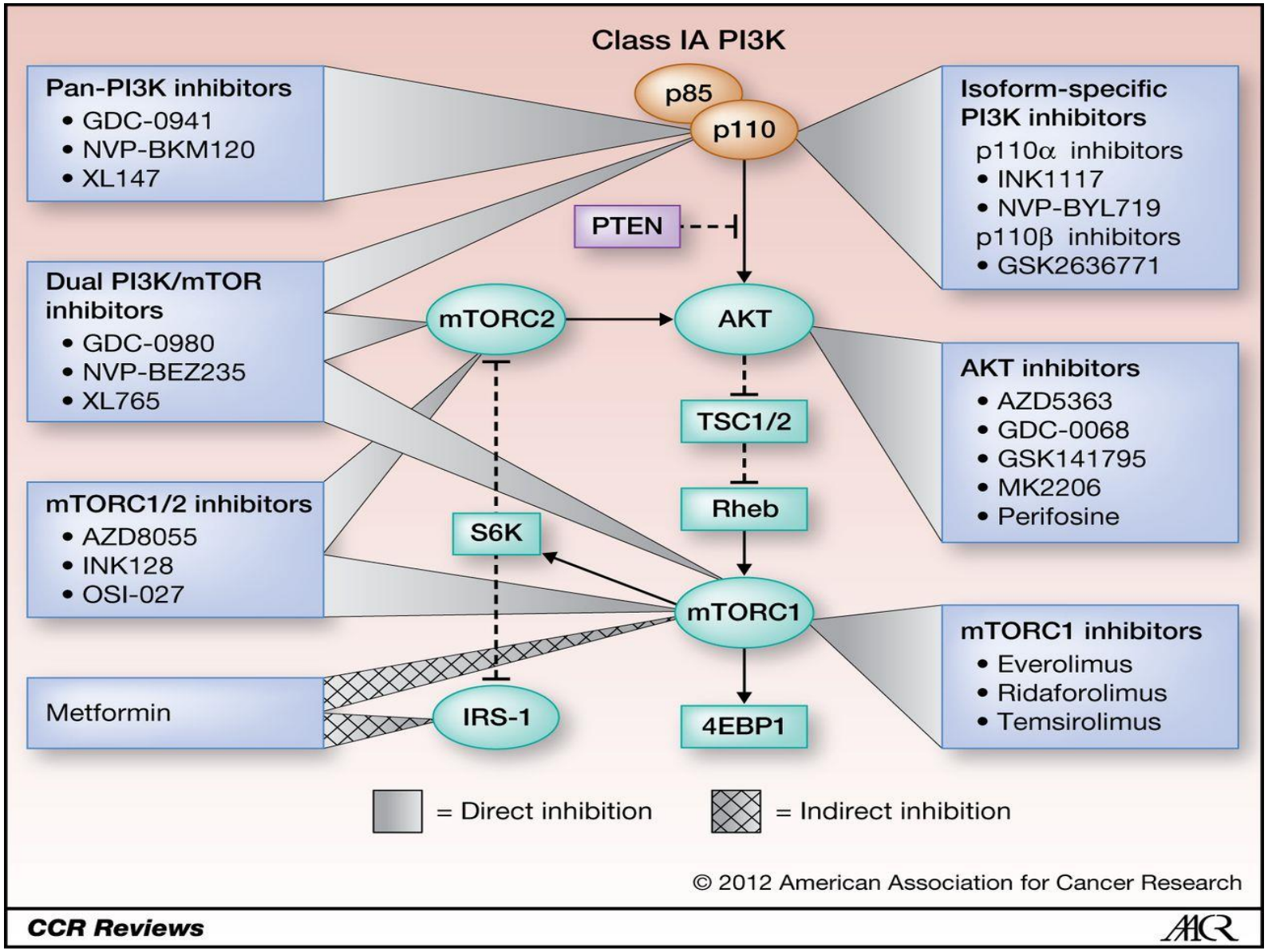
Frequency of mutations affecting the PI3K/AKT/mTOR pathway in lung cancer

			NonSquamous			
		Squamous (%)	Adenocarcinoma (%)	Large Cell (%)	Total (%)	Reference
Receptor tyrosine kinases						
EGFR	Mutation	5	12–20	3–9	15–20 (up to 60 Asians)	25,26,111–115
	Increased copy number	UNK	41	UNK	29–40	26,43,111,112,116,117
ALK	Mutation	5	1	7	2	115
	Rearrangement (EML4-ALK)	1	3–7	UNK	2–7	36–38,115,118–120
MET	Mutation	1	2	UNK	2–14	23,27,115,121
	Amplification	21	20	UNK	2–21 (higher frequency in patients with acquired resistance to TKIs)	27,28,43,44,122–124
RAS/RAF/MEK pathway components						
KRAS	Mutation	6–9	12–53	18	8–21	25,26,111,115,125
PI3K/AKT/mTOR pathway components						
PTEN	Mutation	6	1	3	4–5	115,126
	Loss/reduction	Loss/ reduction: 70	Loss/ reduction: 77	Loss/ reduction: 62	Loss: 24–44; reduction: 29–46 Promoter hypermethylation at *PTEN*: 26, at *PTENP1*: 66	22,26,45
PIK3CA	Mutation	2–7	2	3	2–5	115,126–130
	Amplification	33–70	6–19	38	12–20	126,130–134
LKB1	Mutation	27	33–54	43	9–33	53,135–138
AKT1	Mutation (E17K)	1	<1	UNK	1–2	19,115,139,140

Papadimitrakopoulou V. et al JTO 2012; 1315-1326

PI3K/AKT/mTOR pathway inhibitors in lung cancer



nature medicine

Effective use of PI3K and MEK inhibitors to treat mutant *Kras* G12D and *PIK3CA* H1047R murine lung cancers

