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ORIGINAL REPORT

Randomized Double-Blind Placebo-Controlled Trial of Thalidomide in Combination With Gemcitabine and Carboplatin in Advanced Non–Small-Cell Lung Cancer

Siow Ming Lee, Robin Rudd, Penella J. Woll, Christian Ottensmeier, David Gilligan, Allan Price, Stephen Spiro, Nicole Gower, Mark Jitlal, and Allan Hackshaw

From the University College Hospital, London, Barts and the London Hospital; Cancer Research UK and University College London Cancer Trials Centre, London; Weston Park Hospital, Sheffield; Southampton University Hospitals, Southampton; Addenbrooke's and Papworth Hospitals, Cambridge; and the Edinburgh Cancer Centre, Edinburgh, United Kingdom.

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Corresponding author: Siow Ming Lee, MD, PhD, FRCP, Department of Oncology, University College Hospital, 250 Euston Rd, London NW1 2PG, United Kingdom; e-mail: sm.lee@uclh.nhs.uk.

The Acknowledgment and Appendix are included in the full-text version of this article; they are available online at www.jco.org. They are not included in the PDF version (via Adobe® Reader®).

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ABSTRACT

Purpose
Cancers rely on angiogenesis for their growth and dissemination. We hypothesized that thalidomide, an oral antiangiogenic agent, when combined with chemotherapy, and as maintenance treatment, would improve survival in patients with advanced non–small-cell lung cancer (NSCLC).

Patients and Methods
Seven hundred twenty-two patients were randomly assigned to receive placebo or thalidomide capsules 100 to 200 mg daily for up to 2 years. All patients received gemcitabine and carboplatin every 3 weeks for up to four cycles. End points were overall survival (OS), progression-free survival (PFS), response rate, grade 3/4 toxicity, and quality of life (QoL).

Results
The median OS rates were 8.9 months (placebo) and 8.5 months (thalidomide). The hazard ratio (HR) was 1.13 (95% CI, 0.97 to 1.32; $P = .12$). The 2-year survival rate was 16% and 12% in the placebo and thalidomide arms, respectively. The PFS results were consistent with those for OS. The risk of having a thrombotic event was increased by 74% in the thalidomide group: HR of 1.74 (95% CI, 1.20 to 2.52; $P = .003$). There were no differences in hematologic toxicities, but a slight excess of rash and neuropathy in the thalidomide group. QoL scores were similar but thalidomide was associated with less insomnia, and more constipation and peripheral neuropathy. In a retrospective analysis, patients with nonsquamous histology in the thalidomide group had a poorer survival: 2-year risk difference of 10% (95% CI, 4% to 16%; $P < .001$).

Conclusion
In this large trial of patients with NSCLC, thalidomide in combination with chemotherapy did not improve survival overall, but increased the risk of thrombotic events. Unexpectedly, survival was significantly worse in patients with nonsquamous histology.

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INTRODUCTION

Lung cancer is the most common cause of cancer death worldwide causing the death of more than 1 million patients each year, and non–small-cell lung cancer (NSCLC) accounts for approximately 80%.[1,2] Most patients present with advanced disease that is unsuitable for radical surgery or radiotherapy. The median survival using current first-line platinum-based treatments is low at 8 to 10 months.[3,4]

Angiogenesis, the proliferation of new blood vessels, is necessary for tumors to grow.[5] Elevated expression of vascular endothelial growth factor (VEGF) and other proangiogenic factors are strong prognostic markers in NSCLC and associated with early postoperative relapse and reduced survival.[6-11] Treatments using the anti-VEGF antibody, bevacizumab, combined with chemotherapy has improved response rate, progression-free survival and overall survival in patients with advanced nonsquamous NSCLC.[12] Thalidomide is an oral antiangiogenic agent, inhibiting angiogenesis mediated by VEGF- and basic fibroblast growth factors, and microvessel formation in experimental models.[13-15] This antiangiogenic activity is thought to be a contributing factor for its antitumor effects in multiple myeloma although the mechanism is not fully understood. It also has a synergistic activity when combined with cytotoxic agents and potentially has wider therapeutic activity compared with bevacizumab which is currently restricted to nonsquamous NSCLC.[12,16-18] Other advantages of thalidomide are convenient oral administration and

lower costs, and potentially beneficial anticachexia, and immunomodulatory properties.[19-21]

