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Phase I Study of the Antiangiogenic Antibody Bevacizumab and the mTOR/Hypoxia-Inducible Factor Inhibitor Temsirolimus Combined with Liposomal Doxorubicin: Tolerance and Biological Activity

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Abstract

Purpose: Preclinical data suggest that combining the mTOR/hypoxia-inducible factor (HIF) inhibitor temsirolimus and the antiangiogenesis antibody bevacizumab may augment antitumor activity as well as resensitize cells to anthracyclines.

Experimental Design: We initiated a phase I study of bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced malignancies. Patients ($N = 136$) were enrolled according to a modified 3 + 3 design plus dose expansion in responsive tumor types.

Results: The most common cancers were breast ($n = 29$), epithelial ovarian ($n = 23$), and colorectal cancer ($n = 17$). The median number of prior chemotherapy regimens was four (range: 0–16). Grade 3 or higher adverse events (> 5%) included pancytopenia, mucositis, hand–foot syndrome, hypertension, and fistula. This regimen led to a 21% ($n = 28$) stable disease (SD) $\geq$ 6 months and 21% ($n = 29$) rate of partial or complete remission [PR/CR; (total SD $\geq$ 6 months/PR/CR = 42% ($n = 57$)]. PR/CR was most common in parotid gland adenocarcinoma (4/6, 67%), metaplastic breast cancer (5/12, 42%), endometrial endometrioid carcinoma (6/15, 40%), and in patients with a *PIK3CA* mutation and/or a *PTEN* mutation/loss (11/28, 39%). The maximum tolerated dose was liposomal doxorubicin 30 mg/m^2 and bevacizumab 15 mg/kg every three weeks with temsirolimus 25 mg weekly.

Conclusions: Patients tolerated bevacizumab and temsirolimus together with liposomal doxorubicin. Further evaluation, especially in patients with parotid, metaplastic breast, and endometrial endometrioid cancer, and in patients with *PIK3CA* and/or *PTEN* aberrations is warranted. *Clin Cancer Res; 18(20); 5796–805. ©2012 AACR.*

Introduction

Tumor hypoxia may be a double-edged sword. Lower tissue oxygen concentrations can exert antitumor effects by inhibiting proliferation, limiting metastases, promoting differentiation, and inducing apoptosis and necrosis (1–4). In contrast, some tumor clones, under conditions of hypoxic stress, develop adaptive processes through modification of gene expression that confer an aggressive phenotype, promoting locoregional and distant tumor growth (5–7). Tumor hypoxia can be caused by antiangiogenic therapy (8), which then mediates resistance to antiangiogenesis (9–11). The hypoxia-mediated increase of hypoxia-inducible factors (HIF) is critical to the establishment and progression of many cancers via HIF-dependent activation of genes that allow cancer cells to survive, metastasize, and develop resistance to chemotherapeutic agents (12–17).

In addition to inhibiting the expression of proteins critical to cell cycling, mTOR inactivation suppresses angiogenesis by reducing the expression of HIFs (18). Such dual inhibition would facilitate maintaining the benefits of attenuating angiogenesis while avoiding the negative consequences of increased hypoxia, including an induced aggressive change in tumor biology (19); decreasing HIFs may also resensitize cancer cells to doxorubicin (20, 21). Importantly, mTOR inhibitors interfere with signaling via the PI3K/AKT/mTOR axis, a pathway critical in many types of cancers. Finally, clinical experience indicates that antiangiogenic agents, mTOR inhibitors, and doxorubicin have nonoverlapping side effects, suggesting that they might combine well without producing excessive toxicity.

We hypothesized that simultaneous inhibition of the VEGF and tumor hypoxia–mediated adaptation

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Translational Relevance

Simultaneous multiagent inhibition of redundant tumor hypoxia–mediated adaptation pathways might provide opportunities to improve outcomes compared with monotherapy, which may augment sensitivity to other chemotherapeutic agents. The goal of this phase I trial was to develop an active and tolerable regimen that combined bevacizumab and temsirolimus with liposomal doxorubicin for advanced cancer therapy. This regimen led to responses in parotid gland adenocarcinoma, metaplastic breast cancer, and endometrial endometrioid carcinoma, among others. Molecular analyses revealed an association between tumor response and a *PIK3CA* mutation and/or *PTEN* loss/mutation. These results supported further evaluation in patients with the above mentioned malignancies and in those with *PIK3CA* and/or *PTEN* aberrations.

pathways might provide opportunities to improve outcomes compared with antiangiogenic agents alone, and that these agents, together with doxorubicin, might augment sensitivity to the latter drug. Toward that end, we conducted a clinical study (NCT00761644) that combined bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced malignancies.

