A Randomized, Phase II Trial of Two Dose Levels of Temsirolimus (CCI-779) in Patients with Extensive-Stage Small-Cell Lung Cancer Who Have Responding or Stable Disease after Induction Chemotherapy: A Trial of the Eastern Cooperative Oncology Group (E1500)

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Hypothesis: To study the progression-free survival (PFS) and toxicity with 25- or 250-mg doses of temsirolimus (CCI-779) after induction chemotherapy in patients with extensive small-cell lung cancer.

Methods: Patients with either stable or responding disease to four to six cycles of cisplatin or carboplatin plus etoposide or irinotecan were randomized between 4 and 8 weeks after completion of induction therapy to receive either 25 or 250 mg of temsirolimus intravenously every week until disease progression.

Results: Eighty-seven patients entered between January 2002 and December 2003, of whom 85 were eligible: 44 received 25 mg (arm A), and 41 received 250 mg (arm B). The overall median follow-up time for all eligible patients was 34.6 months. Median age was 59 years (range, 39–80); 42 (49.4%) were male and 43 (50.6%) female; 12.9% had brain metastases. The overall median and 1-year PFS were 2.2 months (95% confidence interval [CI]: 1.8, 2.9) and 4.7% (95% CI: 0.2%, 9.2%), respectively. The median PFS (95% CI) for arm A was 1.9 months (1.6, 2.3); for arm B, it was 2.5 months (1.9, 3.4; $p = 0.24$). The median overall survival from randomization was 8 months (95% CI: 6.5, 9.5). Among the 86 patients with reported toxicities, 36 (42%) had grade 3 toxicities, the most common of which were thrombocytopenia, hypophosphatemia, and fatigue, and an additional 12 (14%) had grade 4 toxicities, the most common of which was neutropenia. No patients experienced lethal toxicities.

Conclusion: Temsirolimus (CCI 779), given at 25 or 250 mg weekly, seemed not to increase the PFS in this patient population.

Key Words: Small-cell lung cancer, Temsirolimus, CCI-779, Phase II study.

(*J Thorac Oncol.* 2007;2: 1036–1041)

Lung cancer is the number one cause of cancer deaths in both men and women in the United States. It was estimated that approximately 174,470 new cases of lung cancer would be diagnosed in the United States in 2006 and that approximately 13% of these patients would have small-cell lung cancer (SCLC).[1] Histologically and biologically distinct, SCLC displays rapid cell proliferation, abrupt clinical presentation, and a median survival of less than 3 months if left untreated.[2] Combination chemotherapy produces high initial response rates, especially among patients with limited-stage disease. Unfortunately, the disease invariably relapses, especially in patients with extensive-stage disease, causing death of the patient. A search for newer approaches to improve relapse-free and overall survival is clearly indicated for patients with extensive-stage SCLC.

Temsirolimus (CCI-779), an ester of sirolimus, is a novel mammalian target of rapamycin inhibitor, with properties of a cytostatic agent. It binds to and forms a complex with the cytoplasmic protein, FK506 binding protein.[3–5] This complex inhibits mammalian target of rapamycin, which leads to the inhibition of phosphorylation of the eukaryotic translation initiation factor 4E binding protein-1 and the 40S ribosomal protein p70 S6 kinase that regulate the progression of the cell cycle from the G-1 to the S phase. In vitro, temsirolimus has been shown to inhibit the growth of a number of hitologically diverse tumor cells, and in vivo antitumor activity in early-phase clinical trials has been reported with temsirolimus in patients with several tumor types,6 including renal

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This study was conducted by the Eastern Cooperative Oncology Group (Robert L. Comis, MD, chair) and supported in part by Public Health Service Grants CA23318, CA66636, CA21115, CA11083, CA16116, CA21076, CA27525, CA49957 and from the National Cancer Institute, National Institutes of Health and the Department of Health and Human Services. Its contents are solely the responsibility of the authors and do not necessarily represent the official views of the National Cancer Institute.

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ISSN: 1556-0864/07/0211-1036

cancer,[7] breast cancer,[8] and mantle cell lymphoma.[9] These studies have shown activity of temsirolimus at doses of 25, 75, and 250 mg/wk with an acceptable toxicity profile. None of these studies were done in combination with standard chemotherapy agents. This study was undertaken as part of broad phase II exploration of this agent in solid tumors. It was felt that as a "cytostatic" agent, it would be appropriate to use it in a consolidation study design for SCLC.