Thalidomide has been shown to significantly inhibit tumor growth in mice injected with NSCLC cell lines,[22] and early phase trials in humans have also indicated that this therapy was well tolerated and merited further investigation.[23,24]

A phase II trial in patients with small-cell lung cancer indicated that low-dose thalidomide was well tolerated and survival appeared to be better than expected.[25] Similar results were seen in a small randomized placebo-controlled trial, in which the hazard ratio (HR) for overall survival was 0.74, though not statistically significant.[26] We therefore examined the effect of thalidomide on survival when given concurrently with gemcitabine and carboplatin chemotherapy and as maintenance therapy in patients with advanced NSCLC.

PATIENTS AND METHODS

Design

We performed a randomized, phase III double-blind, placebo-controlled trial to test whether thalidomide improves survival among patients with NSCLC receiving chemotherapy. Multicenter and local research ethics approvals were obtained. Written informed consent was obtained from all patients.

Patients

Seven hundred twenty-two patients were recruited between June 2003 and September 2005, from 66 United Kingdom centers in the National Cancer Research Institute network. Eligibility criteria included: histologically or cytologically confirmed NSCLC, stage IIIb or IV disease, no previous chemotherapy or radiotherapy for their cancer, age older than 18 years, Eastern Cooperative Oncology Group (ECOG) performance status 0 to 2, life expectancy longer than 8 weeks, adequate renal function (EDTA clearance $>$ 60 mL/min or calculated creatinine clearance $>$ 50 mL/min), and a negative pregnancy test. Patients with symptomatic brain metastases that required immediate radiotherapy or a previous malignancy within 3 years (unless nonmelanoma skin cancer or early cervical cancer) were excluded. Follow-up continued until September 2008, when the database was closed for analysis.

Patients were randomly assigned to receive thalidomide or placebo after telephoning the Cancer Research UK and University College London Cancer Trials Centre. Trial staff and patients were unaware of the allocation. Stratified randomization was used with a block size of four, incorporating disease stage (IIIb *v* IV), ECOG performance status (0 and 1 *v* 2), and center.

Trial Treatments

All patients were scheduled to receive gemcitabine 1,200 mg/m^2 intravenous (days 1 and 8 of 21-day cycle) and carboplatin area under the curve 5 or 6, dependent on method of glomular filtration rate estimation (day 1), for a maximum of 4 cycles. Cytotoxic drugs were given at full dose every 3 weeks or delayed until hematologic recovery after the previous cycle. Day 8 gemcitabine was omitted if the WBC were lower than 2.0, absolute neutrophil count lower than 1.0, or platelets were lower than 50. All other comedications were given according to local practice. Dose delays or reductions were allowed if indicated by pretreatment blood tests or renal function, as specified in the study protocol.

Thalidomide or matching placebo capsules were taken orally once daily from the start of chemotherapy for 2 years. The starting dose was 100 mg/d and, if tolerated, increased to 150 mg/d at the end of chemotherapy for 1 month, then to 200 mg/d for the rest of the trial. The protocol specified that the dose could be either reduced or stopped (in practice, often temporarily) if the patient suffered symptoms including drowsiness, sensory neuropathy, constipation, and dizziness. Strict guidelines were given regarding requirements for contraception and pregnancy testing.

