

A First-in-Human, Phase I, Dose-Escalation Study of TAK-117, a Selective PI3K α Isoform Inhibitor, in Patients with Advanced Solid Malignancies



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Abstract

Purpose: To evaluate the safety, MTD, pharmacokinetics, pharmacodynamics, and preliminary antitumor activity of TAK-117 (MLN1117/INK1117), an investigational PI3K α -selective inhibitor, in patients with advanced solid tumors.

Experimental Design: Seventy-one patients received oral TAK-117 once daily [100–300 mg ($n = 24$)] or 3 days per week [Monday–Wednesday–Friday (MWF), 200–1,200 mg ($n = 27$); Monday–Tuesday–Wednesday (MTuW), 200–900 mg ($n = 20$)], in 21-day cycles. Dose escalation proceeded via a 3 + 3 design.

Results: TAK-117 once-daily dosing was associated with dose-limiting grade ≥ 3 alanine/aspartate aminotransferase (ALT/AST) elevations, resulting in a narrow range of tolerable doses (100–150 mg once daily). With MWF/MTuW dosing, no dose-limiting ALT/AST elevations occurred until the MTD of 900 mg; total weekly dose was 2.6-fold that of 150 mg once daily. Drug-related grade ≥ 3 adverse events occurred in 25%/22%/35% (including

hyperglycemia in 0%/7%/15%) of once-daily/MWF/MTuW patients. TAK-117 (100–1,200 mg) exhibited moderately fast oral absorption, a generally dose proportional increase in exposure, and plasma half-life of approximately 11 hours. Total weekly exposures with 900 mg MWF/MTuW dosing were approximately 4 times greater than with 150 mg once daily. Skin pS6 expression was suppressed at ≥ 200 mg. There were 3/1/0 partial responses (once daily/MWF/MTuW) and 5/7/5 patients had stable disease lasting ≥ 3 months (all *PIK3CA* mutated).

Conclusion: Intermittent dosing of TAK-117 had an acceptable safety profile and enabled higher doses and total weekly exposures versus once-daily dosing. Although the potential for TAK-117 as single-agent therapy appears limited, further evaluation in combination approaches for advanced solid tumors is warranted. *Clin Cancer Res*; 1–9. ©2017 AACR.

Introduction

The PI3K pathway is a frequently dysregulated signaling cascade in human cancer (1, 2). Activating mutations in

PIK3CA (encoding the p110 α catalytic subunit of PI3K α) are strongly implicated in oncogenic PI3K signaling (2–4). The high frequency of *PIK3CA* mutations (~5%–25% of solid tumors) suggests a therapeutic role for PI3K α inhibitors in tumors driven by PI3K pathway activation (4–7). Although several nonselective class I PI3K (pan-PI3K) pathway inhibitors are in development (8–15), in theory, PI3K α -selective inhibitors should provide more specific inhibition of PI3K α while minimizing the side effects caused by nonselective blockade of other PI3K isoforms. A higher selectivity, wider therapeutic window, and potentially improved benefit/risk profile would also provide opportunities for combining PI3K α -selective inhibitors with other therapies.

TAK-117 (MLN1117/INK1117) is a potent and selective oral PI3K α isoform inhibitor (IC₅₀ of 21 nmol/L against PI3K α) that has demonstrated >100-fold selectivity relative to other class I PI3K family members (PI3K β / γ / δ) and mTOR, and a high degree of selectivity against many other kinases. TAK-117 administration in *PIK3CA*-mutant tumor cell lines resulted in potent PI3K pathway inhibition, blockade of cellular proliferation, and apoptosis (16). Administration of TAK-117 also led to dose-dependent inhibition of tumor growth in murine xenograft models of human cancer (e.g., breast carcinoma) bearing *PIK3CA* oncogenic mutations, with corresponding inhibition of PI3K pharmacodynamic markers in tumor tissue (16). Preclinical antitumor activity of single-agent TAK-117 has been shown to be independent of dosing schedules and driven by total plasma exposures

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Translational Relevance

The PI3K signaling pathway is frequently dysregulated in human cancer, and activating mutations in *PIK3CA* (encoding the p110 α catalytic subunit of PI3K α) are strongly implicated in oncogenic PI3K signaling. In addition, activation of PI3K pathway has also been implicated as a tumor cell survival mechanism in response to chemotherapy. PI3K α -selective inhibitors, versus pan-PI3K pathway inhibitors, should provide more specific inhibition of PI3K α while minimizing the side effects caused by nonselective blockade of other PI3K isoforms. This first-in-human phase I study investigated TAK-117, a potent and selective oral PI3K α isoform inhibitor, in adult patients with advanced solid tumors. TAK-117 demonstrated an acceptable safety profile at the MTDs and preliminary evidence of single-agent antitumor activity in this study. In addition, results showed that intermittent dosing of TAK-117 (3 days/week) had improved tolerability versus continuous daily dosing of TAK-117. Intermittent TAK-117 dosing resulted in fewer transaminase elevations versus once-daily dosing and allowed for higher dose levels (thus, higher total weekly doses and exposure). This high-dose intermittent schedule may allow TAK-117 to be combined with other antitumor therapies, to effectively block the PI3K pathway activation that is a part of the adaptive survival mechanism of tumor cells following exposure to cellular stress and insults introduced by other drugs.

(17, 18). Conversely, TAK-117 was not efficacious in tumor models harboring *PTEN* and/or *KRAS* mutations (16). Preclinical studies showed TAK-117 to have low potential for disrupting glucose metabolism or for causing cardiac adverse events; in rats and monkeys, doses up to 50 mg/kg/day were well tolerated.