Materials and Methods

Eligibility criteria

Patients 12 years of age or older were eligible if they had a histologically confirmed advanced malignancy, with no standard therapy that improved survival for at least 3 months. Children ($n = 3$) were included as the study regimen might have potential therapeutic value in pediatric cancers. All participants of both genders had measurable or evaluable disease that had progressed before study entry and an Eastern Cooperative Oncology Group (ECOG) performance status of 2 or better (22). Additional eligibility criteria included adequate marrow function (absolute neutrophil count $\geq$ 1,500/μL and platelet count $\geq$ 100,000/μL), serum creatinine $\leq$ 3 times the upper limit of normal, total bilirubin $\leq$ 2.0 mg/dL, alanine transaminase (ALT) $\leq$ 5 times the upper limit of normal or 8 times the upper limit of normal if liver metastases present, and cardiac left ventricular ejection fraction $\geq$ 50%. Patients with the following conditions were excluded: poorly controlled hypertension, defined as systolic blood pressure more than 150 mm Hg and/or diastolic blood pressure more than 100 mm Hg; prior cumulative doxorubicin dose more than 300 mg/m^2; clinically significant cardiovascular disease; pregnant or lactating women; and unwillingness or inability to sign an informed consent, as previously described (23).

Study design and treatment

The objectives of this study were to define the safety and biologic activity of this regimen. This phase I clinical trial was conducted using a modified 3 + 3 design. There were at least 2 patients entered on each cohort for initial assessment of safety. An additional 3 patients were allowed on cohorts as needed for safety assessments and, if benefit was observed in a specific type of cancer, a mini-expansion of up to 14 patients was permitted at the highest dose level considered to be safe at the time of patient entry. Therefore, each dose level might enroll up to 14 × N patients with specific tumor types (N) who displayed antitumor activity defined as below, which ended up with various enrollments into different dose levels as patients were enrolled at the highest dose level deemed safe at the time of enrollment.

Treatment was administered on an outpatient basis with intravenous temsirolimus weekly plus intravenous bevacizumab and liposomal doxorubicin once on day 1 every 21 days, as long as the patient had no evidence of tumor progression or prohibitive toxicity. Each cycle was 21 days. The trial was conducted at The University of Texas MD Anderson Cancer Center (Houston, TX) after approval by the Institutional Review Board (IRB) in accordance with the IRB guidelines. All patients signed an informed consent.

Safety evaluation, maximum tolerated dose, and dose-limiting toxicity

All patients who received one dose of any of the study agents were considered evaluable for safety. The severity of adverse events was graded according to the Common Terminology Criteria for Adverse Events v3.0 (24). All patients underwent close cardiac monitoring: baseline clinical evaluations and then as frequently as indicated, baseline 12-lead electrocardiogram, and then as frequently as indicated, baseline cardiac scan (MUGA: multi-gated acquisition scan) or 2-dimensional echocardiogram, and then once after every 100 mg/m^2 increment of liposomal doxorubicin whenever cumulative anthracycline and/or liposomal doxorubicin dose was higher than 300 mg/m^2, with cardiology consultation as indicated. Dose-limiting toxicity (DLT) was defined as (first cycle) any grade 3 or higher study agent–related (possibly, probably, or definitely) toxicity, including fatigue, with the following exceptions: hematologic toxicities that were required to be grade 4 lasting 2 weeks or longer despite supportive care and nausea or vomiting that were required to be grade 4 lasting for more than 5 days despite maximum antiemetic treatment. Also, DLT included symptoms/signs of vascular leak or cytokine release syndrome; or any severe or life-threatening complication or abnormality not defined in the NCI-CTCAE v3.0 that was possibly, probably, or definitely related to the therapy. Correctable electrolyte imbalance and alopecia were not considered DLTs. Maximum tolerated dose (MTD) was defined as the dose level below the dose at which 33% or more of patients experienced drug-related DLT in their first treatment cycle.

Efficacy evaluation

All patients who received one dose of any of the study agents were considered evaluable for efficacy. All histologies

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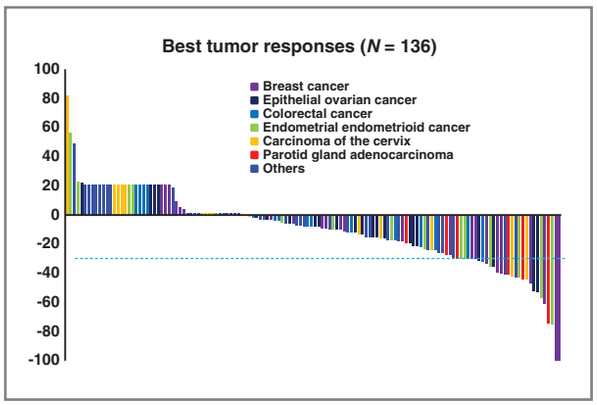

Figure 1. The waterfall plot displays best tumor responses by RECIST 1.1 criteria. All 136 patients are shown. Patients represented by 21% tumor increases either have new tumor lesions, early tumor progression, early withdrawal for other reasons, and are arbitrarily designated as having a 21% disease progression, or actual tumor progression by 21%. An earlier analysis of patients with gynecologic tumors and metaplastic breast cancer has previously been reported.

were centrally reviewed at MD Anderson Cancer Center. Radiographic imaging studies were repeated approximately every 2 cycles (6 weeks) of therapy. Response Evaluation Criteria in Solid Tumors (RECIST) 1.1 were used to characterize tumor responses (25). Patients who were removed from the study before the first scheduled restaging workup because of progression, serious drug-related adverse events, or any other reasons were considered treatment failures and arbitrarily designated as having 21% progression in a waterfall plot showing best tumor responses (Figs. 1 and 2).