Assessments

Within 4 weeks before starting treatment, patients had a physical examination, full blood count, serum chemistry, chest radiograph, and computed tomography of chest and abdomen. Bone and brain scans were undertaken if clinically indicated. At the start of each chemotherapy cycle, we performed physical and neurologic examinations, hematology and chemistry, a chest radiograph, and computed tomography scan of the thorax and abdomen if clinically indicated. After chemotherapy, clinic assessments were scheduled every 2 months for the first 2 years, then every 3 months. Study drug compliance and toxicity were monitored during chemotherapy and follow-up. Quality of life (QoL) assessments using the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 and LC-14 were made at the time of random assignment, during each chemotherapy cycle, at the end of chemotherapy, then every 6 months until 24 months.[27]

Statistical Considerations

The primary end point was overall survival (OS) measured from the date of random assignment. Secondary end points were progression-free survival (PFS), tumor response rates (using the Response Evaluation Criteria in Solid Tumors), toxicity (using National Cancer Institute Common Toxicity Criteria, version 2.0), and QoL. Analyses were by intention to treat, unless otherwise specified. For each toxicity, the maximum grade was used for each patient during chemotherapy and follow-up, and the proportions compared. Quality of life measurements were examined using a repeated measures analysis allowing for baseline values (Proc Mixed in SAS, SAS Institute, Cary, NC).

The target sample size was 720 patients, to detect a difference in the 2-year OS rate of 7% (12% placebo *v* 19% thalidomide),[4] with 85% power and 5% two-sided test of statistical significance (log-rank test).

Compliance to trial treatment was examined by calculating, for each patient, the time from random assignment until death or when the treatment was stopped early. From this we estimated the median time on study drug in each arm. We also expressed the number of days when the patient was taking the study drug as a percentage of the total number of days spent in the study (ie, from time of random assignment until death or date last seen), to allow for those who temporarily stopped their drug. For example, if a patient allocated to receive thalidomide was in the trial for 12 months (from time of random

Table 1. Baseline Characteristics

Characteristic	Thalidomide (n = 372) No.	%	Placebo (n = 350) No.	%
Age at random assignment, years				
≥ 50	342	92	324	93
Median	63		62	
Range	35-84		33-84	
Sex				
Male	242	65	223	64
Female	130	35	127	36
ECOG performance status				
0	113	30	108	31
1	217	58	210	60
2	42	11	32	9
Stage				
IIIb	167	45	155	44
IV	205	55	195	56
With pleural effusion: IIIb	56 of 167	34	52 of 155	34
Cell type				
Squamous cell	115	31	124	35
Adenocarcinoma	139	37	129	37
Large cell	22	6	25	7
Other	96	26	72	21

Abbreviation: ECOG, Eastern Cooperative Oncology Group.

