

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.

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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 ligand, leads to the modulation of two different pathways: the eukaryotic initiation factor 4E binding protein-1 and the 40S ribosomal protein S6 kinase (p70s6k).⁵ The tumor suppressor gene phosphatase and tensin homolog (PTEN), is a negative regulator of the pathway. Loss or inactivating mutations of this gene result in gain of function of the phosphoinositide-3-kinase, catalytic, alpha polypeptide gene itself and the constitutively active mutant forms of receptor tyrosine kinases or the Ras oncogene, which occur frequently in NSCLC.⁴ The mTOR inhibitors such as temsirolimus, everolimus, and deforolimus are being evaluated in cancer clinical trials. Everolimus and temsirolimus have been approved for the therapy of renal cell carcinoma.^{6,7}

It had been assumed that the efficacy of novel agents in NSCLC will be more accurately determined if these agents were tested in the frontline setting because of the emergence

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of resistance arising from exposure to various therapies over time. On the basis of this assumption, a frontline “window-of-opportunity” study was designed. Patients with previously untreated NSCLC received single-agent temsirolimus, and were closely monitored. Standard platinum-based chemotherapy was introduced at the first sign of progression. Furthermore, putative predictive markers of temsirolimus activity (p70S6k, Akt, and PTEN) were evaluated.

METHODS

Chemotherapy naïve patients with histologic or cytologic evidence of measurable metastatic NSCLC were eligible for this study. Other eligibility criteria were standard for phase II studies (see Supplementary Content, <http://links.lww.com/JTO/A274>).

Temsirolimus at a dose of 25 mg dissolved in 250 ml of 0.9% saline was administered intravenously over 30 minutes every week (4 week-cycle length) until progression, unacceptable toxicity, patient refusal, or investigator’s decision to remove patients from the study.

Biomarkers of temsirolimus effect were evaluated in tumor biopsy samples obtained from 13 patients at baseline. Thirteen usable tumor biopsy samples were obtained. Immunohistochemistry was performed for p70s6 kinase, Phospho-p70s6 kinase, Akt, phospho-Akt, and PTEN expression. PTEN mutation was also evaluated by direct sequencing. Immunohistochemistry was graded as previously described and the staining index was calculated as staining intensity (0–3 scale) multiplied by percentage of tumor cells stained (see Supplementary Content, <http://links.lww.com/JTO/A274>).⁸

A two-stage single arm Phase II study based on a Fleming design⁹ was used to assess the primary endpoint of confirmed response rate (CRR), which is complete response and partial response (PR) by Response Evaluation Criteria in Solid Tumors¹⁰ in patients with metastatic NSCLC to temsirolimus on two consecutive evaluations at least more than 4 weeks apart. The treatment would be considered promising if at least four of the first 25 evaluable patients have a CRR or at least six of the 50 evaluable patients at the end of study have a CRR. If only one success out of 25 patients is observed at the end of stage I, the treatment regimen would be considered ineffective and the study would be terminated. However, in the event that only 2 or 3 successes were observed in stage I, the study would proceed to stage II. This design with a sample size of 50 evaluable patients had an exact significance level of 0.05 and 94% power to detect an effective treatment given that the true CRR is at least 20%.

The secondary endpoints included the 24-week PFS rate, OS, clinical benefit rate (confirmed response and confirmed stable disease [SD; lasting 8 weeks or more from the time of first SD assessment]), and evaluation of predictive markers of activity of temsirolimus.

RESULTS

Patient and Treatment Characteristics

A total of 55 patients (52 evaluable) were enrolled between February 27, 2004 and November 3, 2006. One

patient died before study initiation and 2 were deemed ineligible. Baseline characteristics for the 52 patients are summarized in Table 1. The median follow-up for the two surviving patients is 17.9 months (range, 4.1–31.7). The median number of treatment cycles delivered was 2 (range, 1–18). 39 patients (75%) discontinued treatment because of disease progression, six patients (12%) died on study because of their disease, five patients (10%) refused further treatment, one patient (2%) changed to alternate-treatment, and one patient (2%) discontinued because of adverse events.

All 52 evaluable patients were assessed for adverse events according to the common terminology criteria for adverse events version 3.0. Grade 3+ adverse events were reported in 33 patients (64%). Grade 4+ adverse events were reported in 12 patients (23%). The most common (occurring in three or more patients) grade 3/4 events were dyspnea (12%), fatigue (10%), hyperglycemia (8%), hypoxia (8%), nausea (8%), and rash/desquamation (6%). There were no toxic deaths.

At stage I, two confirmed PRs were observed and thus per design, the study reopened for stage II accrual. Among all 52 evaluable patients, the clinical benefit rate was 35% (18/52). Four patients (8%, 95% confidence interval (CI); 2–19%) achieved a confirmed PR (Fig. 1) and 14 patients (27%, 95% CI; 16%–41%) had confirmed SD. The 24-week PFS rate was 25% (13/52; 95% CI: 14%–39%). The median PFS and OS were 2.3 (95% CI: 1.8–3.7) and 6.6 (95% CI: 3.5–10.4) months, respectively (Fig. 2).

In order to identify possible temsirolimus predictive markers, we assessed Akt, phosphorylated Akt, p70s6 kinase, phosphorylated p70s6 kinase, and PTEN in pretreatment tumor specimens (Fig. 3). There was no statistically significant

TABLE 1. Baseline Patient Characteristics

Characteristics	N (%)
Median age (range)	64 (44–85)
Gender	
Female	20 (38.5)
Male	32 (61.5)
Race	
White	49 (94.2)
Asian	2 (3.9)
Native Hawaiian or other Pacific Islander	1 (1.9)
Performance score	
0	25 (48.1)
1	23 (44.2)
2	4 (7.7)
Staging	
T4 (pleural effusion)	8 (15.4)
IV	44 (84.6)
Hepatic metastases	
Yes	10 (19.2)
No	42 (80.8)
Status of primary tumor	
Recurrence	4 (7.7)
Newly diagnosed	48 (92.3)

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