This phase I study of TAK-117 (NCT01449370) aimed to determine the MTD and/or optimal biologic dose and dose-limiting toxicities (DLTs) when administered on a continuous daily (once daily) or intermittent dosing schedule to patients with advanced solid tumors and known *PIK3CA* mutation status. Further objectives were to investigate safety/tolerability, pharmacokinetics, pharmacodynamics, and preliminary single-agent antitumor activity.

Patients and Methods

Study design

This phase I dose-escalation study evaluated 3 dosing schedules of oral TAK-117: once daily or intermittent [Monday, Wednesday, Friday (MWF) or Monday, Tuesday, Wednesday (MTuW)] dosing in 21-day cycles until disease progression or unacceptable toxicities. TAK-117 was administered as capsules on an empty stomach, at approximately the same time each dosing day. Dose escalation followed a modified 3 + 3 design for all 3 dosing schedules. Dose escalation and dose modification guidelines are available in the Supplementary Material.

The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. Institutional Review Boards approved all aspects of the study. All participants provided written informed consent.

Patients

Eligible patients were ≥ 18 years old, had locally advanced or metastatic solid tumors (excluding primary brain tumors) with evidence of disease progression per RECIST v1.1 (19), had failed or were not eligible for standard-of-care therapy, had an Eastern Cooperative Oncology Group performance status of 0–1, and adequate organ function (Supplementary Material). Prior assessment of tumor *PIK3CA* mutation status was a requirement for study enrollment. This was performed by means of local testing, using archival tissue samples. Patients were eligible to enter the study regardless of the presence or absence of *PIK3CA* mutations. Once enrolled, all patients who received at least one dose of TAK-117 had their *PIK3CA* mutation status reassessed at a central laboratory.

Assessments

The primary objective was determination of TAK-117 MTDs for daily and intermittent dosing schedules. The MTD was defined as the highest dose level at which no more than 1 DLT occurred during cycle 1 in a minimum of 6 patients. DLTs are defined as any of the following toxicities, provided that they were considered to be related to TAK-117 and that they occurred in cycle 1 (i.e., the first 21 days) following the patient's first administration of TAK-117:

- Grade 3 nausea and/or vomiting, or diarrhea lasting >7 days despite optimal treatment.
- Grade 2 fasting hyperglycemia lasting >14 days despite optimal treatment, or grade 3 fasting hyperglycemia lasting >24 hours despite optimal treatment.
- Grade 3 rash lasting >7 days despite optimal treatment (all subjects could receive topical steroid treatment, oral antihistamines, and pulse oral steroids, if necessary).
- Other grade ≥ 3 nonhematologic toxicity considered clinically significant by the investigator.
- Grade 3 thrombocytopenia with bleeding.
- Grade 4 neutropenia (absolute neutrophil count ≤ 500) lasting >7 days in the absence of growth factor support.
- Grade 4 neutropenia of any duration associated with fever $\geq 38.5^\circ\text{C}$ and/or systemic infection.
- Any other grade ≥ 4 hematologic toxicity.
- Inability to administer $\geq 75\%$ of the planned doses of TAK-117 within cycle 1 due to drug-related toxicity.
- Any clinically significant occurrence that the investigators and sponsor agreed would place patients at an undue safety risk.

Safety was assessed throughout the study and according to NCI Common Terminology Criteria for Adverse Events (NCI-CTCAE) v4.03. Antitumor activity was evaluated every 3 cycles according to RECIST v1.1. Blood samples were collected on day 1 at the following time points: predose (within 1 hour), 0.5, 1, 2, 4, and 8 hours postdose, at 24 ± 2 hours postdose (predose on day 2), and at 48 ± 3 hours postdose (predose on day 3; MWF only); additional sampling time points are described in the Supplementary Material. The plasma concentration of TAK-117 was measured using liquid chromatography mass spectrometry with an assay range of 1 to 1,000 ng/mL. TAK-117 pharmacodynamics were evaluated via IHC analysis of phosphorylated S6 (pS6) expression at Ser235/236 in formalin-fixed paraffin-embedded sections of skin and tumor tissues. Skin biopsies from all patients and tumor biopsies from a subset of patients (who signed

optional consent) were collected at screening and within 2 to 4 hours after dosing in week 2 of cycle 1 (once-daily dosing) or on day 1 of cycle 2 (intermittent dosing). A histochemical score (H-score) was assigned to each sample based on levels and areas of pS6 expression in the epidermis of a skin sample or tumor sample section as described previously (20).

Statistical analysis

Patients evaluated for safety had received ≥ 1 dose of TAK-117. Response-evaluable patients had received ≥ 1 dose of TAK-117 and had ≥ 1 posttreatment response assessment. DLT-evaluable patients included those who either experienced a DLT, or received $\geq 75\%$ of the planned TAK-117 doses in cycle 1 and were viewed by the sponsor and investigators to have adequate safety data to conclude that no DLTs occurred in cycle 1. Pharmacokinetics-evaluable patients had received ≥ 1 dose of TAK-117 and had sufficient concentration–time data to calculate ≥ 1 pharmacokinetic parameter.

Antitumor activity was assessed by summarizing the objective response rate [ORR; complete response plus partial response (PR)] and clinical benefit rate (CBR; stable disease ≥ 3 months plus ORR). The safety population and pharmacodynamic parameters were summarized by dose group using descriptive statistics. Pharmacokinetic parameters were estimated using noncompartmental methods (WinNonlin[®] Professional v6.1+).