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Somatic mutations that activate phosphoinositide 3-kinase (PI3K) have been identified in the p110-α catalytic subunit (encoded by *PIK3CA*)[1]. They are most frequently observed in two hotspots: the helical domain (E545K and E542K) and the kinase domain (H1047R). Although the p110-α mutants are transforming *in vitro*, their oncogenic potential has not been assessed in genetically engineered mouse models. Furthermore, clinical trials with PI3K inhibitors have recently been initiated, and it is unknown if their efficacy will be restricted to specific, genetically defined malignancies. In this study, we engineered a mouse model of lung adenocarcinomas initiated and maintained by expression of p110-α H1047R. Treatment of these tumors with NVP-BEZ235, a dual pan–PI3K and mammalian target of rapamycin (mTOR) inhibitor in clinical development, led to marked tumor regression as shown by positron emission tomography–computed tomography, magnetic resonance imaging and microscopic examination. In contrast, mouse lung cancers driven by mutant *Kras* did not substantially respond to single-agent NVP-BEZ235. However, when NVP-BEZ235 was combined with a mitogen-activated protein kinase kinase (MEK) inhibitor, ARRY-142886, there was marked synergy in shrinking these *Kras*-mutant cancers. These *in vivo* studies suggest that inhibitors of the PI3K-mTOR pathway may be active in cancers with *PIK3CA* mutations and, when combined with MEK inhibitors, may effectively treat *KRAS* mutated lung cancers.

To generate mice with inducible expression of human p110α H1047R, we injected a DNA segment consisting of seven direct repeats of the tetracycline operator (Tet-op) sequence, followed by human *PIK3CA* complementary DNA encoding the H1047R mutation and the *SV40* polyadenosine tail into FVB/N fertilized eggs as previously described[2,3]. Ten Tet-op-*PIK3CA* founders were identified and then crossed to clara cell secretory protein (CCSP)-reverse tetracycline transactivator protein (rtTA) mice (in which expression of rtTA is specifically targeted to type II alveolar epithelial cells[4]) to generate inducible, double-transgenic mouse cohorts harboring both the activator and the responder transgenes[4,5]. The Tet-op-*PIK3CA* copy numbers from the two most commonly used founders (13 and 121) were determined by quantitative real-time PCR (**Supplementary Fig. 1a** online).

To induce expression of p110-α H1047R in mouse lung epithelial cells, we administered doxycycline chow to double-transgenic mice from each of the founder lines, monitored them for labored breathing and imaged dyspneic mice with magnetic resonance imaging (MRI) to identify abnormalities. Three founder lines (13, 121 and 3011) had labored breathing and MRI images consistent with lung tumors after 12, 26 and 60 weeks, respectively (data not shown). These mice were killed, and gross inspection revealed multiple small tumor nodules. Histological analyses revealed mixed adenocarcinomas with bronchioloalveolar features (**Fig. 1a**). As founder line 13 showed the shortest latency period, it was used for subsequent experiments.

The inducibility of the *PIK3CA* mutant transgene expression in the lung was evaluated at the RNA level by RT-PCR. PIK3CA H1047R expression was readily observed after 12 weeks of doxycycline administration (**Supplementary Fig. 1b**). Doxycycline withdrawal led to a loss of mutant PIK3CA expression (**Supplementary Fig. 1b**). We observed expression of mutant p110-α protein in PI3K immunoprecipitations only from the double-transgenic mice induced with doxycycline (**Supplementary Fig. 1c**). Of note, expression of the transgene did not substantially increase total p110-α protein expression (**Supplementary Fig. 1c**). This is expected, as p110-α that is not bound to p85 is unstable, and any p110-α expressed in excess of p85 is rapidly degraded[6–8].