Molecular assays for genetic aberrations and protein expression

Testing for genetic aberrations, such as *HER2* amplification, *PIK3CA*, *PTEN*, *KRAS*, *BRAF*, *EGFR*, *C-MET*, and *p53* mutations, and protein expression (immunohistochemistry), such as PTEN loss (DAKO antibody), estrogen receptor, progesterone receptor, and HER2, was conducted in a Clinical Laboratory Improvement Amendment (CLIA)-certified molecular diagnostic laboratory at MD Anderson Cancer Center using archival formalin-fixed, paraffin-embedded tissue blocks or material from fine-needle aspiration of tumor tissues, as described previously (23, 26). Mutation testing was conducted by analyzing extracted DNA with a PCR-based DNA sequencing method. For *PIK3CA* mutations, codons (c)532 to c554 of exon 9 (helical domain) and c1011 to c1062 of exon 20 (kinase domain), which included the mutation hotspot region of the *PIK3CA* protooncogene, were examined. Sanger sequencing was conducted after amplification of 276– and 198–base pair amplicons, respectively, using primers designed by the MD Anderson Molecular Diagnostic Laboratory.

Statistical considerations

Expansion was generally added as antitumor activity was seen. For the purpose of mini-expansions, as planned in advance, of up to 14 participants with specific tumor types in which activity was seen, a tumor response signal was defined as one or more of the following: stable disease (SD) for 4 months or more, decrease in measurable tumor by 20% or more, decrease in tumor markers by 25% or more, or a partial response (PR) according to the Choi response criteria (27), that is, decrease in size by $\geq$ 10%, or a decrease in tumor density, as measured by Hounsfield units (HU), by 15% or more. A sample size of 14 patients will have 82% power to detect effects sizes of 0.85, based on the 2-sided Wilcoxon signed rank test at a significance level of 0.05, where effect size is defined as mean change divided by standard deviation.

Descriptive summary statistics were used to assess demographics, safety, and antitumor activity. Categorical data were summarized using frequency and percentages.

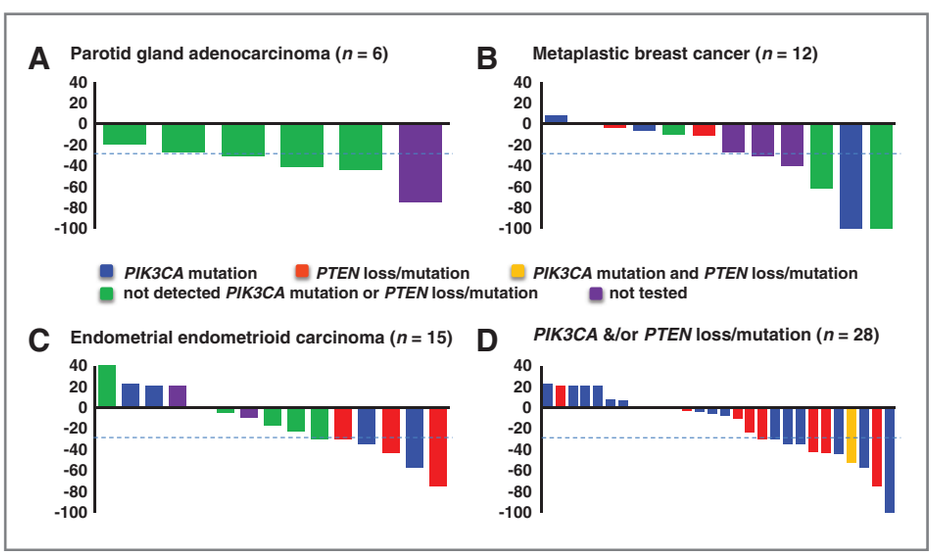

Figure 2. The waterfall plots display best tumor responses by RECIST 1.1 criteria according to specific tumor types. A, parotid gland adenocarcinoma ($n = 6$): of 5 patients tested, none had a *PIK3CA* mutation or *PTEN* loss/mutation. B, metaplastic breast cancer ($n = 12$): nine patients were tested. Four patients had a *PIK3CA* mutation (44%), 2 had *PTEN* loss/mutation (22%), and 3 had neither a *PIK3CA* mutation nor a *PTEN* loss/mutation. C, endometrial endometrioid carcinoma ($n = 15$): 13 patients were tested. Four patients had a *PIK3CA* mutation (31%), 4 had a *PTEN* loss/mutation (31%), and 5 had neither a *PIK3CA* mutation nor a *PTEN* loss/mutation. D, all 28 patients with either a *PIK3CA* mutation and/or *PTEN* loss/mutation.

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Continuous data were summarized by mean, median, range, and coefficient of variation ± standard deviation. Differences in categorical variables were determined by Fisher exact tests. The median duration of responses was estimated using the Kaplan–Meier method. Statistical inferences were based on 2-sided tests at a significance level of $P < 0.05$. Statistical analyses were carried out using GraphPad Prism 5 software (GraphPad Software, Inc).