Results

Patients

From October 6, 2011 to April 21, 2014, 71 patients were enrolled from 5 centers in the United States, United Kingdom, and Spain (Table 1). In total, 24 patients were assigned to once-daily (6 at 100 mg, 6 at 150 mg, 8 at 200 mg, and 4 at 300 mg), 27 to

MWF (3 patients each at 200, 300, 400, and 600 mg, 12 at 900 mg, and 3 at 1,200 mg), and 20 to MTuW (3 patients each at 200, 400, and 600 mg, and 11 patients at 900 mg) dosing.

Sixty-one patients (86%) had *PIK3CA*-mutated tumors; the most common tumors were colorectal (25%) and breast (23%). Discontinuations before treatment completion ($n = 69$) were due to disease progression ($n = 54$), adverse events (AEs; $n = 9$), subject decision ($n = 4$), or other reasons ($n = 3$).

DLTs and MTD

In total, 67 patients were DLT evaluable: 24 once daily, 25 MWF, and 18 MTuW patients. At data cutoff (September 14, 2015), cycle 1 DLTs, all grade 3 in severity, had occurred in 7 patients: 2 on the once-daily schedule [1 at 200 mg: drug-induced hepatitis; 1 at 300 mg: elevated alanine aminotransferase (ALT) and aspartate aminotransferase (AST)], 4 on the MWF schedule (2 at 900 mg: 1 with ALT and AST elevation, 1 with hyperosmolar state; 2 at 1,200 mg: 1 with nausea, vomiting, diarrhea, and hyperglycemia, 1 with decreased appetite), and 1 on MTuW dosing (at 900 mg: nausea). The MTD of TAK-117 for the once-daily schedule was 150 mg. For both intermittent schedules, the MTD was 900 mg.

No patients in the 100 mg once-daily group and none of the initial 3 patients in the 200 mg once-daily group reported DLTs. Dose was escalated to 300 mg once daily, and 1 of 4 patients experienced DLTs of grade 3 AST elevation and grade 3 ALT elevation from day 8, with resolution to grade 1 intensity within 2 to 11 days. Following dose deescalation to 200 mg, an additional 5 patients were treated, and 1 patient experienced a DLT of grade 3 drug-induced hepatitis from days 25 to 28. All AEs resolved without sequelae. Although tolerability of the 200-mg and 300-mg once-daily doses during cycle 1 was acceptable, AEs

Table 1. Patient characteristics and baseline demographics

Characteristic	Total N = 71	TAK-117 QD 100–300 mg n = 24	TAK-117 MWF 200–1,200 mg n = 27	TAK-117 MTuW 200–900 mg n = 20
Median age, years (range)	58.0 (31–80)	58.5 (35–75)	59.0 (31–77)	56.0 (41–80)
Gender male:female, %	31:69	33:67	22:78	40:60
Race, n (%)				
White	65 (92)	23 (96)	24 (89)	18 (90)
Black/African American	2 (3)	0	1 (4)	1 (5)
Asian	3 (4)	1 (4)	1 (4)	1 (5)
Other/not reported	1 (1)	0	1 (4)	0
<i>PIK3CA</i> mutation, n (%)				
Positive	61 (86)	21 (88)	24 (89)	16 (80)
Wild-type	8 (11)	2 (8)	2 (7)	4 (20)
Unknown	2 (3)	1 (4)	1 (4)	0
Number of prior therapies, median (range)	5.0 (1–26)	6.0 (2–16)	4.0 (1–26)	5.0 (2–13)
Tumor type, n (%)				
Colorectal	18 (25)	7 (29)	6 (22)	5 (25)
Breast	16 (23)	9 (38)	5 (19)	2 (10)
Ovarian	9 (13)	0	7 (26)	2 (10)
Lung	6 (8)	2 (8)	1 (4)	3 (15)
Head and neck	5 (7)	2 (8)	1 (4)	2 (10)
Gastric	2 (3)	2 (8)	0	0
Endometrial	3 (4)	0	2 (7)	1 (5)
Prostate	1 (1)	0	0	1 (5)
Renal	1 (1)	1 (4)	0	0
Other ^a	10 (14)	1 (4)	5 (19)	4 (20)
Median time since initial diagnosis, years (range)	3.8 (0.8–28.2)	3.6 (1.0–28.2)	3.8 (0.8–20.4)	3.9 (0.9–25.8)

Abbreviation: QD, once daily.

^aIncludes squamous cell carcinoma, cervical cancer, squamous cell carcinoma of the tonsil, ocular melanoma, adenoid cystic carcinoma of the hard palate, metastatic poorly differentiated transitional cell carcinoma of the bladder, serous carcinoma of fallopian tube, cervical squamous cell carcinoma, transitional cell carcinoma of the bladder, and penile carcinoma ($n = 1$ each).

Table 2. Summary of safety profiles of TAK-117 by dosing schedule

AE, n (%)	Total		TAK-117 QD		TAK-117 MWF		TAK-117 MTuW	
	N = 71		100–300 mg		200–1,200 mg		200–900 mg	
	All-cause	Drug-related	All-cause	Drug-related	All-cause	Drug-related	All-cause	Drug-related
All grades	71 (100)	63 (89)	24 (100)	21 (88)	27 (100)	24 (89)	20 (100)	18 (90)
Grade ≥ 3	38 (54)	19 (27)	13 (54)	6 (25)	12 (44)	6 (22)	13 (65)	7 (35)
SAE	30 (42)	7 (10)	11 (46)	2 (8)	11 (41)	3 (11)	8 (40)	2 (10)
Discontinuations due to AEs	9 (13)	4 (6)	4 (17)	1 (4)	2 (7)	1 (4)	3 (15)	2 (10)
Dose modifications/interruptions due to AEs	29 (41)	20 (28)	11 (46)	5 (21)	9 (33)	7 (26)	9 (45)	8 (40)
On-study deaths ^a	6 (8)	0	3 (13)	0	3 (11)	0	0	0

Abbreviations: QD, once daily; SAE, serious AE.