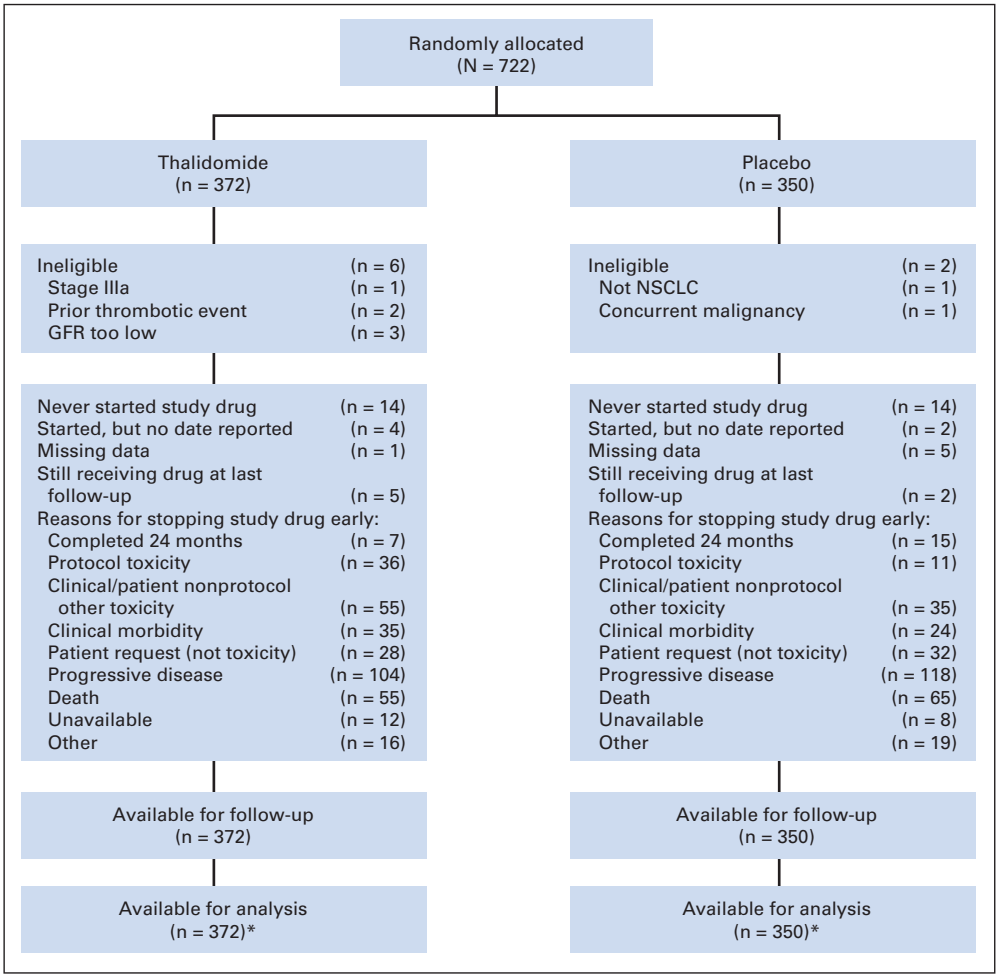

Fig 1. CONSORT diagram. (*) Includes the ineligible patients, as they were already randomly assigned and are few in number. GFR, glomerular filtration rate; NSCLC, non–small-cell lung cancer.

assignment until death), and during this time had stopped the drug for 3 months in total, the proportion of time spent on study drug was 75%.

RESULTS

A total of 722 patients were randomly assigned to treatment, 350 to placebo and 372 to thalidomide. Table 1 shows the baseline characteristics of the patients. The two groups were well balanced.

Treatment Administration

Figure 1 (CONSORT diagram) shows the numbers of patients who started and continued study drug, and reasons for stopping early. Six hundred eighty-eight patients (95%) started placebo/thalidomide, 28 did not start at all, and data were missing for six. The median time on study drug was 6.0 months (25th to 75th centile, 3.0 to 10.0 months) and 4.3 months (25th to 75th centile, 1.6 to 8.2 months) for patients on placebo and thalidomide, respectively (Data Supplement Fig 1), a statistically significant difference ($P = .004$). Seventy-three percent of patients in the placebo group and 62% in the thalidomide group took the allocated treatment for at least half the time they were in the study (Data Supplement Fig 2).

Study drug administration did not affect the tolerance for chemotherapy. The proportion of patients who completed all planned four chemotherapy cycles was similar between the placebo and thalidomide groups (66% for thalidomide and 71% for placebo; Data Supplement Tables 1 and 2). The proportion of patients whose chemotherapy dose was delayed or reduced also did not differ between the placebo and thalidomide groups. Chemotherapy dose delays/reductions occurred in 43%/25% and 46%/28%, during any cycle, in the placebo and thalidomide groups, respectively.

Efficacy

Objective tumor response rates (complete and partial) during chemotherapy were similar between the groups (40% *v* 42% for thalidomide and placebo, respectively). The proportion of patients with stable disease was also similar (40% *v* 38%).