The objectives of this clinical trial were to study progression-free survival (PFS) and determine toxicity in patients who received weekly doses of either 25 or 250 mg of temsirolimus, after induction chemotherapy in stable or responding extensive-stage SCLC.

MATERIALS AND METHODS

Patients

Patients were required to be older than 18 years old and have histologically or cytologically confirmed SCLC of the lung with extensive disease, defined as disease beyond the hemithorax and adjacent nodes, supraclavicular node involvement or pleural effusion with positive cytology, and a performance status of 0, 1, or 2. Patients with limited disease were ineligible. Patients were required to have received induction chemotherapy with platinum (cisplatin or carboplatin) plus either etoposide or irinotecan (minimum of three and a maximum of six cycles), and show responding or stable disease using the Response Evaluation Criteria in Solid Tumors (RECIST) since the initiation of systemic chemotherapy (i.e., patients who exhibited disease progression were not eligible), and to have recovered from all toxicity related to prior chemotherapy (except alopecia and/or neuropathy). Patients were allowed no fewer than 4 and no more than 8 weeks between the last induction chemotherapy treatment and randomization and no more than 32 weeks between the first dose of induction chemotherapy and date of randomization. No prior treatment with biological response modifiers was allowed. Patients with brain metastases were eligible as long as they had received treatment, were asymptomatic and were no longer taking corticosteroids or anticonvulsants. Patients who developed brain metastases after completion of induction chemotherapy were ineligible. Patients who were immunocompromized, had an active infection or serious intercurrent infection, or had received known immunosuppressive therapies within 3 weeks of randomization were ineligible. Patients were required to practice adequate contraception and to not become pregnant during treatment. Patients were required to have baseline measurements/evaluations of disease <4 weeks before randomization, and to meet the following laboratory criteria (evaluated <2 weeks before randomization): WBC $>4000/mm$ or ANC $>1500/mm$ and platelet count $>100,000/mm$; total bilirubin <1.5 mg/dl; creatinine <1.5 mg/dl; cholesterol level <350 mg/dl; and trigylcerides <400mg/dl. All patients gave written informed consent.

Patients who had not progressed entered the study within 8 weeks of completing induction therapy and were randomized to receive either 25 mg (arm A) or 250 mg (arm B) of temsirolimus, given intravenously each week for 30 minutes until disease progression or unacceptable toxicity (Figure 1). The National Cancer Institute Common Toxicity Criteria version 2.0 were used to grade toxicity and to guide dose modifications. Temsirolimus was held if the ANC was $<1000/mm^3$ or platelets $<80,000/mm^3$, and resumed at 75% of the dose on full recovery for ANC between 750 and $999/mm^3$ or platelets between 50,000 and $80,000/mm^3$, and at 50% of the dose on full recovery for ANC $<750/mm^3$ or platelets $<50,000/mm^3$. Temsirolimus was also held for any grade 3 or 4 nonhematologic toxicity (except for nausea and