^aWithin 30 days of last dose of study drug.

that occurred during cycles 2 and 3 resulted in dose interruptions and reductions. Thus, the dose was deescalated to 150 mg, at which none of the 6 patients reported DLTs.

As once-daily dosing resulted in dose-limiting transaminase elevations, intermittent dosing was evaluated in both MWF and MTuW schedules. On the MWF dosing schedule, no DLTs were reported in the 200, 300, 400, and 600 mg MWF groups. At 900 mg, among the initial 6 patients treated, 1 patient experienced a DLT of grade 3 AST elevation and grade 3 ALT elevation from days 19 to 44. Dose was escalated to 1,200 mg, and 2 of the 3 patients had DLTs (all were grade 3): 1 patient experienced nausea, vomiting, diarrhea, and hyperglycemia, and 1 patient experienced grade 3 decreased appetite. Following dose deescalation to 900 mg, an additional 6 patients were treated, and 1 patient experienced grade 3 hyperosmolar state from days 13 to 26. All AEs resolved without sequelae.

There were no reports of DLTs in the 200, 400, and 600 mg MTuW groups. At 900 mg, none of the initial 3 patients reported a DLT, but 1 patient experienced a dose reduction to 600 mg. Of the next 3 patients who enrolled at 900 mg, 1 patient experienced a DLT of grade 3 nausea from days 8 to 22 and a subsequent dose reduction to 600 mg; AEs resolved without sequelae. Two of the 5 patients in the next enrollment for the 900 mg MTuW group experienced dose reduction to 600 mg. Dose escalation did not proceed in this schedule.

Treatment exposure

All 71 patients received at least 1 dose of TAK-117. Patients on the once-daily schedule received a median of 3 cycles (range, 1–18); 7 patients received ≥ 5 cycles. Those on the MWF schedule

received a median of 3 cycles (range, 1–15); 9 patients received ≥ 5 cycles. In the MTuW arm, patients received a median of 3 cycles (range, 1–27); 4 patients received ≥ 5 cycles. Median (range) treatment duration was 7.5 (1.0–53.1), 8.7 (0.7–44.7), and 7.4 (2.3–80.4) weeks on the once-daily, MWF, and MTuW schedules, respectively.

Safety

All patients reported at least 1 AE (most commonly nausea, vomiting, and fatigue; Tables 2 and 3), 89% of patients reported at least 1 drug-related AE (most commonly nausea, hyperglycemia, and vomiting), and 54% of patients reported at least 1 grade ≥ 3 AE (with drug-related grade ≥ 3 AEs in 27%). The most frequently observed grade ≥ 3 AEs were elevated liver transaminases (15% of patients) and hyperglycemia (8%); these were considered to be drug related in 14% and 7% of patients, respectively (Supplementary Table S1). Compared with once-daily dosing, intermittent dosing was associated with a lower incidence of grade ≥ 3 drug-related ALT/AST elevations (once daily/MWF/MTuW, 21%/15%/5%), but an increased incidence of grade ≥ 3 drug-related hyperglycemia (once daily/MWF/MTuW, 0%/7%/15%).

Overall, serious AEs and discontinuations due to AEs were reported in 42% and 13% of patients, respectively, and these were drug related in 10% and 6% of patients. Three patients each in the once-daily and MWF dosing groups died within 30 days of the last dose of study drug, primarily due to disease progression or disease burden; no deaths were attributed to TAK-117. Further details of the safety profile of TAK-117 are provided in the Supplementary Material.

Table 3. Summary of most common any-cause AEs by dosing schedule (any grade in $\geq 20\%$ and grade ≥ 3 in $\geq 5\%$ of patients overall)

AE, n (%)	Total		TAK-117 QD		TAK-117 MWF		TAK-117 MTuW	
	N = 71		100–300 mg		200–1,200 mg		200–900 mg	
	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3	All grades	Grade ≥ 3
Nausea	43 (61)	3 (4)	14 (58)	1 (4)	15 (56)	1 (4)	14 (70)	1 (5)
Vomiting	36 (51)	2 (3)	8 (33)	1 (4)	16 (59)	1 (4)	12 (60)	0
Fatigue	34 (48)	3 (4)	12 (50)	1 (4)	12 (44)	1 (4)	10 (50)	1 (5)
Diarrhea	33 (46)	2 (3)	12 (50)	0	12 (44)	1 (4)	9 (45)	1 (5)
Hyperglycemia	26 (37)	6 (8)	7 (29)	0	10 (37)	2 (7)	9 (45)	4 (20)
Decreased appetite	24 (34)	2 (3)	8 (33)	0	10 (37)	1 (4)	6 (30)	1 (5)
Constipation	25 (35)	0	9 (38)	0	9 (33)	0	7 (35)	0
Elevated AST	24 (34)	5 (7)	10 (42)	3 (13)	10 (37)	2 (7)	4 (20)	0
Elevated ALT	19 (27)	6 (8)	9 (38)	3 (13)	7 (26)	2 (7)	3 (15)	1 (5)
Anemia	15 (21)	2 (3)	4 (17)	0	9 (33)	2 (7)	2 (10)	0
Cough	14 (20)	0	5 (21)	0	6 (22)	0	3 (15)	0
Hypokalemia	14 (20)	1 (1)	3 (13)	0	7 (26)	0	4 (20)	1 (5)
Respiratory failure	4 (6)	4 (6)	1 (4)	1 (4)	3 (11)	3 (11)	0	0

Abbreviations: QD, once daily; SAE, serious AE.