The median follow-up was 38 months (censoring those who had died) and 665 patients had died, 321 placebo, and 344 thalidomide; 94% from progressive NSCLC (Data Supplement Table 3). Figure 2 shows the results on OS and PFS. There was no evidence of an effect of thalidomide on either OS or PFS. The median OS was 8.5 and 8.9 months in the thalidomide and placebo groups, respectively. The unadjusted HR for OS was 1.13 (95% CI 0.97-1.32; $P = .12$), which became 1.14 (95% CI 0.97-1.34) after allowing for the stratification factors used in the randomisation. One-year and two-year survival

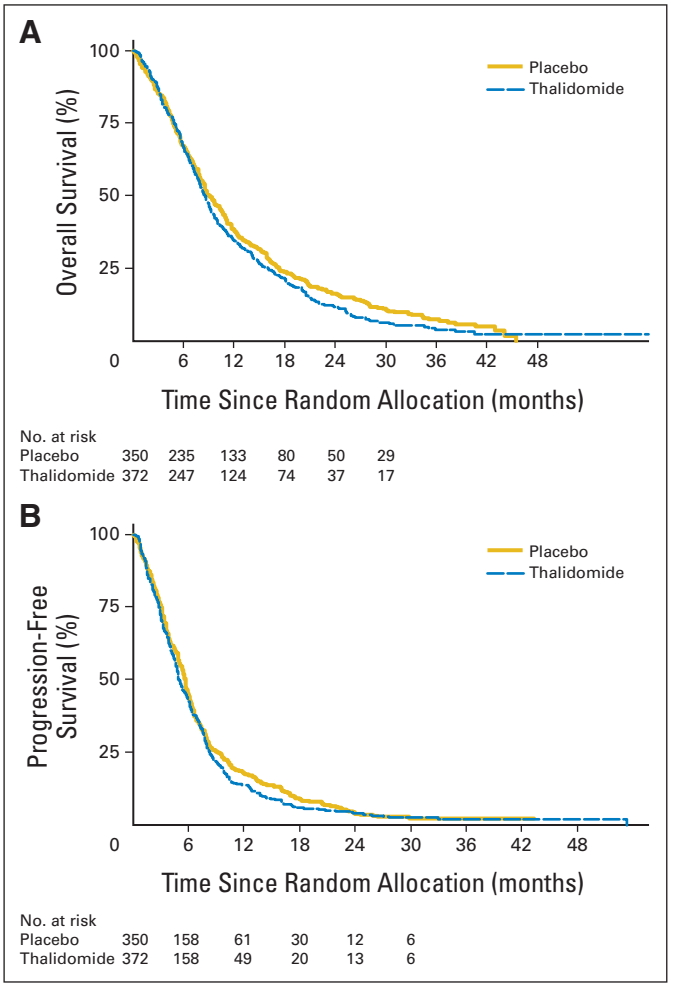

Fig 2. (A) Overall survival and (B) progression-free survival curves according to treatment arms in all patients.