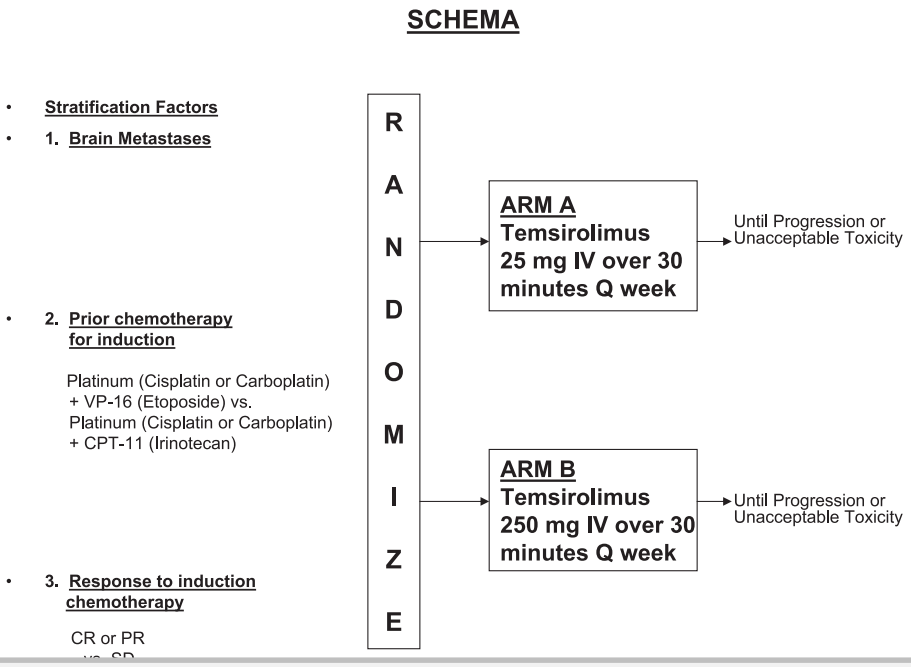

FIGURE 1. Schema

vomiting) and resumed at 75% for grade 3 and 50% for grade 4 after recovery to grade 0 to 2. After a dose reduction, no dose escalation was allowed.

Disease assessment with appropriate imaging study was required every 8 weeks, or sooner if clinical progression became evident. As is the norm in all cooperative group studies, there was no central review of imaging studies.

Statistical Considerations

Treatment assignments were determined using an online, Web-based patient-registration program, stratifying on brain metastases (yes versus no), prior chemotherapy for induction (cisplatin or carboplatin) plus etoposide versus cisplatin or carboplatin plus irinotecan), and response to induction chemotherapy (complete recovery or partial recovery versus stable disease).

The primary objective of this study was to test whether a higher or lower dose of temsirolimus was better at prolonging PFS in patients with extensive-stage SCLC who had complete recovery, partial recovery, or stable disease after induction chemotherapy and who had not progressed before randomization to this trial. It was expected that the treatment with a high dose of temsirolimus (250 mg, intravenously, weekly) would result in more toxicities than the regimen with a low dose (25 mg, intravenously, weekly). Hence, the high dose of temsirolimus would only be investigated in a phase III trial if it prolonged PFS to a sufficient extent. On the basis of the median PFS time in the observation arm of E7593,[10] it was assumed that the median PFS time of the low-dose arm of this trial would be at least 2.3 months. With 72 eligible patients entered during 3 years and an additional 6 months of follow-up, this design had 85% power to detect an increase in median PFS time to 4 months in the high-dose arm (log–rank test, one-sided significance level = 0.1).

The secondary endpoint of this study was the determination of the toxicity rates of the two doses of temsirolimus. In this analysis, any documented toxicity of grade 3 or higher was considered. There was 86% power to detect a difference in the true toxicity rates of 0.1 in the low-dose arm and 0.35 in the high-dose arm (Fisher exact test, one-sided significance level = 0.1).

Statistical Methods

PFS is defined as the interval from the date of entry (randomization) on the study to the appearance of new metastatic lesions or objective tumor progression or death from any cause without progression. Overall survival is defined as the time from date of entry (randomization) to death from any cause. Patients without documented progression or death were censored at the time of the last documented disease evaluation.

Kaplan–Meier[11] curves were used to estimate event–time distributions. PFS was compared using log–rank tests. Adverse events, patient demographics, disease characteristics, and response rates were compared using Fisher exact tests. All p values are two sided. Confidence intervals are at the 95% level.

RESULTS

Between January 9, 2002 and December 9, 2003, 87 patients were entered on this study. One patient had no data forms, and one patient was ineligible because of a diagnosis of prostate cancer within the previous 5 years; these two cases were removed from this analysis. The median follow-up of eligible patients still alive was 34.6 months. At the time of this analysis (June 19, 2006), four patients were still alive. Patient demographic factors and disease characteristics for the 85 eligible patients are shown in Table 1. The median age was 59 years (range, 39–80). There were more female patients ($p = 0.05$) and more patients with brain metastases on arm A ($p = 0.03$). Among the 85 eligible patients, 76.8% of them received at least two cycles of treatment with temsirolimus (Table 2). Table 3 shows the reasons for treatment termination, the distribution of which varied significantly between the two arms ($p = 0.02$). A higher proportion of patients relapsed on the low-dose arm (65.1% versus 35.0%), but a higher proportion of patients experienced high-grade toxicity/side effects on the high-dose arm (40.0% versus 18.6%). Note that no reason for termination was provided for