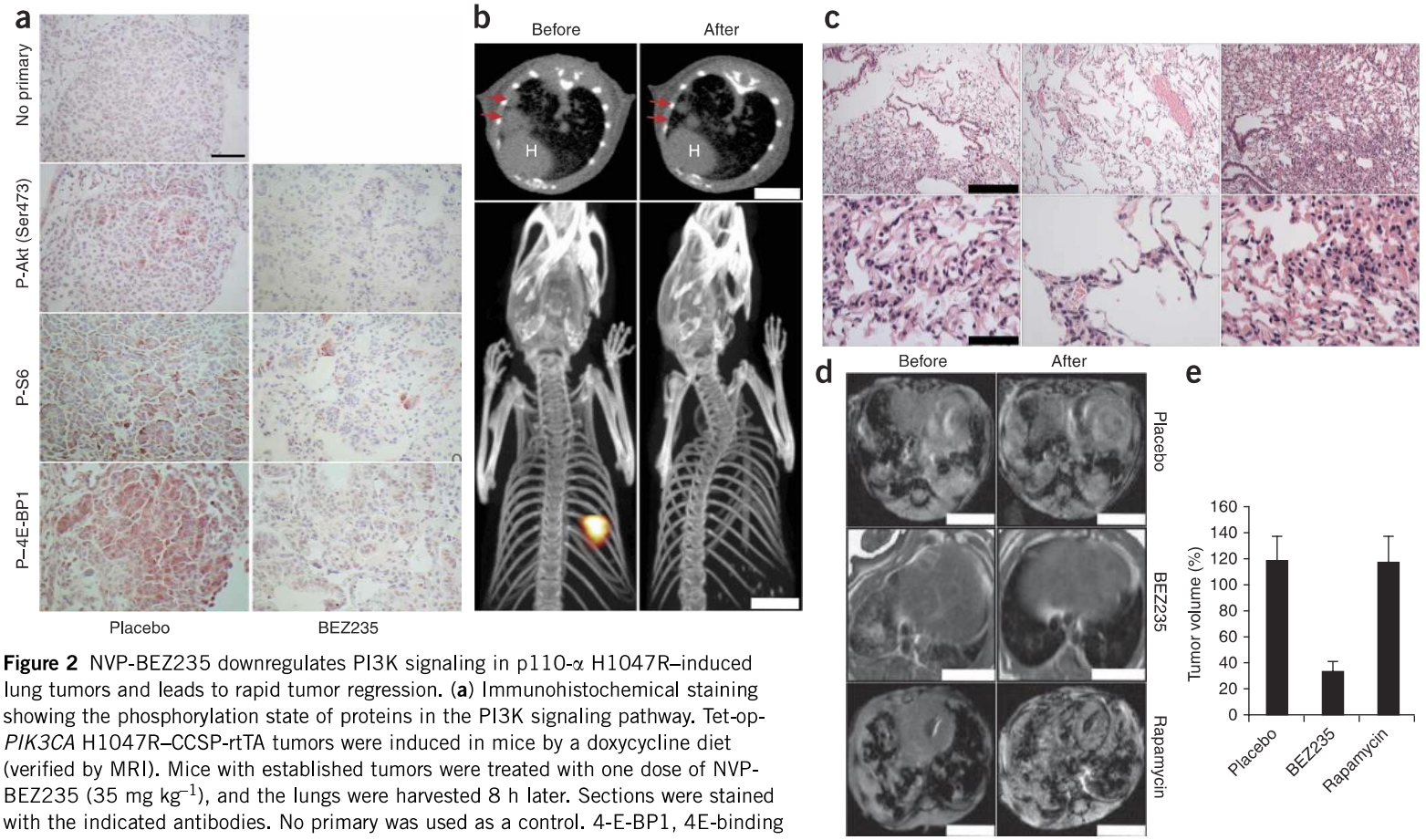

Figure 2 NVP-BEZ235 downregulates PI3K signaling in p110-α H1047R–induced lung tumors and leads to rapid tumor regression. (**a**) Immunohistochemical staining showing the phosphorylation state of proteins in the PI3K signaling pathway. Tet-op-*PIK3CA* H1047R–CCSP-rtTA tumors were induced in mice by a doxycycline diet (verified by MRI). Mice with established tumors were treated with one dose of NVP-BEZ235 (35 mg kg^{-1}), and the lungs were harvested 8 h later. Sections were stained with the indicated antibodies. No primary was used as a control. 4-E-BP1, 4E-binding protein-1. Scale bar, 50 μM. (**b**) CT scans (top) and PET scans (bottom) of Tet-op-*PIK3CA* H1047R–CCSP-rtTA double-transgenic mice treated with doxycycline until tumors developed and then treated with NVP-BEZ235 35mg kg^{-1} per day for 4 d. Red arrows on the CT scans indicate tumor. H, heart. Scale bar, 5 mm. (**c**) H&E staining showing the histological effects of NVP-BEZ235 on the p110-α H1047R–driven lung tumors. Tet-op-*PIK3CA* H1047R–CCSP-rtTA double-transgenic mice were treated with doxycycline until they developed tumors (confirmed by MRI). Mice with established tumors were treated with NVP-BEZ235 35 mg kg^{-1} for 3 d (left and middle) or 2 d (right), and the lungs were examined histologically. Scale bars: top, 200 μM; bottom, 50 μM. (**d**,**e**) Tet-op-PIK3CA H1047R–CCSP-rtTA mice with established tumors were treated with either placebo, 35 mg kg^{-1} NVP-BEZ235 or 6 mg kg^{-1} rapamycin daily for 2 weeks. (**d**) A representative MRI is shown before and after treatment for each group. Scale bar, 4.5 mm. (**e**) The average tumor volumes of three mice in each treatment group after 2 weeks are shown relative to pretreatment tumor volumes. Values are means ± s.d. ($P < 0.05$ BEZ235 versus placebo).