Pharmacokinetics and pharmacodynamics

Among 69 pharmacokinetic-evaluable patients, TAK-117 exhibited moderately fast oral absorption with a median time to maximum observed plasma concentration of 1.5 to 6 hours (Fig. 1A; Supplementary Table S2). TAK-117 plasma exposures were generally dose proportional over the 100 to 900 mg dose range, albeit with a moderate-to-high intersubject variability (%CV around AUC_{0-24} 6.6–123). Based upon a preliminary power-model analysis to assess dose linearity over the entire dose range (100–1,200 mg), the slope of the dose versus area under the plasma concentration–time curve from 0 to 24 hours ($AUC_{0-24\text{ h}}$) was 0.871 (95% confidence interval, 0.627–1.115), suggesting that TAK-117 exhibits a slightly less than dose proportional increase in exposures over the entire dose range (Fig. 1B).

The mean terminal half-life of TAK-117 was approximately 11 hours (range, 6–14 hours). There was no meaningful accumulation of TAK-117 with repeated dosing for any schedule (Supplementary Table S3). Intermittent schedules achieved higher total weekly doses and exposures of TAK-117. In previously tested

preclinical tumor models and dose ranges, TAK-117 antitumor activity correlated linearly with plasma exposures, and no evidence of an exposure threshold for efficacy was observed (17, 18). Based upon a preliminary pharmacokinetic model that simulated various dosing scenarios (Fig. 1C), compared with once-daily dosing, intermittent dosing schedules were predicted to achieve higher total weekly exposures of TAK-117 and a longer duration above pharmacologically active thresholds based upon nonclinical exposure–antitumor response evaluation. The total weekly doses were 1,050 mg at an MTD of 150 mg once daily and 2,700 mg at the recommended phase II dose of 900 mg MWF or MTuW. These doses were predicted to provide total weekly AUC at steady state (AUC_{ss}) values of approximately 105,000 ng/hour/mL for once-daily dosing and approximately 470,000 ng/hour/mL for the intermittent dosing schedules. Dosing with the once-daily schedule resulted in ALT/AST elevations and prompted the evaluation of an alternative intermittent dosing schedule. The prediction of higher total weekly exposures with intermittent dosing was confirmed following completion of the 900 mg MTuW and MWF cohorts (Supplementary Table S2). The administration of TAK-117 via the intermittent dosing schedule more than doubled the weekly dose and achieved higher weekly total exposures (maximize AUC_{ss}) than the once-daily schedule. In addition, based upon the pharmacokinetic model predictions, the duration above the preclinically estimated desirable average plasma concentration (C_{avg}) for once-daily dosing was approximately 16 hours/week versus approximately 75 hours/week for the 2 intermittent dosing schedules.

Sixty patients had sufficient skin samples for pharmacodynamic evaluation. TAK-117 at doses between 200 and 900 mg suppressed pS6 expression to varying degrees in skin biopsies (Fig. 2A). Of 5 paired tumor samples examined, a TAK-117–induced reduction in pS6 expression was seen in tumor biopsies taken from 2 patients on the 200 mg MWF/MTuW schedules (Fig. 2B).

Antitumor activity

Among 61 response-evaluable patients (once daily, $n = 20$; MWF, $n = 25$; MTuW, $n = 16$), 53 patients had tumors with *PIK3CA* mutation. Four patients (all *PIK3CA* mutants) achieved a PR, 3 with breast cancer and 1 with gastric cancer (Fig. 3). The median duration of PR was 7 months (range, 3.6–12.2 months). Twenty-seven of 61 patients (44%) were assessed by investigators to have stable disease. Seventeen patients (28%; all *PIK3CA* mutants) had stable disease lasting ≥ 3 months. CBR was 34%; rates (40%, 32%, 31%), and median durations of clinical benefit (4.8, 4.8, 5.3 months) were comparable between the once-daily, MWF, and MTuW schedules, respectively.

Discussion

TAK-117 has demonstrated preclinical antitumor activity in tumor cell lines and xenograft models of human solid tumors bearing *PIK3CA* mutations (16). In this study of 71 patients with advanced solid tumors who had received prior treatments (86% of whom were *PIK3CA* mutated), 3 different dose schedules of TAK-117 were evaluated. The MTD of TAK-117 was established as 150 mg once daily and 900 mg for both intermittent (MWF/MTuW) schedules.