TABLE 1. Patient Characteristics at Baseline: 85 Eligible Patients

	Low Dose (Arm A) ($n = 44$)	High Dose (Arm B) ($n = 41$)	Total ($n = 85$)
Age (yr)			
Mean	61	59	60
Median	61	59	59
Range	42–78	39–80	39–80
Male	17 (38.6%)	25 (61.0%)	42 (49.4%)
Female	27 (61.4%)	16 (39.0%)	43 (50.6%)
White	37 (84.1%)	35 (85.4%)	72 (84.7%)
Black	1 (2.3%)	2 (4.9%)	3 (3.5%)
Other	6 (13.6%)	4 (9.8%)	10 (11.8%)
0	21 (47.7%)	17 (43.6%)	38 (45.8%)
1	21 (47.7%)	20 (51.3%)	41 (49.4%)
2	2 (4.6%)	2 (5.1%)	4 (4.8%)
Missing/unknown	0	2	2
Weight loss in previous 6 months			
<5%	35 (81.4%)	31 (77.5%)	66 (79.5%)
5%–10%	4 (9.3%)	8 (20.0%)	12 (14.5%)
10%–20%	4 (9.3%)	1 (2.5%)	5 (6.0%)
Missing/unknown	1	1	2
Type of induction chemotherapy			
Platinum + etoposide	35 (79.5%)	34 (82.9%)	69 (81.2%)
Platinum + irinotecan	9 (20.5%)	7 (17.1%)	16 (18.8%)
Response to induction chemo			
Complete recovery	9 (20.5%)	4 (10.0%)	13 (15.5%)
Partial recovery	23 (52.3%)	26 (65.0%)	49 (58.3%)
Stable disease	12 (27.3%)	10 (25.0%)	22 (26.2%)
Missing	0	1	1
Brain metastases			
No	36 (81.8%)	38 (92.7%)	74 (87.1%)
Yes	8 (18.2%)	3 (7.3%)	11 (12.9%)

TABLE 2. Total Number of Cycles of Treatments Received

Number of Cycles	Low Dose (Arm A) (n = 44)	High Dose (Arm B) (n = 41)	Total (n = 85)
1	14 (34.1%)	19 (46.3%)	33 (40.2%)
2	17 (41.5%)	13 (31.7%)	30 (36.6%)
3	2 (4.9%	3 (7.3%)	5 (6.1%)
4	3 (7.3%)	3 (7.3%)	6 (7.3%)
5	4 (9.8%)	1 (2.4%)	5 (6.1%)
6	0 (0%)	1 (2.4%)	1 (1.2%)
>6	1 (2.4%)	1 (2.4%)	2 (2.4%)
Missing	3	0	3

TABLE 3. Reason for Treatment Termination

Reason	Low Dose (Arm A) (n = 44)	High Dose (Arm B) (n = 41)	Total (n = 85)
Progression/relapse	28 (65.1%)	14 (35.0%)	42 (38.6%)
Toxicity/side effects	8 (18.6%)	16 (40.0%)	24 (28.9%)
Withdrawal/refusal	2 (4.7%)	6 (15.0%)	8 (9.6%)
Other complicating disease	0 (0%)	1 (2.5%)	1 (1.2%)
Missing/unknown	1	1	2

No reason was provided for eight patients: five on the lowdose arm, and three on the high-dose arm.

eight patients; five of these patients were on the low-dose arm, and three were on the high-dose arm.