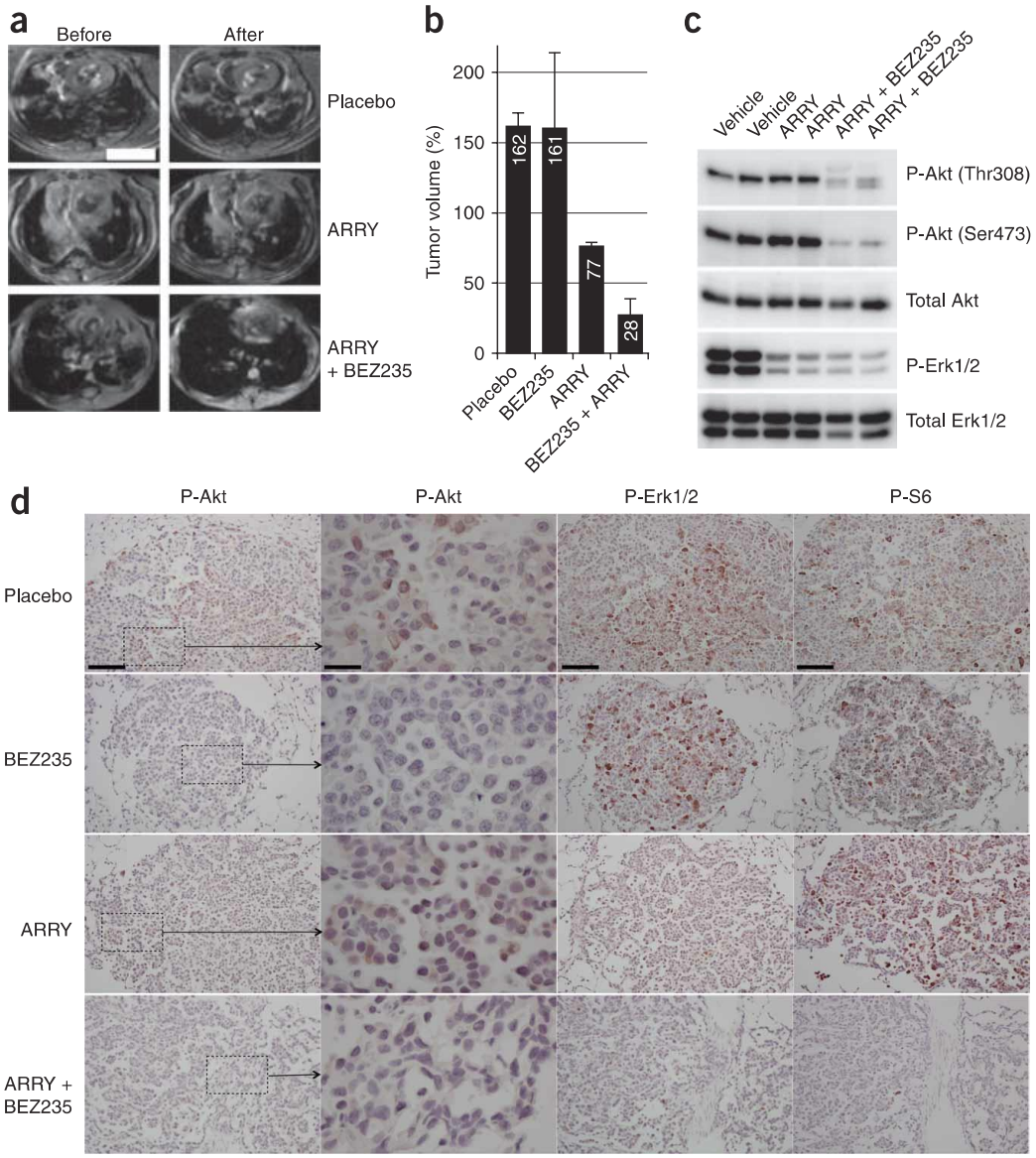

Figure 4 Combined PI3K and MEK inhibition shrinks Kras G12D induced lung tumors. (**a**,**b**) LSL *Kras* G12D mice were induced to develop tumors by adenoviral Cre inhalation. After the establishment of sizeable tumors (determined by MRI), mice were treated with either placebo, 35 mg kg^{-1} NVP-BEZ235 once daily, 25 mg kg^{-1} ARRY-142886 twice daily or 35 mg kg^{-1} NVP-BEZ235 once daily and 25 mg kg^{-1} ARRY-142886 once daily for two weeks. (**a**) Representative axial MRIs of the chest are shown. Scale bar, 4.5 mm. (**b**) The average tumor volumes of three mice in each treatment group after 2 weeks are shown relative to pretreatment tumor volumes. $P < 0.05$, BEZ235 + ARRY versus each of the other three treatment groups. (**c**,**d**) Mice were treated as in **a** for 1.5 d. Six hours after their dose on day 2 of treatment, the mice were killed. (**c**) Western blot analysis using the indicated antibodies of one lung that had been snap-frozen in liquid nitrogen. (**d**) Immunohistochemistry assessment with the indicated antibodies of the other lung (fixed in formalin). Microscopy was performed at two magnifications for the P-Akt immunohistochemistry. Scale bar for the high-magnification P-Akt images, 25 μM. Scale bar for all other images, 100 μM. H&E stains of the nodules examined by immunohistochemistry are shown in **Supplementary Figure 6** online.

and immunohistochemistry (**Fig. 4c**,**d**). Of note, we invariably detected low-level P-Akt staining in the *Kras* G12D mouse nodules that was lost upon treatment of the mouse with NVP-BEZ235 (**Fig. 4d**).

KRAS-mutated lung cancers remain a huge cancer problem, as they comprise 20–30% of

IJC
International Journal of Cancer

Antitumor activity of pimasertib, a selective MEK 1/2 inhibitor, in combination with PI3K/mTOR inhibitors or with multi-targeted kinase inhibitors in pimasertib-resistant human lung and colorectal cancer cells

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The RAS/RAF/MEK/MAPK and the PTEN/PI3K/AKT/mTOR pathways are key regulators of proliferation and survival in human cancer cells. Selective inhibitors of different transducer molecules in these pathways have been developed as molecular targeted anti-cancer therapies. The *in vitro* and *in vivo* anti-tumor activity of pimasertib, a selective MEK 1/2 inhibitor, alone or in combination with a PI3K inhibitor (PI3Ki), a mTOR inhibitor (everolimus), or with multi-targeted kinase inhibitors (sorafenib and regorafenib), that block also BRAF and CRAF, were tested in a panel of eight human lung and colon cancer cell lines. Following pimasertib treatment, cancer cell lines were classified as pimasertib-sensitive (IC_{50} for cell growth inhibition of 0.001 μM) or pimasertib-resistant. Evaluation of basal gene expression profiles by microarrays identified several genes that were up-regulated in pimasertib-resistant cancer cells and that were involved in both RAS/RAF/MEK/MAPK and PTEN/PI3K/AKT/mTOR pathways. Therefore, a series of combination experiments with pimasertib and either PI3Ki, everolimus, sorafenib or regorafenib were conducted, demonstrating a synergistic effect in cell growth inhibition and induction of apoptosis with sustained blockade in MAPK- and AKT-dependent signaling pathways in pimasertib-resistant human colon carcinoma (HCT15) and lung adenocarcinoma (H1975) cells. Finally, in nude mice bearing established HCT15 and H1975 subcutaneous tumor xenografts, the combined treatment with pimasertib and BEZ235 (a dual PI3K/mTOR inhibitor) or with sorafenib caused significant tumor growth delays and increase in mice survival as compared to single agent treatment. These results suggest that dual blockade of MAPK and PI3K pathways could overcome intrinsic resistance to MEK inhibition.