Results

Patient characteristics

Patient characteristics are listed in Table 1. A total of 136 patients (median age, 53 years; range, 12–75 years) were recruited to 8 dose levels during dose escalation ($n = 39$), as well as during dose expansion ($n = 97$). Patients were heavily pretreated with a median of 4 prior chemotherapy regimens. The greater enrollment of women was directly related to increased dose expansions in patients with breast cancer and gynecologic malignancies, which was reported previously (23, 26). The planned dose expansions in patients of each tumor type that showed tumor response signals were eventually discontinued because of the ongoing liposomal doxorubicin shortage in the United States (28).

Table 1. Baseline demographic data ($N = 136$)

Characteristics	Number of patients (%)
Age, y	
Median (range)	53 (12–75)
Gender	
Women	110 (81%)
Men	26 (19%)
ECOG performance status	
0	38 (28%)
1	78 (57%)
2	18 (13%)
3	2 (1%)
Prior chemotherapy	
Regimens: Median (range)	4 (0–16)
Prior doxorubicin	50 (37%)
Prior bevacizumab	46 (34%)
Prior radiation therapy	
Yes	67 (49%)
Primary diagnosis	
Breast cancer	29 (21%)
Epithelial ovarian cancer	23 (17%)
Colorectal cancer	17 (13%)
Endometrial endometrioid carcinoma	15 (11%)
Carcinoma of the cervix	15 (11%)
Sarcoma	9 (7%)
Thymoma	7 (5%)
Parotid gland adenocarcinoma	6 (4%)
Others	15 (11%)

Evaluation of safety

All 136 patients were evaluable for toxicity. There were no treatment-related deaths. One DLT of grade 4 fistula was observed in one patient at dose level 3, and 2 DLTs consisting of one grade 4 thrombocytopenia and one grade 4 neutropenia were observed in 2 of the 3 patients treated at dose level 7, which was deemed beyond the MTD. Six patients showed decreased left ventricular ejection fraction including grade 2 ($n = 4$) and grade 3 ($n = 2$) heart failure (Table 2). Two dose levels were expanded as seen in Table 3. Initially, a safety dose expansion with an additional 14 patients at dose level 6 was conducted: no DLTs were observed. As per study design, up to 14 patients with the same tumor type who showed clinical response signals were allowed to be enrolled onto the highest dose level shown to be safe. A total of 57 such patients were enrolled onto dose level 6 without DLTs being observed. However, 20 patients (35%) eventually required a dose reduction, mainly because of grade 2 or higher hand–foot syndrome, mucositis, thrombocytopenia, or fatigue beyond the DLT window of the first cycle. Thus, another dose expansion was conducted at dose level 5 to include patients with diseases in which responses had been seen. A total of 49 such patients were enrolled: no DLTs were observed. At dose level 5, 14 patients (29%) eventually required a dose reduction, mainly for mucositis, which was felt to be due to temsirolimus. Therefore, a new intermediate dose level, designated dose level 5A, was created to administer higher doses of liposomal doxorubicin and lower doses of temsirolimus, as seen in Table 2. Because of the national shortage of liposomal doxorubicin (28), only 3 patients were enrolled: no DLTs and additional toxicities were observed. Therefore, dose level 6 was determined to be the MTD.

Overall, approximately 32% of patients ($n = 43$) required a dose reduction, generally after the first 2 cycles. The most common reasons for dose reduction were thrombocytopenia ($n = 11$, 26%), fatigue ($n = 8$, 19%), mucositis ($n = 7$, 16%), neutropenia ($n = 6$, 14%), hand–foot syndrome ($n = 5$, 12%), infusion reactions ($n = 5$, 12%), increased creatinine ($n = 2$, 5%), uncontrolled hypertension ($n = 1$, 2%), decreased left ventricular ejection fraction ($n = 1$, 2%), and nausea ($n = 1$, 2%). Grade 3 or higher treatment-related adverse events (>5%) included anemia, neutropenia, thrombocytopenia, mucositis, hand–foot syndrome, hypertension, and fistula, as shown in Table 2. No Grade 3 or higher adverse events in blood glucose and lipid profiles were seen. The most common grade 2 side effects at dose level 6 (MTD) were anemia ($n = 26$, 46%), mucositis ($n = 10$, 18%), hand–foot syndrome ($n = 8$, 14%), thrombocytopenia ($n = 7$, 12%), hypercholesterolemia ($n = 7$, 12%), hypertriglyceridemia ($n = 6$, 11%), neutropenia ($n = 3$, 5%), and increased creatinine ($n = 3$, 5%).