PFS

There were 85 patients available for the primary analysis, 44 on the low-dose arm and 41 on the high-dose arm. All but one patient on the low-dose arm had disease progression. Figure 2A provides overall PFS, and Figure 2B provides PFS by treatment. The overall median PFS was 2.2 months (95% confidence interval [CI]: 1.8, 2.9), and the 1-year PFS rate was 4.7% (95% CI: 0.2%, 9.2%). There is no evidence of a difference in PFS between the two treatment arms: median PFS = 1.9 months (95% CI: 1.6, 2.3) for the low-dose arm, and median PFS = 2.5 months (95% CI: 1.9, 3.4) for high-dose arm, log–rank p value = 0.24. The resultant p value corresponds to a one-sided p value of 0.12, which is close to the one-sided $\alpha = 0.10$ ($p < 0.1$) significance level specified in the study design. The median PFS of patients entering the study with responding disease (partial recovery/complete recovery) was 2.3 months (95% CI: 1.8, 3.3), and the median PFS for those with stable disease was 1.9 months (95% CI: 1.6, 2.2). The median PFS of patients without brain metastases was 2.2 months (95% CI: 1.8, 2.3), and the median PFS for those with brain metastases was 2.3 months (95% CI: 1.2, 7.6). For males, the treatment differences were significant (median PFS = 1.7 months for the low-dose arm and 3.0 months for the high-dose arm; $p = 0.03$), but not for females (median PFS = 2.2 months for the low-dose arm and

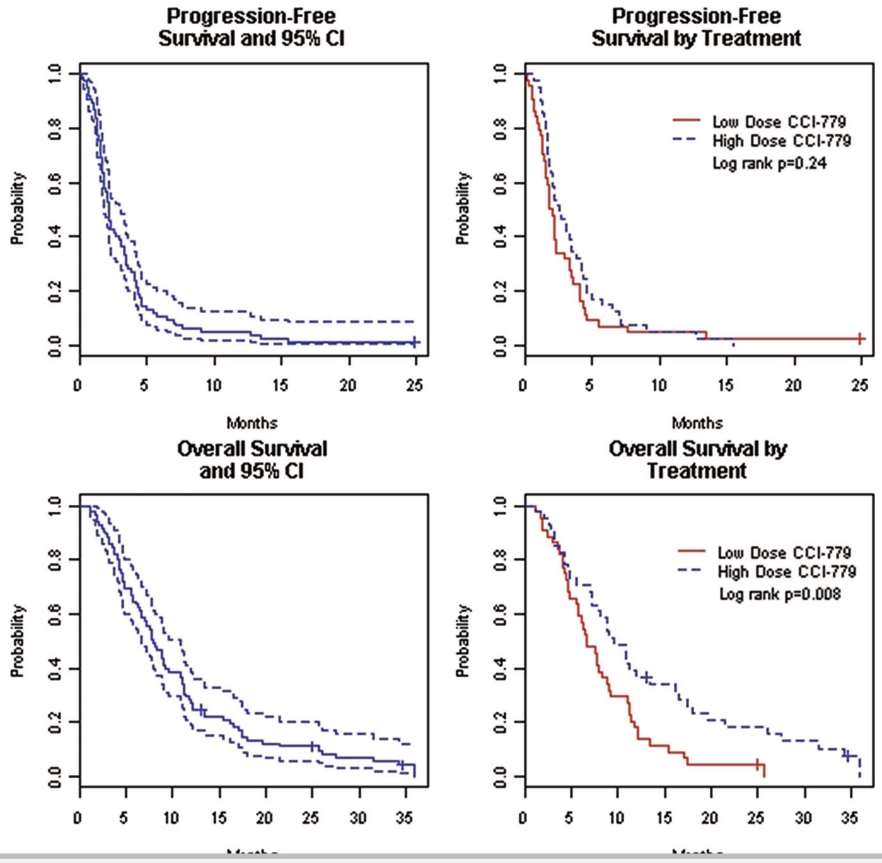

FIGURE 2. Progression-free survival (PFS) and survival: overall PFS (*A*), PFS by treatment (*B*), overall survival (*C*), and survival by treatment (*D*).

TABLE 4. ProgressionFree Survival Hazard Ratios and Log–Rank Tests

Group	High Dose vs. Low Dose	95% Confidence Interval	Log–Rank Test *p* Value
Overall	0.77	(0.50, 1.19)	0.24
Gender			
Male	0.50	(0.26, 0.96)	0.03
Female	1.06	(0.56, 1.98)	0.86
Race			
White	0.82	(0.52, 1.31)	0.41
Nonwhite	0.49	(0.14, 1.69)	0.25

1.9 months for the high-dose arm; $p = 0.86$). There were no differences based on race. Log–rank test results according to gender and race are shown in Table 4.