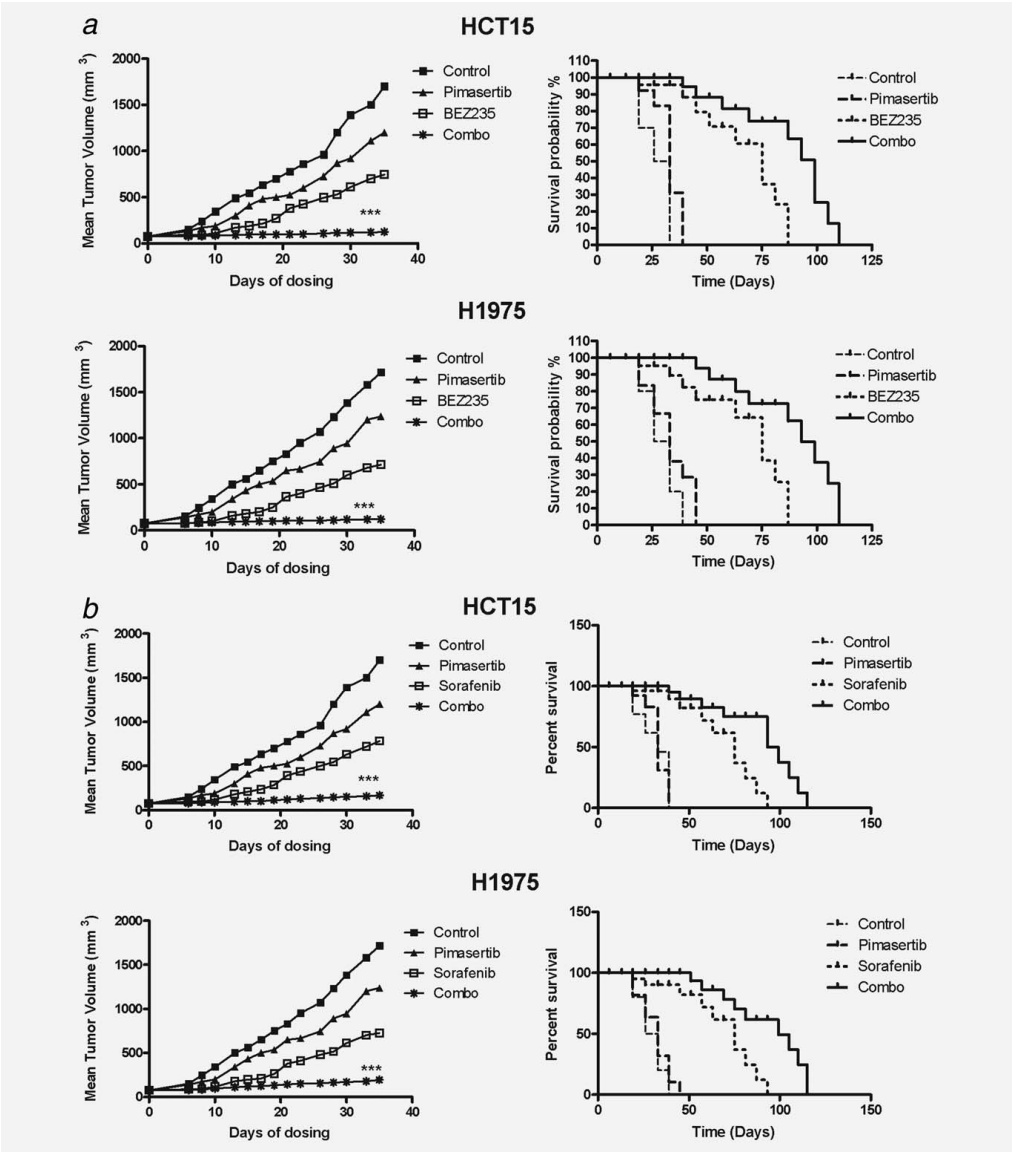

Figure 6. (*a*) Effects of pimasertib in combination with BEZ235, a dual PI3K/mTOR inhibitor on HCT15 and H1975 tumor xenografts. HCT15 and H1975 cells were grown as subcutaneous tumor xenografts in nude mice. After tumor establishment (100–150 mm^3), mice were treated with pimasertib (10 mg/kg; oral gavage) and/or BEZ235 (40 mg/kg; oral gavage) for 3 weeks. Animals were sacrified when tumors achieved 2.000 mm^3 in size. Each group consisted of 10 mice. *** $p < 0.0001$. (*b*) Effects of pimasertib in combination with sorafenib on HCT15 and H1975 tumor xenografts. HCT15 (*b*) and H1975 (*b*) cells were grown as subcutaneous tumor xenografts in nude mice. After tumor establishment (100–150 mm^3), mice were treated with pimasertib (10 mg/kg; oral gavage) and/or sorafenib (25 mg/kg; oral gavage) for 3 weeks. Animals were sacrified when tumors achieved 2.000 mm^3 in size. Each group consisted of 10 mice. ***$p < 0.0001$.

Brief Report: A Phase II "Window-of-Opportunity" Frontline Study of the mTOR Inhibitor, Temsirolimus Given as a Single Agent in Patients with Advanced NSCLC, an NCCTG Study

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Background: In an effort to evaluate the single agent activity of temsirolimus in previously untreated non–small-cell lung cancer, the North Central Cancer Treatment Group undertook a frontline "window-of-opportunity" study.