Evaluation of antitumor activity

All patients were included for efficacy evaluation. As shown in Fig. 1, of 136 patients treated, 28 patients (21%) attained SD at 6 months or more, 27 patients (20%) a PR, and 2 patients (1%) achieved a CR [total

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Table 2. Frequency of grade 3 or higher toxicity per dose levels

Dose levels (number of patients)	Bevacizumab (mg/kg i.v. Q3W)	Temsirolimus (mg i.v. QW)	Liposomal doxorubicin (mg/m^2 i.v. Q3W)	Toxicity grades	Neutropenia	Anemia	Thrombocytopenia	Mucositis	Hand–foot syndrome	Headache	Heart Failure	Hypertension	Fistula	Increased creatinine	Hypercholesterolemia	Hypertriglyceridemia	DLT
DL 1 ($n = 5$)	5	12.5	10	2	1	2	2	0	0	2	0	0	0	1	1	1	0
				3	0	0	1	0	0	0	0	0	0	0	0	0	
				4	0	0	0	0	0	0	0	0	0	0	0	0	
DL 2 ($n = 4$)	5	12.5	20	2	1	1	0	0	1	1	0	0	0	0	0	0	0
				3	1	2	3	1	1	0	0	0	0	0	0	0	
				4	0	0	0	0	0	0	0	0	1	0	0	0	
DL 3 ($n = 8$)	5	25	20	2	1	1	1	2	1	3	0	0	0	0	0	0	1
				3	1	3	2	1	1	1	0	0	0	0	0	0	
				4	0	0	0	0	0	0	0	0	1[a]	0	0	0	
DL 4 ($n = 7$)	10	25	20	2	1	4	2	1	2	3	0	0	0	1	1	2	0
				3	0	1	1	3	2	1	0	0	0	0	0	0	
				4	0	0	0	0	0	0	0	0	0	0	0	0	
DL 5 ($n = 49$)	15	25	20	2	8	12	6	6	6	2	3	3	0	9	3	2	0
				3	4	6	8	1	2	0	0	4	0	0	1	2	
				4	0	1	3	0	0	0	0	0	0	0	0	0	
DL 5A ($n = 3$)	15	20	25	2	0	1	0	0	0	0	0	0	0	1	1	3	0
				3	0	0	0	0	0	0	0	0	0	0	0	0	
				4	0	0	0	0	0	0	0	0	0	0	0	0	
DL 6 ($n = 57$)	15	25	30	2	3	26	7	10	8	5	0	6	0	3	7	6	0
				3	9	4	3	4	4	1	2	6	0	2	0	0	
				4	0	0	3	0	0	0	0	0	5	0	0	0	
DL 7 ($n = 3$)	15	25	40	2	1	2	0	2	1	1	1	0	0	0	0	0	2
				3	0	0	0	0	0	0	0	0	0	0	0	0	
				4	1[a]	0	2[a]	0	0	0	0	0	0	0	0	0	

Abbreviations: DL, dose level; i.v., intravenous infusion; QW, weekly; Q3W, once every 3 weeks.

[a]DLTs with one grade 4 fistula observed in one patient at DL3 and 2 DLTs with grade 4 thrombocytopenia and one grade 4 neutropenia observed in 2 patients at DL 7. Thus, dose level 6 was considered the MTD.

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Table 3. Comparison of patients in 2 expansion dose levels

Characteristics	Dose level 5 ($N = 49$)	Dose level 6 ($N = 57$)	*P*
Age, y			
Median (range)	55 (29–75)	52 (18–73)	0.064
Gender			
Women	42 (86%)	48 (84%)	1.0
Men	7 (14%)	9 (16%)	
ECOG performance status			
0	17 (35%)	18 (32%)	0.64
1	27 (55%)	32 (56%)	
2	4 (8%)	7 (12%)	
3	1 (2%)	0 (0%)	
Prior therapy			
Median (range) systemic regimens	3 (1–8)	3 (0 to16)	0.61
Prior doxorubicin	15 (31%)	24 (42%)	0.23
Prior bevacizumab	22 (45%)	14 (25%)	0.04
Prior mTOR inhibition	3 (6%)	5 (9%)	0.72
Prior radiation therapy	19 (39%)	34 (60%)	0.051
Primary diagnosis			< 0.001
Breast cancer	10 (20%)	19 (33%)	0.19
Ovarian cancer	13 (27%)	2 (4%)	0.001
Colorectal cancer	12 (24%)	2 (4%)	0.003
Uterine cancer	7 (14%)	4 (7%)	0.34
Cervical cancer	3 (6%)	9 (16%)	0.14
Sarcoma	1 (2%)	6 (11%)	0.12
Thymoma	1 (2%)	4 (7%)	0.37
Parotid adenocarcinoma	0 (0%)	5 (9%)	0.06
Others	2 (4%)	6 (11%)	0.28
Study therapy received			
Total number of cycles	294	363	
Median (range)	6 (1–20)	4 (1–37)	0.82
Study agent dose reduction			
Total patients	14 (29%)	20 (35%)	0.53
Liposomal doxorubicin	8 (16%)	19 (33%)	0.07
Temsirolimus	9 (18%)	7 (12%)	0.42
Bevacizumab	3 (6%)	1 (2%)	0.33
Reasons for dose reduction			
Decreased LV ejection fraction	1 (2%)	0 (0%)	0.6
Fatigue	2 (4%)	5 (9%)	
Hand–foot syndrome	1 (2%)	4 (7%)	
Hypertension	1 (2%)	0 (0%)	
Increased creatinine	1 (2%)	0 (0%)	
Infusion reactions	1 (2%)	2 (4%)	
Mucositis	3 (6%)	2 (5%)	
Nausea	0 (0%)	1 (2%)	
Neutropenia	2 (4%)	2 (4%)	
Thrombocytopenia	2 (4%)	4 (7%)	
Major clinical outcomes			
$\geq$ Grade 3 nonhematologic toxicity	4 (8%)	6 (11%)	0.75
$\geq$ Grade 4 hematologic toxicity	3 (6%)	3 (5%)	1.0
DLT	0 (0%)	0 (0%)	1.0
Complete remission	1 (2%)	1 (2%)	1.0
Partial remission	9 (18%)	15 (26%)	0.4
Stable disease $\geq$ 6 months	11 (22%)	6 (11%)	0.12
Any tumor regression	28 (57%)	36 (63%)	0.56