Overall Survival

The median overall survival for the 85 eligible patients was 8.0 months (95% CI: 6.5, 9.5; Figure 2C). The median overall survival for the 44 patients on arm A was 6.6 months (95% CI: 5.5, 8.9) and, for the 41 patients on arm B, 9.5 months (95% CI: 7.3, 13.3). One patient on arm A and three patients on arm B had not died by the time of this analysis (June 19, 2006). A log–rank test for the equality of the overall survival distributions of arms A and B resulted in a *p* value of 0.008 (Figure 2D).

Objective Response

Responses were evaluated using RECIST. One patient (1.2%) experienced a partial response among the 85 eligible patients. Six patients (7.2%) experienced stable disease, and 74 patients (89.2%) experienced progressive disease.

Toxicity

Toxicity was evaluated by using the National Cancer Institute Common Toxicity Criteria (version 2.0). Table 5 shows the incidence rates of grade 3 and 4 treatment-related toxicities for 86 of 87 entered patients (no data were submitted for one patient). Among the 86 patients with reported toxicities, 36 (41.9%) had grade 3 toxicities, and the most common grade 3 toxicities were thrombocytopenia, hypophosphatemia, and fatigue. Twelve patients (14.0%) had grade 4 toxicities, the most common of which was neutropenia. No patient experienced lethal (grade 5) toxicity. Comparing toxicities between the treatment arms, 22 patients (49.9%) had grade 3 or higher-grade toxicities on the low-dose arm, and 26 patients (63.4%) had grade 3 or higher-grade toxicities on the high-dose arm ($p = 0.20$).

TABLE 5. Toxicity Incidence ($n = 86$)

	Low Dose (Arm A) ($n = 45$) Grade		High Dose (Arm B) ($n = 41$) Grade	
Toxicity Type	**3 (*n*)**	**4 (*n*)**	**3 (*n*)**	**4 (*n*)**
Allergic reaction	1	—	1	—
Anemia	2	—	2	—
Neutropenia	4	1	1	4
Thrombocytopenia	3	—	7	2
Febrile neutropenia	1	—	—	—
Infection without neutropenia	1	—	3	—
Arrhythmia	1	—	1	—
Hypotension	—	—	1	—
Fatigue	2	—	6	—
Rash/desquamation	2	—	3	—
Urticaria	—	—	2	—
Stomatitis	1	—	3	—
Diarrhea	1	—	2	—
Hypercholesterolemia	1	—	3	—
Hyperglycemia	—	—	6	—
Hypertriglyceridemia	2	—	1	2
Hypocalcemia	—	—	—	1
Hypophosphatemia	2	—	5	1
Conjunctivitis	—	—	1	—
Dyspnea	1	1	3	1
Hypoxia	1	—	—	1
Pneumonitis/pulmonary infiltrates	1	—	2	1
Creatinine	—	1	—	—
Renal/GU—other	—	1	—	—
Total	19	3	17	9

DISCUSSION

There has been a great deal of interest in "consolidation" or "maintenance" treatment for SCLC, as patients who respond to induction therapy invariably relapse at a later date. So far, there is no evidence to support the use of prolonged maintenance chemotherapy.[12] It was hoped that a cytostatic agent such as temsirolimus might provide prolongation of PFS by suppressing the regrowth of cancer cells. The study was a phase II exploratory design to see whether temsirolimus at any of these two doses gave enough of a signal to warrant a placebo-controlled phase III trial. In this population of patients with extensive-stage SCLC, weekly "consolidation" treatment with temsirolimus at 25 or 250 mg did not seem to result in any improvement in PFS compared with what was seen in the observation arm of E7593,[10] which was a prospective randomized study to determine whether topotecan given after induction chemotherapy would result in improved PFS compared with observation. PFS after induction chemotherapy in stable or responding patients was significantly better with topotecan compared with observation (3.6 versus 2.3 months; $p < 0.001$); nevertheless, the overall survival from randomization was not significantly different (8.9 vs 9.3 months, respectively; $p = 0.43$). The median PFS of 2.2 months and the median overall survival of 8 months after induction chemotherapy in the current study suggest a lack of any meaningful clinical activity for temsirolimus in this setting.

The estimated PFS hazard ratio (high dose/low dose) among males was statistically significant (hazard ratio = 0.50; 95% CI: 0.26, 0.96), but it was not statistically significant among females (hazard ratio = 1.06; 95% CI: 0.56, 1.98). The lack of stratification based on gender may be the

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