Methods: Patients received 25 mg of temsirolimus administered intravenously as a weekly 30 minute infusion, on a 4-week cycle. Based on a two-stage Fleming design, the treatment would be promising if at least four of the first 25 evaluable patients in stage I or at least six of the 50 evaluable patients at the end of stage II have a confirmed response. Fresh tumor biopsies were obtained to evaluate predictive markers of temsirolimus activity.

Results: A total of 55 patients were enrolled with 52 patients being evaluable. The median age was 64 years. Adverse events (grade 3/4) occurring in 33 patients included dyspnea (12%), fatigue (10%), hyperglycemia (8%), hypoxia (8%), nausea (8%), and rash/desquamation (6%). The clinical benefit rate was 35% with four patients achieving a confirmed partial response and 14 patients with stable disease for 8 weeks or more. The 24-week progression-free survival rate was 25%. Median progression-free survival and overall survival were 2.3 and 6.6 months, respectively. Expression of p70s6 kinase, phospho-p70s6 kinase, Akt, phospho-Akt, and phosphatase and tensin homolog mutation did not correlate with clinical outcome.

Conclusions: Temsirolimus given as a single agent in frontline therapy in patients with non–small-cell lung cancer was tolerable and demonstrated clinical benefit but did not meet the primary objective in this study. Patient selection will be needed to enhance the efficacy.

Key Words: mTOR inhibitors, Advanced non–small-cell lung carcinoma, Temsirolimus, Window of opportunity.

(*J Thorac Oncol.* 2012;7: 919–922)

The prognosis of advanced non–small-cell lung cancer (NSCLC) patients treated with platinum-doublet regimens remains poor with a median progression-free survival (PFS) of 3.1 to 5.5 months and a median overall survival (OS) of 7. to -11.3 months.[1] Advances in maintenance chemotherapy still yield a median OS of 12 to 15 months with pemetrexed or erlotinib.[2,3] Thus, novel therapies are required to improve treatment outcomes.

The phosphoinositide 3–kinase/Akt/mammalian target of rapamycin (mTOR) pathway is one of the key signaling pathways in cancer. It plays roles in cell growth, cell proliferation, angiogenesis, and protein synthesis. It is also dysregulated in many human cancers including NSCLC.[4] Phosphorylation of mTOR, in response to the activation of a growth receptor by its

original article

Annals of Oncology 20: 1674–1681, 2009
doi:10.1093/annonc/mdp060
Published online 23 June 2009

Efficacy of everolimus (RAD001) in patients with advanced NSCLC previously treated with chemotherapy alone or with chemotherapy and EGFR inhibitors

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Received 21 October 2008; revised 11 February 2009; accepted 16 February 2009

Background: Treatment options are scarce in pretreated advanced non-small-cell lung cancer (NSCLC) patients. RAD001, an oral inhibitor of the mammalian target of rapamycin (mTOR), has shown phase I efficacy in NSCLC.
Methods: Stage IIIb or IV NSCLC patients, with two or fewer prior chemotherapy regimens, one platinum based (stratum 1) or both chemotherapy and epidermal growth factor receptor tyrosine kinase inhibitors (stratum 2), received RAD001 10 mg/day until progression or unacceptable toxicity. Primary objective was overall response rate (ORR). Analyses of markers associated with the mTOR pathway were carried out on archival tumor from a subgroup using immunohistochemistry (IHC) and direct mutation sequencing.
Results: Eighty-five patients were enrolled, 42 in stratum 1 and 43 in stratum. ORR was 4.7% (7.1% stratum 1; 2.3% stratum 2). Overall disease control rate was 47.1%. Median progression-free survivals (PFSs) were 2.6 (stratum 1) and 2.7 months (stratum 2). Common ≥grade 3 events were fatigue, dyspnea, stomatitis, anemia, and thrombocytopenia. Pneumonitis, probably or possibly related, mainly grade 1/2, occurred in 25%. Cox regression analysis of IHC scores found that only phospho AKT (pAKT) was a significant independent predictor of worse PFS.
Conclusions: RAD001 10 mg/day was well tolerated, showing modest clinical activity in pretreated NSCLC. Evaluation of RAD001 plus standard therapy for metastatic NSCLC continues.
Key words: everolimus, mTOR, non-small-cell lung cancer, NSCLC, RAD001

Published in final edited form as:
Cancer. 2010 August 15; 116(16): 3903–3909. doi:10.1002/cncr.25264.

Phase I and pharmacokinetic study of everolimus, an mTOR inhibitor, in combination with docetaxel for recurrent/refractory non-small cell lung cancer

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Abstract

Purpose—Everolimus is a novel inhibitor of the mammalian target of rapamycin (mTOR) pathway, which is aberrantly activated in non-small cell lung cancer (NSCLC). We conducted a phase I and pharmacokinetic study of everolimus and docetaxel for recurrent NSCLC.

Methods—Patients with advanced stage NSCLC and progression following prior platinum-based chemotherapy were eligible. Sequential cohorts were treated with escalating doses of docetaxel (day 1) and everolimus (PO daily, days 1–19), every 3 weeks. Pharmacokinetic (PK) sampling of everolimus and docetaxel were done in cycle 1. The primary endpoint was determination of the recommended phase II doses (RP2D) of the combination.