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SD $\geq$ 6 months/PR/CR = 57 (42%); Fig. 1]. The median duration of PR/CR was 9 months (range: 4–36+ months) as determined using the Kaplan–Meier method. It was of great interest to note that only patients with metaplastic breast cancer achieved a CR. One patient received a total of 8 months of study therapy with resolution of her perihepatic implants, right retrocrural node, nodular pleural disease, and right subcarinal node. The other patient who had a PI3K mutation (H1047R) received a total of 12 months of study therapy with biopsy-proven right lower lobe metastasis resolved. For personal reasons, these 2 patients then continued taking an mTOR inhibitor (temsirolimus or everolimus) as a single agent without evidence of tumor progression for 36+ and 18+ months, respectively.

Effect of prior drug exposure on antitumor efficacy. As shown in Table 4, patients without a history of bevacizumab

Table 4. Characteristics of antitumor activities

	Status	Patient number	CR/PR	*P*	SD $\geq$ 6 months/ PR/CR	*P*
Tumor Types		136	29 (21%)		57 (42%)	
Breast cancer, metaplastic		12	5 (42%)		6 (50%)	
Breast cancer, non-metaplastic		17	4 (24%)		5 (29%)	
Carcinoma of the cervix		15	2 (13%)		5 (33%)	
Colorectal carcinoma		17	2 (12%)		8 (47%)	
Endometrial endometrioid carcinoma		15	6 (40%)		8 (53%)	
Epithelial ovarian carcinoma		23	4 (17%)		10 (43%)	
Parotid gland adenocarcinoma		6	4 (67%)		5 (83%)	
Sarcoma		9	1 (11%)		2 (22%)	
Thymoma		7	0		4 (57%)	
Prior exposure						
Doxorubicin	Yes	50	11 (22%)	NS	20 (40%)	NS
	No	86	18 (21%)		37 (43%)	
Bevacizumab	Yes	46	5 (11%)	0.045	17 (37%)	NS
	No	90	24 (26%)		40 (44%)	
Temsirolimus	Yes	11	1 (9%)	NS	3 (27%)	NS
	No	125	28 (22%)		54 (43%)	
Radiation therapy	Yes	67	15 (22%)	NS	27 (40%)	NS
	No	69	14 (20%)		29 (42%)	
Molecular aberrations						
PIK3CA mutation	Yes	19	7 (37%)	NS	10 (53%)	NS
	No	80	14 (17%)		32 (40%)	
PTEN loss/mutation	Yes	11	5 (45%)	NS	5 (45%)	NS
	No	37	9 (24%)		17 (46%)	
PIK3CA mutation and/or *PTEN* loss/mutation	Yes	28	11 (39%)	0.018	14 (50%)	NS
	No	74	12 (16%)		31 (42%)	
EGFR mutation	Yes	2	1 (50%)	NS	2 (100%)	NS
	No	79	19 (24%)		38 (48%)	
KRAS mutation	Yes	14	4 (29%)	NS	9 (64%)	NS
	No	78	21 (27%)		38 (49%)	
BRAF mutation	Yes	1	1 (100%)	NS	1 (100%)	NS
	No	71	21 (30%)		37 (52%)	
C-MET mutation	Yes	0	0	NS	0	NS
	No	26	11 (42%)		14 (54%)	
p53 mutation	Yes	1	0	NS	0	NS
	No	6	3 (50%)		3 (50%)	
ER+ or PR+	Yes	26	10 (38%)	NS	13 (50%)	NS
	No	37	7 (19%)		14 (38%)	
HER2+	Yes	0	0	NS	0	NS
	No	53	15 (28%)		21 (40%)	

Abbreviations: CR, complete response; PR, partial response; SD, stable disease; *n*, number of patients; NS, not significant.

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exposure had a significantly greater chance of achieving PR/CR than those with prior bevacizumab exposure (24/90, 26% vs. 5/46, 11%; $P = 0.045$). If SD at 6 months or more was included, there was no significantly statistical difference between those with and without prior bevacizumab exposure.