The safety profile of TAK-117 was acceptable and consistent with profiles reported for other small-molecule PI3K inhibitors

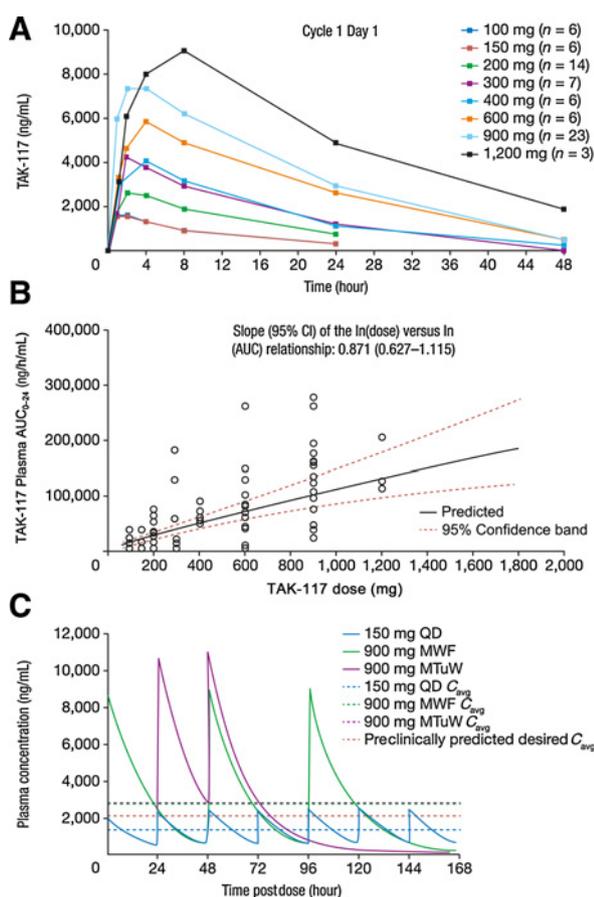


Figure 1.

Pharmacokinetic analyses of TAK-117: **A**, Mean TAK-117 plasma concentration–time profile by dose level on day 1 of cycle 1. **B** and **C**, Dose proportionality plot of TAK-117 dose versus $AUC_{0-24\text{ h}}$ (**B**); and simulated TAK-117 plasma concentration–time profiles over a dosing week for the once-daily and intermittent dosing schedules (**C**). $AUC_{0-24\text{ h}}$, area under the TAK-117 plasma concentration–time curve from 0 to 24 hours; C_{avg} , average TAK-117 plasma concentration; CI, confidence interval; QD, once daily.

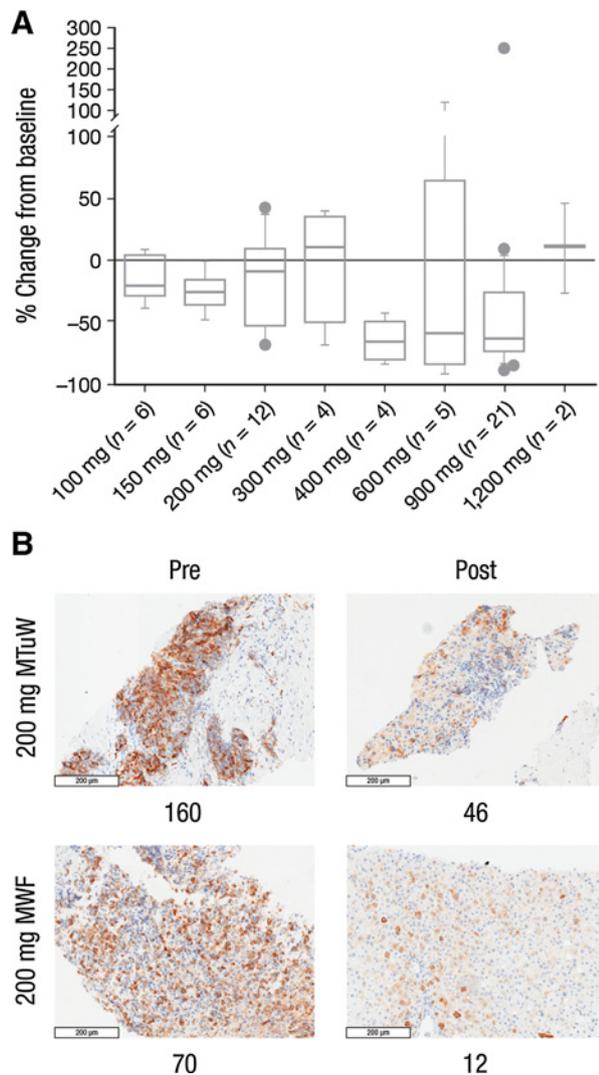


Figure 2. Pharmacodynamic effects of TAK-117: **A** and **B**, Box-and-whisker plot showing changes from baseline in pS6 expression in skin biopsies [**A**; boxes, interquartile distance (Q1-Q3); bars, median; whiskers, 10th and 90th percentiles; circles, observations outside 90% distribution interval]; and representative images of tumor biopsies from patients dosed at 200 mg on the intermittent schedules showing decreased pS6 expression (**B**; indicated by the IHC H-score provided below each image). Scale bar, 200 mmol/L.

(10, 12, 13, 21–25). Drug-related grade ≥ 3 AEs occurred in 27% of patients, and discontinuations due to all-cause AEs in 13%. Common AEs included gastrointestinal and constitutional toxicities, along with changes in liver transaminases and blood glucose elevation, both of which were transient in nature.