Results—Twenty-four patients were enrolled. Median age, 62 yrs; Females, 11; number of prior regimens, 1(n=13), 2 (n=6), ≥3 (n=5) ECOG PS 0(n=6), 1(n=17). The dose-limiting toxicities (DLT) were fever with grade 3/4 neutropenia, grade 3 fatigue and grade 3 mucositis. None of the 7 patients treated at the RP2D (docetaxel 60 mg/m^2 and everolimus 5 mg daily) experienced DLT. Everolimus area under the concentration time curve (AUC) was not different with 60 or 75 mg/m^2 docetaxel. Mean ±SD AUC-based accumulation factors (R) for everolimus on days 8 and 15 were 1.16 ± 0.37 and 1.42 ± 0.42, respectively. Docetaxel day 1 half-life was 9.4 ± 3.4 hours. Among 21 patients evaluable, 1 had a partial response, and 10 had disease stabilization.

Conclusions—The RP2D of docetaxel and everolimus for combination therapy are 60 mg/m^2 and 5 mg PO daily, respectively. Promising anti-cancer activity has been noted.

Keywords

Everolimus; docetaxel; phase I; pharmacokinetics; non-small cell lung cancer

Everolimus in Combination with Pemetrexed in Patients with Advanced Non-small Cell Lung Cancer Previously Treated with Chemotherapy

A Phase I Study Using a Novel, Adaptive Bayesian Dose-Escalation Model

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Introduction: Pemetrexed is an established second-line therapy for non-small cell lung cancer (NSCLC). Everolimus has previously been shown to have some clinical activity when used as a single agent in NSCLC. The aim of this phase I study was to evaluate the safety and feasibility of combining pemetrexed with everolimus in patients with NSCLC who had disease progression after one previous treatment.

Methods: Patients with stage IIIb/IV NSCLC and one previous chemotherapy regimen were enrolled. A Bayesian dose-escalation model was used to determine the feasible doses of daily or weekly everolimus combined with pemetrexed (500 mg/m^2 q3w). The primary end point was rate of cycle 1 dose-limiting toxicities (DLTs). Secondary end points included safety, relative dose intensity of pemetrexed, pharmacokinetics, and tumor response.

Results: Twenty-four patients received daily everolimus (2.5, 5, 7.5, or 10 mg) and 19 received weekly everolimus (30 or 50 mg) with pemetrexed. Cycle 1 DLTs in the daily regimen included febrile neutropenia, neutropenia, rash/pruritus, and thrombocytopenia; in the weekly regimen, DLTs included neutropenia and stomatitis. The most frequent grade 3/4 adverse events were neutropenia, dyspnea, and thrombocytopenia. Three partial responses were observed with everolimus 5 mg/d and two with 50 mg/wk. Pharmacokinetics did not suggest an influence of everolimus on pemetrexed parameters; pemetrexed resulted in a minor decrease in everolimus exposure with both daily and weekly regimens.

Conclusions: Everolimus 5 mg/d or 50 mg/wk with the standard regimen of pemetrexed are feasible dosages in patients with stage IIIb/IV NSCLC.

Key Words: Everolimus, Non-small cell lung cancer, Pemetrexed, Phase I, Adaptive Bayesian dose-escalation model.

(*J Thorac Oncol.* 2011;6: 2120–2129)

Current first-line standard of care for patients with advanced non-small cell lung cancer (NSCLC) is platinum-based chemotherapy.[1] Adding targeted therapies such as bevacizumab or cetuximab to platinum-based chemotherapy has improved overall survival.[2–4] However, many patients relapse after the initial response to first-line therapy, and second-line treatment options (i.e., docetaxel, pemetrexed, or erlotinib) offer only modest survival benefit.[5,6] No second-line combination of cytotoxic drugs has yielded further survival benefit in large randomized clinical trials. Therefore, combined administration of chemotherapy and targeted therapies is an area deserving further exploration in patients with progressing disease after previous treatment for NSCLC.

Activation of the phosphoinositide 3-kinase (PI3K)/Akt/mammalian target of rapamycin (mTOR) pathway regulates protein synthesis and stimulates cell growth, proliferation, and angiogenesis.[7] The activated pathway is detected frequently in

Phase II Trial of Gefitinib and Everolimus in Advanced Non-small Cell Lung Cancer

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Introduction: Concurrent signal transduction inhibition with the epidermal growth factor receptor (EGFR) inhibitor gefitinib and the mammalian target-of-rapamycin inhibitor everolimus has been hypothesized to result in enhanced antitumor activity in patients with non-small cell lung cancer (NSCLC). This phase II trial assessed the efficacy of the combination of gefitinib and everolimus in patients with advanced NSCLC.

Methods: Two cohorts of 31 patients with measurable stage IIIB/IV NSCLC were enrolled: (1) no prior chemotherapy and (2) previously treated with cisplatin or carboplatin and docetaxel or pemetrexed. All patients received daily everolimus 5 mg and gefitinib 250 mg. Response was assessed after 1 month and then every 2 months. Pretreatment tumor specimens were collected for mutation testing.

Results: Sixty-two patients were enrolled (median age: 66 years, 50% women, 98% stage IV, all current/former smokers, and 85% adenocarcinoma). Partial responses were seen in 8 of 62 patients (response rate: 13%; 95% confidence interval: 5–21%); five responders had received no prior chemotherapy. Three partial responders had an *EGFR* mutation. Both patients with a *KRAS* (G12F) mutation responded. The median time to progression was 4 months. Median overall survival was 12 months, 27 months for no prior chemotherapy patients, and 11 months for patients previously treated with chemotherapy.

Conclusions: The 13% partial response rate observed did not meet the prespecified response threshold to pursue further study of the combination of gefitinib and everolimus. The response rate in patients with non-*EGFR* mutant tumors was 8%, likely reflecting activity of everolimus. Further investigation of mammalian target-of-rapamycin inhibitors in patients with NSCLC with *KRAS* G12F-mutated tumors is warranted.

Key Words: Non-small cell lung cancer, Gefitinib, Everolimus.