Relationship between dose level and antitumor activity. Of the 76 patients treated at dose levels 1 to 5A, 33 (43%) achieved SD $\geq$ 6 months/PR/CR; of the 60 patients treated at dose level 6 or above, 24 (40%) achieved SD $\geq$ 6 months/PR/CR ($P = 0.73$); 13 (17%) patients treated at dose levels 1 to 5A achieved PR/CR compared with 16 (27%) at dose level 6 or higher ($P = 0.2$). These results suggested that there was no statistical difference between the SD $\geq$ 6 months/PR/CR rate at higher versus lower dose levels. Furthermore, some tumor regression was seen in 4 of 5 patients treated at the lowest dose level, and 3 of 5 patients at that dose level achieved SD $\geq$ 6 months/PR/CR, in spite of the small doses used (bevacizumab 5 mg/kg IV every 3 weeks, temsirolimus 12.5 mg IV weekly and liposomal doxorubicin 10 mg/m^2 every 3 weeks). These results indicate that there is no clear relationship between dose and rate of SD $\geq$ 6 months/PR/CR, and that salutary effects can be achieved even at very low dose levels. On the other hand, there was a numerically higher rate of PR/CR at dose level 6 or more (albeit statistically insignificant) and the CRs only occurred at dose levels 5 and 6.

Relationship between diagnoses and antitumor activity. Table 4 shows PR/CR rates of 67% (5/8), 42% (5/12), and 40% (6/15), in parotid gland adenocarcinoma, metaplastic breast cancer, and endometrial endometrioid carcinoma, respectively (Fig. 2). Among 4 patients with clear cell carcinoma of the ovary, 2 achieved SD $\geq$ 6 months/PR/CR (50%). In non-metaplastic breast cancer, the rate of SD $\geq$ 6 months/PR/CR was 30% (5/17); in epithelial ovarian cancer, 43% (10/23); in carcinoma of the cervix, 33% (5/15); in colorectal cancer, 47% (8/17); in high-grade sarcoma, 22% (2/9); and in thymoma, 57% (4/7). Therefore, salutary effects were achieved in a wide variety of tumors.

Relationship between mutational status and efficacy. The majority of patients ($n = 120$) had at least one baseline molecular biomarker (Table 4). Among these biomarkers, only *PIK3CA* mutation and/or *PTEN* loss/mutation was associated with significantly higher PR/CR rates [39%, 11/ 28 patients with *PIK3CA* mutation and/or *PTEN* loss/mutation versus 16%, 12/74 patients without *PIK3CA* mutation and/or *PTEN* loss/mutation ($P = 0.018$)]. However, if SD of 6 or more months was included, there was no difference in rates of SD $\geq$ 6 months/PR/CR (50%, 14/28 versus 42%, 31/74; $P = 0.51$). Of 29 patients who achieved PR/CR, 11 (38%) had a *PIK3CA* mutation and/or *PTEN* loss/mutation. Of 15 patients with endometrial endometrioid carcinoma, 13 were tested for *PIK3CA* mutation and/or *PTEN* loss/mutation and 8 were found to be positive (62%). Five out of 8 patients (63%) with a *PIK3CA* mutation and/or *PTEN* loss/mutation achieved SD $\geq$ 6 months/PR/CR, whereas 1 of 5 patients (20%) without these aberrations achieved SD $\geq$ 6 months/PR/CR ($P = 0.27$). Six out of 9 tested patients with metaplastic breast cancer had a *PIK3CA* mutation or *PTEN* loss/mutation (67%); 3 of 6 patients with a *PIK3CA* mutation and/or *PTEN* loss/mutation achieved SD $\geq$ 6 months/PR/CR, whereas 2 of 3 patients without a *PIK3CA* mutation and/or *PTEN* loss/mutation achieved SD $\geq$ 6 months/PR/CR. Among 5 patients with parotid cancer tested, none had a *PIK3CA* mutation and/or *PTEN* loss/mutation.

Discussion

Activated redundant pathways in advanced malignancies along with evolving self-induced protective mechanisms in response to single-agent therapy contribute to low clinical response rates. It has become increasingly clear that simultaneous inhibition of multiple intracellular signaling pathways is required to improve clinical efficacy. This can be best accomplished with combination therapy composed of multiple agents. Accordingly, we conducted this phase I study using combined bevacizumab and temsirolimus plus liposomal doxorubicin in patients with advanced malignancies to define the safety profile and identify tumor response signals. Overall, patients tolerated the combined regimen with bevacizumab and temsirolimus at their FDA-approved dosages plus liposomal doxorubicin at 30 mg/m^2 every 3 weeks. Although the number of patients in each subgroup is small, this regimen led to a high rate of SD $\geq$ 6 months/PR/CR in several tumor types, including parotid, metaplastic breast, endometrial, ovarian, thymoma, and colorectal cancer (all over 40%) and in cervical, nonmetaplastic breast cancer, and sarcoma (between 22% and 33%; Table 4), despite patients having a median of 4 prior chemotherapy regimens. The overall rate of SD $\geq$ 6 months/PR/CR was 42% (57/136 participants; Table 4). Responses were durable and the median duration of PR/CR was 6 months (range, 1.5–22 months).