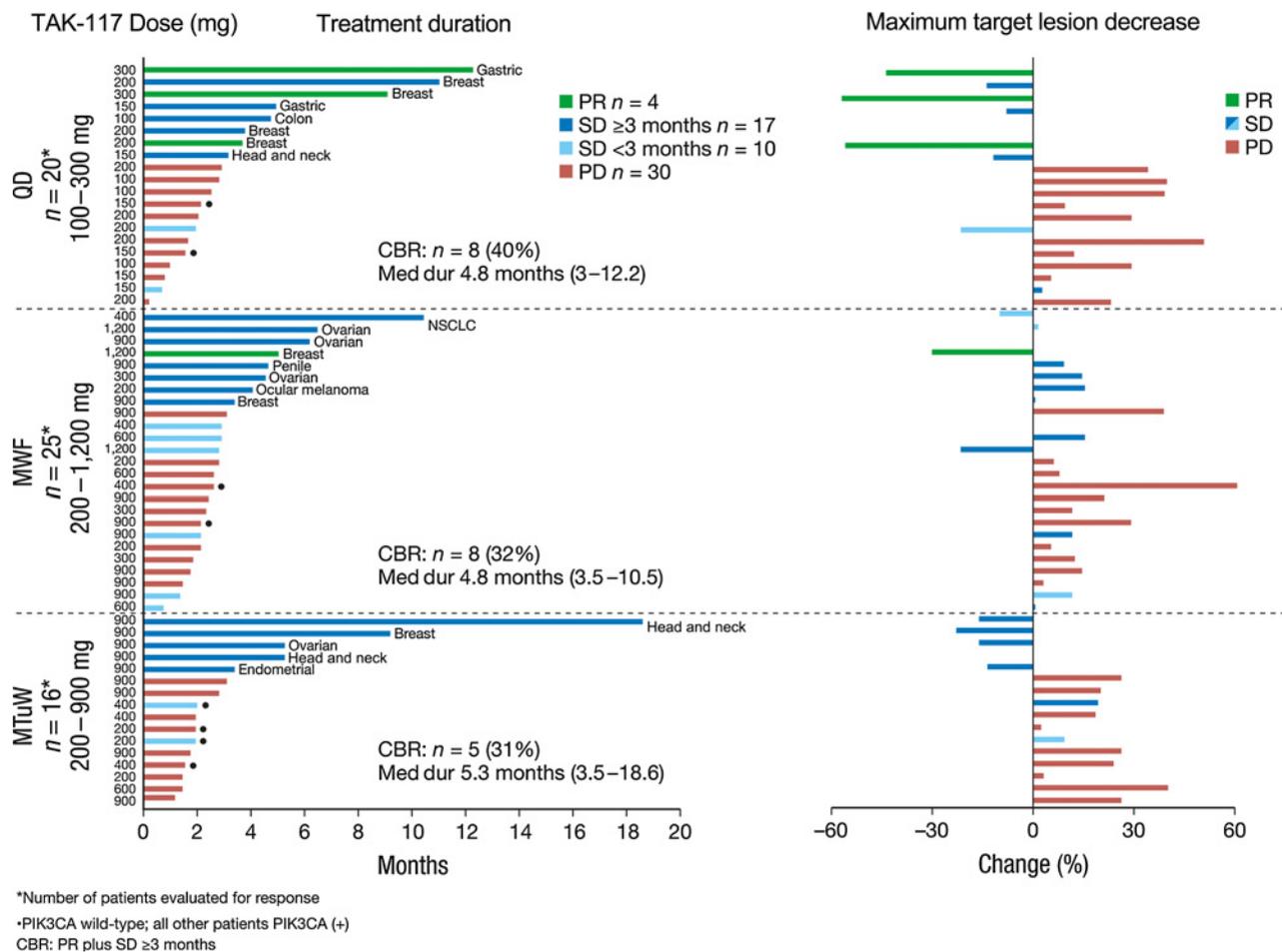
Although TAK-117 administration resulted in hyperglycemia, a known side effect of PI3K inhibition (10, 12, 13, 21, 22, 24, 25), the rate of drug-related grade ≥ 3 hyperglycemia (7% of patients overall; 3% of patients receiving 150 mg once daily or 900 mg intermittently) observed with TAK-117 was generally lower than rates previously reported with other PI3K inhibitors. Grade ≥ 3 hyperglycemia occurred more frequently in patients on the intermittent schedules (MWF, 7%; MTuW, 15%) versus once-daily dosing (0%). This higher rate of severe hyperglycemia with

intermittently administered TAK-117 may reflect the higher weekly dose and exposure achieved relative to once-daily dosing. TAK-117-related grade ≥ 3 rash was not reported in the current study. In comparison, grade ≥ 3 rash occurred in 8% of patients who received continuous daily pictilisib (15–450 mg), including 2 DLTs at the 450 mg dose level (12). Grade ≥ 3 rash was also previously reported in 7% of patients who received continuous daily buparlisib (24). Furthermore, TAK-117 was not associated with mood alterations, as reported with buparlisib (21, 22). Further studies are required to fully assess the safety profile of TAK-117 relative to other pan-PI3K or selective PI3K α inhibitors.

Preliminary pharmacokinetic simulations predicted that, compared with once-daily dosing at 150 mg, intermittent dosing (MTuW or MWF) at the MTD of 900 mg would achieve higher total weekly plasma exposures of TAK-117 and longer durations over which the C_{avg} would exceed the desirable pharmacologically active concentrations predicted from preclinical data. Patients treated with the once-daily schedule (150 mg MTD; weekly total dose of 1,050 mg) demonstrated an increased rate of ALT/AST elevations and dose modifications/interruptions, thus prompting evaluation of alternative schedules to dose escalate and maximize AUC. Intermittent dosing at 900 mg (total weekly dose of 2,700 mg) allowed a larger dose of TAK-117 to be administered to achieve higher total weekly exposures with improved tolerability, without increasing toxicity with the exception of grade ≥ 3 hyperglycemia. Preclinical xenograft studies of TAK-117 suggested that its inhibitory effect on tumor growth is dependent on total systemic exposure levels, regardless of whether TAK-117 is given via continuous or intermittent dosing (17, 18). Furthermore, pharmacodynamic analysis in the current study indicated that the systemic exposures seen with intermittent dosing at 200 to 900 mg resulted in PI3K pathway modulation as evidenced by suppression of pS6 expression, thus confirming the on-target activity and dose range required for clinical response. On the basis of these data, intermittent dosing of TAK-117 (900 mg MTuW) has been taken forward into new trials.