(*J Thorac Oncol.* 2010;5: 1623–1629)

The epidermal growth factor receptor (EGFR) pathway is critical to some lung adenocarcinoma cells. The EGFR-tyrosine kinase inhibitors (TKIs), gefitinib (Iressa, AstraZeneca, USA) and erlotinib (Tarceva, Genentech, South San Francisco, CA), have emerged as valuable treatments for some patients with non-small cell lung cancer (NSCLC). Sensitivity to these agents is largely conferred by activating mutations in the EGFR tyrosine kinase domain[1–3] with partial responses seen in 58 to 90% in patients with EGFR-mutant tumors.[4,5]

Unfortunately, the clinical benefit of the EGFR-TKIs is limited both by primary and acquired resistance. Patients who initially respond to EGFR TKIs develop acquired resistance after a median time of approximately 12 months.[6] *KRAS* mutations occur in 15 to 30% of patients with NSCLC and are associated with primary resistance to EGFR-TKIs.[7–9] Evi-

Cancer Treatment Reviews 40 (2014) 445–456

Contents lists available at ScienceDirect

Cancer Treatment Reviews

journal homepage: www.elsevierhealth.com/journals/ctrv

New Drugs

Strategies for co-targeting the PI3K/AKT/mTOR pathway in NSCLC

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ARTICLE INFO

Article history:
Received 20 May 2013
Received in revised form 11 August 2013
Accepted 16 August 2013

Keywords:
PI3K
NSCLC
Lung cancer
PI3K inhibition
PIK3CA
mTOR
Co-targeted inhibition
MEK
Chemoresistance
Radioresistance

ABSTRACT

The PI3K/AKT/mTOR pathway regulates cell growth and proliferation and is often dysregulated in cancer due to mutation, amplification, deletion, methylation and post-translational modifications. We and others have shown that activation of this pathway in non-small cell lung cancer (NSCLC) leads to a more aggressive disease which correlates to poor prognosis for patients. A multitude of selective inhibitors are in development which target key regulators in this pathway, however the success of PI3K targeted inhibition has been hampered by a high rate of innate and acquired resistance. Response to PI3K inhibition may be improved by co-targeting potential mediators of resistance, such as related cell surface receptors or other intracellular signaling pathways which cross-talk with the PI3K pathway. Inhibition of the PI3K pathway may also overcome radioresistance, chemoresistance and immune evasion in NSCLC. The identification of appropriate patient cohorts who will benefit from PI3K co-targeted inhibition strategies will be key to the success of these inhibitors.

Table 2
PI3K Pathway Inhibitors.

Inhibitor	Target	Phase (lung)	Availability
Wortmannin	Class I PI3K	–	–
LY294002	Class I PI3K	–	–
GDC-0941	Class I PI3K	II (II)	Oral
BKM120	Class I PI3K	I (—)	Oral
PX-866	Class I PI3K	II (II)	Oral
XL147	Class I PI3K	II (I)	Oral
BYL719	p110α	II (II)	Oral
INK1117	p110α	I (I)	Oral
CNX-1351	p110α	—	—
GSK-2636771	p110β	II (II)	Oral
SAR260301	p110β	II (II)	Oral
CAL-101	p110δ	III (—)	Oral
AMG319	p110δ	I (—)	Oral
RP-5237	p110δ	—	—
X-339	p110δ	—	—
XL-499	p110δ	—	—
RP-5090	p110δ	—	—
KAR-4141	p110δ	—	—
GDC-0032	p110α, p110γ, p110δ	I (I)	Oral
Rapamycin/Sirolmus	mTORC1	IV (II)	Oral
RAD001/Afinitor/ Everolimus	mTORC1	IV (II)	Oral
Temsirolimus/Toricel	mTOR	IV (II)	Intravenous
Ridaforolimus/MK-8669	mTOR	III (II)	Oral
Perifosine/KRX-0401	AKT	III (II)	Oral
MK-2206	AKT	II (II)	Oral
GDC-0068	AKT	II (I)	Oral
BEZ235	PI3K (Class I) & mTORC1/2	II (I)	Oral
GDC-0980	PI3K (Class I) & mTORC1/2	II (I)	Oral
XL765	PI3K (Class I) & mTORC1/2	II (I)	Oral
OSI-027	4EBP1, AKT, mTORC1/2	I (I)	Oral
Velcade	NFκB (indirect)	IV (II)	Intravenous

AKT, Protein Kinase B; mTOR, mammalian target of rapamycin; mTORC1, mammalian target of rapamycin complex 1; mTORC2, mammalian target of rapamycin complex 2; NFκB, Nuclear factor kappa-light-chain-enhancer of activated B cells; p110α, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha isoform; p110β, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit beta isoform; p110γ, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit gamma isoform; p110δ, Phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit delta isoform; PI3K, Phosphatidylinositide 3-kinase; 4EBP1, Eukaryotic translation initiation factor 4E-binding protein 1.

Targeting the PI3K/AKT/mTOR pathway in lung cancer

- The PI3K/AKT/mTOR pathway is frequently activated in both squamous cell carcinoma and adenocarcinoma of the lung.
- Promising antitumor activity of selected inhibitors (mostly in combination with other molecular targeted agent such as MEK inhibitors) has been shown in preclinical models of lung cancer.
- Several phase I and II clinical studies have been conducted or are currently ongoing with different inhibitors of the pathway alone or in combination with either cytotoxic drugs or molecular targeted drugs.
- Rapamycin derivatives such as everolimus have failed to show clinical efficacy in lung cancer. Novel more selective inhibitors could be active in lung cancer.
- However, the identification of specific biomarkers for patient selection for treatment is a major issue for the development of these drugs in lung cancer.