Of interest, patients with a *PIK3CA* mutation and/or *PTEN* loss/mutation did well. Among patients with a *PIK3CA* mutation and/or *PTEN* loss/mutation, the PR/CR rates were 39% compared with only 16% among those without these aberrations ($P = 0.018$). Furthermore, of the 29 patients who achieved PR/CR, 11 (38%) had a *PIK3CA* mutation and/or *PTEN* loss/mutation. PTEN loss, which often reflects a *PTEN* mutation, as well as *PIK3CA* mutations, activates the PI3K/AKT/mTOR axis (29). Because mTOR is downstream of these pathways, the role of the mTOR inhibitor temsirolimus in attaining a response may be important (30, 31). However, in many tumor types, even patients without a *PIK3CA* mutation and/or *PTEN* loss/mutation responded, and statistically significant differences between patients with and without molecular aberrations were not apparent. This finding could be explained by one or more of the following: (i) the small number of patients with individual histologies precluded a robust analysis; (ii) the existence of other pathway aberrations that were not tested (e.g., *AKT* or *mTOR* mutations); (iii) the presence of *PIK3CA* mutations in areas of the gene not assayed by our CLIA laboratory (as our assay was limited to exons 9 and 20); (iv) the actions of bevacizumab or liposomal

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doxorubicin unrelated to the PI3K/AKT/mTOR axis; (v) the synergy among the 3 agents.

Several other observations were noted. First, several agents with different toxicity profiles when used individually could be combined at their U.S. Food and Drug Administration (FDA)-approved dosages with good tolerance. These data support the practical strategy of using these agents in combination to simultaneously target multiple pathways, thus producing improved antitumor activity without excessive toxicity. Accordingly, in this clinical trial, we were able to administer dosages of bevacizumab and temsirolimus at their FDA-approved maximum doses (32, 33) and schedules while liposomal doxorubicin was given at a dose of 30 mg/m^2 once every 3 weeks (34), equivalent to the dose currently used as a single agent at 40 mg/m^2 once every 4 weeks (35). Second, there was no statistical relationship between dose level and response. Indeed, 4 of 5 patients at the lowest dose level showed some tumor regression. These findings are reminiscent of those previously reported by our group showing that patients taking lower doses of phase I–targeted agents do not fare worse than individuals taking higher doses (36). A caveat is, however, that the response (PR/CR) rate was numerically higher (albeit not statistically significant) at the higher doses, and that the CRs occurred at dose levels 5 and 6.

When considering the clinical relevance of our findings, several limitations should be borne in mind. First, selection bias based on eligibility criteria may limit the generalizability of our findings, as it does for many clinical trials. However, it should be noted that while these patients mostly had a high performance status and intact organ function, they had also been heavily pretreated. Second, we had a limited sample size available for subgroup analyses, which confounded the ability to validate statistical significance in individual histologies. Third, the recommended phase II dose was difficult to establish, in part because of the nationwide shortage of liposomal doxorubicin. On the other hand, a substantial number of patients were treated at various dose levels, producing significant safety data. Further, the MTD was found to be dose level 6. The MTD was based on first cycle toxicity, as is standard practice. The recommended phase II dose may differ from the MTD because it depends on toxicity that emerges over time. With active regimens such as this one, patients may stay on therapy for months or even years. We found that, with time, 35% (20/57) of patients at dose level 6 eventually required dose reductions, mainly because of grade 2 or higher hand–foot syndrome, mucositis, thrombocytopenia, or fatigue. At dose level 5, 29% (14/49) of patients eventually required a dose reduction, in general for mucositis (probably due to temsirolimus). Further analyses showed that dose reduction was significantly associated with SD $\geq$ 6 months/PR/CR both at dose level 5 ($P = 0.0031$) and dose level 6 ($P = 0.006$) or combined ($P < 0.0001$). This observation may have emerged because patients who had antitumor activity stayed on drug longer and, therefore, eventually required dose reduction; alternatively it could be that toxicities reflect target impact and hence that toxicity and response are correlated. Regardless, it seems that approximately one-third of patients on either dose level 5 or 6 will, with time, require a dose reduction, but that the side effects that surface are reversible and not life threatening. Hence, it seems reasonable to start patients on dose level 6 (the MTD) and reduce the dose if chronic side effects necessitate such a change. However, it should be noted that liberal criteria used to define DLT within the first cycle (21 days) in heavily pretreated patients with advanced solid tumors might result in establishing a higher MTD.

In conclusion, the study regimen that combines bevacizumab at 15 mg/kg once every 3 weeks and the mTOR inhibitor temsirolimus at 25 mg once every week plus liposomal doxorubicin at 30 mg/m^2 once every 3 weeks was well tolerated. The overall rate of SD $\geq$ 6 months/PR/CR was over 50% in heavily pretreated metaplastic breast cancer, parotid gland tumor, thymoma, and endometrial endometrioid cancer. Furthermore patients with ovarian cancer, colorectal cancer, sarcoma, cervical and nonmetaplastic breast cancer all achieved rates of SD $\geq$ 6 months/PR/CR of 22% to 47%, albeit in small numbers of individuals. Patients with a *PIK3CA* mutation and/or *PTEN* loss/mutation had a rate of SD $\geq$ 6 months/PR/CR of 50% (PR/CR rate of 39%). The median duration of PR/CR for all 29 patients who achieved tumor responses was 9 months (range: 4–36+ months). These observations suggest that further clinical evaluation of this regimen is warranted.

Disclosure of Potential Conflicts of Interest

R. Kurzrock: commercial research grants from Genentech/Roche, Wyeth, and Janssen; and honoraria from speakers' bureau from Genentech/Roche. No potential conflicts of interest were disclosed by the other authors.

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Clinical Cancer Research

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