Pharmacokinetic analysis demonstrated that the mean terminal half-life of TAK-117 ranged from 6 to 14 hours and that there was no meaningful plasma accumulation of TAK-117 following repeated dosing in any of the dosing schedules. Earlier studies of other PI3K inhibitors (pan-PI3K and PI3K α specific) have mostly used once-daily schedules with the assumption that continuous suppression of the PI3K pathway is required for antitumor effects in *PIK3CA*-mutated tumors (12, 21–24). However, a recent report showed that pulsatile administration (3 times/week) of copanlisib increased the suppression of tumor growth compared with continuous dosing in a *PIK3CA*-mutated breast cancer model. The authors concluded that intermittent target inhibition may allow adequate inhibition of the PI3K pathway without causing excessive toxicity or chronic feedback reactivation of upstream receptors (26). Therefore, evaluation of clinical efficacy of the intermittent versus continuous dosing schedules of PI3K inhibition is warranted. Furthermore, intermittent dosing could potentially provide a better safety and tolerability profile, needed for dose durability and maintenance of patients on treatment.

Antitumor activity was observed with TAK-117 (4 PRs in 67 response-evaluable patients), but its single-agent efficacy was limited. Despite the higher exposure levels achieved with intermittent schedules, both CBRs (40%, 32%, and 31%) and median durations (4.8, 4.8, and 5.3 months) were comparable between the once-daily, MWF, and MTuW dosing groups. Although tumor

**Figure 3.**

Treatment duration and response in patients treated with TAK-117 100 to 1,200 mg. Med dur, median duration of clinical benefit; NSCLC, non-small cell lung cancer; PD, progressive disease; QD, once daily; SD, stable disease.

types were diverse, the majority (86%) were confirmed to carry *PIK3CA* mutations. Assessment of *PIK3CA* mutation status before study enrollment was done by nonstandardized, local testing. Blood-based assays have become available since this study was devised, and the use of such methods would enable improved assessments if the study were re-created today. The antitumor activity we observed with TAK-117 is in line with that of other PI3K inhibitors tested in similar patient populations. For example, daily dosing of single-agent buparlisib (12.5–150 mg) in 83 patients yielded 1 confirmed PR and a disease control rate of 41% (24). Similarly, PX-866 achieved stable disease in 22% and 53% of patients on intermittent (days 1–5 and 8–12 of a 28-day cycle) and once-daily dosing schedules, respectively (23).

It is possible that continuous PI3K pathway suppression (via daily dosing or pulsatile dosing with a tightly controlled off-time) is needed for clinical efficacy in tumors carrying *PIK3CA* mutations, where these activating mutations may function as a driver event in tumorigenesis. However, the requirement for PI3K target inhibition may be significantly different in a combination setting. Activation of the PI3K pathway in tumor cells may represent a compensatory survival mechanism in response to chemotherapy (27–29). Synergistic antitumor activity has been reported with

PI3K inhibition in combination with treatments such as CDK 4/6 inhibition or antagonism of EGFR and HER3 (30, 31). The potential for combining PI3K inhibition with other therapies has also been acknowledged (32, 33) particularly in the context of prostate, breast, and ovarian cancer (27, 29, 34). Ongoing phase I/II trial plans will investigate the efficacy, safety, and tolerability of docetaxel with or without TAK-117 in patients with locally advanced or metastatic squamous or nonsquamous non-small cell lung cancer (ClinicalTrials.gov: NCT02393209). The MTuW schedule of TAK-117 will be used with the expectation that a high-dose, intermittent schedule would be more effective than once-daily dosing in blocking the adaptive response to chemotherapy insult.

In conclusion, the results of this study suggested that the safety profile of TAK-117 is acceptable and manageable. Intermittent dosing schedules achieved higher total weekly doses and exposures compared with once-daily dosing, generally without increasing toxicity. Although single-agent activity was limited, early signs of antitumor activity were observed and the CBR was encouraging. Our results support intermittent rather than continuous dosing of TAK-117, suggesting use of the drug in combination with other therapies for advanced tumors. PI3K

inhibition is expected to block an adaptive survival mechanism to chemotherapy or other stress-inducing agents.

Disclosure of Potential Conflicts of Interest

D. Juric is a consultant/advisory board member for BIND Therapeutics, Eisai, EMD Serono, Natera and Novartis. J.S. de Bono is a consultant/advisory board member for AstraZeneca, Genentech, GSK, and Pfizer. J. Nemunaitis is an employee of and has ownership interests (including patents) at Gradalis, reports receiving speakers bureau honoraria from Amgen, AstraZeneca, and Foundation Medicine, and is a consultant/advisory board member for Amgen and AstraZeneca. C. Patel is an employee of Quantitative Clinical Pharmacology. E.H. Westin has ownership interests (including patents) at Eli Lilly. Y. Shou is an employee of Takeda Pharmaceuticals. J. Tabernero is a consultant/advisory board member for Amgen, Boehringer Ingelheim, Celgene, Chugai, Imlone, Lilly, Merck, Merck Serono, Millennium Pharmaceuticals, Novartis, Roche, Sanofi, and Taiho. No potential conflicts of interest were disclosed by the other authors.

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Other (provision of study materials or patients): D. Juric

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