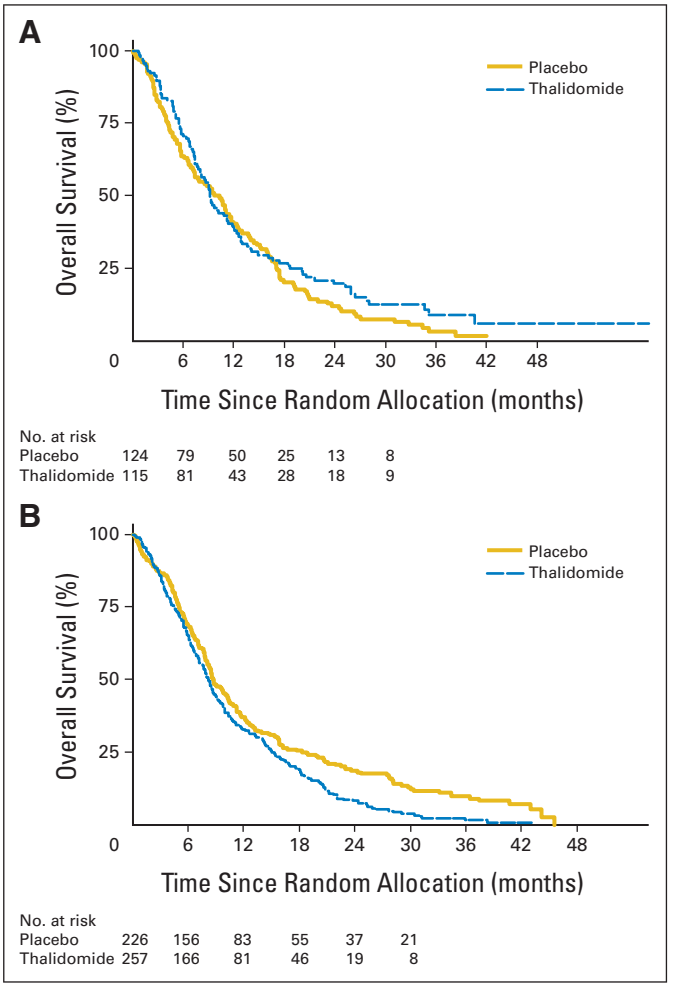

Fig 3. Overall survival curves according to histology: (A) squamous; (B) nonsquamous (adenocarcinoma, large-cell carcinoma, and other histologic types).

rates were 35% and 12% for thalidomide, and 38% and 16% for placebo, respectively.

When examining PFS, there were 359 and 339 events in the thalidomide and placebo groups respectively. The median PFS for thalidomide was 5.0 months and for placebo it was 5.7 months. The HR for PFS was 1.10 (95% CI, 0.95 to 1.28; $P = .20$).

Because of a difference in the time on study drug, we examined OS among the 264 patients who took their trial treatment for at least 80% of the time they were in the study; the HR was 1.02 (95% CI, 0.79 to 1.31; $P = .87$). Among the 186 patients who took their trial treatment for at least 90% of the time the HR was 1.01 (95% CI, 0.75 to 1.37; $P = .94$).

A post hoc analysis was performed for histology because of accumulating evidence of a differential treatment effect according to different subtypes (Fig 3; Data Supplement Fig 3). The interaction between histology and study drug was significant ($P = .006$). Among those with nonsquamous histology, the 2-year survival rate was lower in the thalidomide group than placebo: 8% versus 19%, a difference of −10% (95% CI, −16 to −4%; $P < .001$). The 2-year survival rate was used because the comparison of thalidomide and placebo was not consistent with the assumption of proportional hazards in this group, and this was the time point specified in the trial protocol when estimating sample size. In contrast, there was a suggestion of a benefit for thalidomide in patients with squamous tumors. The HR was 0.84 (95% CI, 0.64 to 1.09; $P = .19$), and the 2-year survival rate was 20% (thalidomide) versus 12% (placebo): a difference of +8, (95% CI, −1 to +17; $P = .10$), the expected treatment effect used in the sample size calculation. The baseline characteristics were well-balanced in patients with either squamous and nonsquamous histology separately.

Toxicity

Thalidomide increased the risk of having a thrombotic event. The Data Monitoring Committee observed this during the trial and the patient information sheet was changed accordingly. Patients already recruited were informed of the risks and reconsented to continuing study drug, and potential new patients were excluded if they had a prior history of thrombotic events. Seventy-seven of 372 patients on thalidomide versus 44 of 350 patients on placebo suffered a thrombotic event, with an HR 1.74 (95% CI, 1.20 to 2.52; $P = .003$). These were mainly pulmonary embolism or deep vein thrombosis, affecting 48 thalidomide and 26 placebo patients). At 6 months, the estimated risk difference was 8%, which remained largely constant afterward (Fig 4; Data Supplement Tables 4 and 5 and Data Supplement Fig 4 provide more details). There were no other material differences between the two treatment arms in the incidence of grade 3 and 4

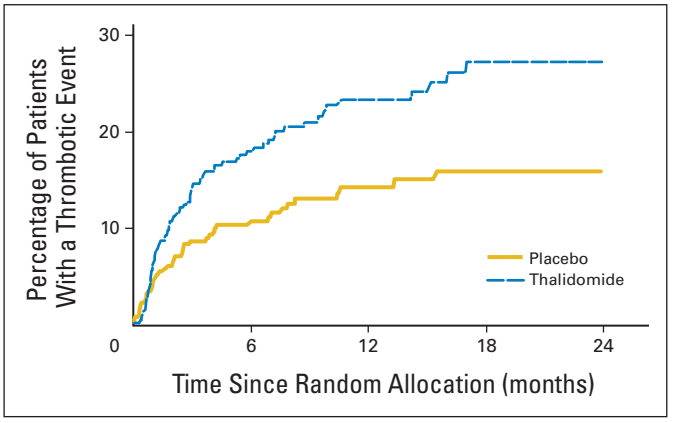

Fig 4. Risk of developing any thrombotic event according to treatment group.

hematologic and nonhematologic toxicities except a relatively small increase in the risk of rash and neuropathy for thalidomide, as expected (Table 2).

QoL

Baseline QoL forms were completed by 97% of patients, with 53% completing forms for at least five time points. There were no significant differences in QoL scores at baseline (each factor was based on a scale of 0 to 100). During the study, the mean difference in scores remained similar over time in the treatment groups (except for peripheral neuropathy). As expected, thalidomide was associated with less insomnia and more constipation and peripheral neuropathy, though the effects were not large. The differences in mean scores were −4.8 (insomnia), +8.6 (constipation), and +7.0 (neuropathy, 24 weeks after random assignment). Details are shown in Data Supplement Tables 6 and 7. We also examined whether thalidomide could have a beneficial effect on body weight during chemotherapy but the mean increase in weight from baseline to the end of chemotherapy was 1.1 and 0.5 kg in the placebo and thalidomide groups, respectively.

Table 2. Reported Grade 3 or 4 Toxicities (except thrombotic events)

Toxicity	Thalidomide (n = 372) No.	Thalidomide (n = 372) %	Placebo (n = 350) No.	Placebo (n = 350) %
Hematologic				
Anemia	34	9	45	13
Leukopenia	71	19	60	17
Neutropenia	140	38	122	35
Thrombocytopenia	81	22	85	24
Other	6	2	4	1
Any (each patient counted once)	183	49	173	49
Absolute risk difference*, %			−0.2	
95% CI			−7.5 to +7.1	
P			.95	
Nonhematologic				
Constipation	17	5	12	3
Diarrhea	6	2	6	2
Nausea	10	3	13	4
Vomiting	8	2	7	2
Mucositis/stomatitis (oral)	2	1	2	1
Anorexia	10	3	9	3
Infection (not neutropenic)	17	5	12	3
Infection (neutropenic)	14	4	12	3
Dizziness	15	4	12	3
Somnolence/drowsiness	18	5	15	4
Neuropathy/sensory	15	4	8	2
Dry skin	3	1	0	
Rash	18	5	4	1
Renal	2	1	2	1
Other	46	12	30	9
Any (each patient counted once)	127	34	99	28
Absolute risk difference*, %			+5.9	
95% CI			−0.9 to +12.6	
P			.09	
Any toxicity	243	65	209	60
Absolute risk difference*, %			+5.6%	
95% CI			−1.4 to +12.7	
P			.12	

NOTE. The table is based on the maximum grade observed during chemotherapy or follow-up.
*Thalidomide minus placebo.

DISCUSSION

Our large phase III trial showed that an antiangiogenic approach using thalidomide was not associated with a survival benefit in patients with NSCLC receiving platinum-based chemotherapy for advanced disease. The main adverse effects associated with thalidomide were thrombotic events (HR, 1.74; 95% CI, 1.20 to 2.52; $P = .003$).

It is unlikely that the lack of overall effect for thalidomide was due to poor compliance since 62% of patients took the drug for at least half the time they were in the study. A higher dose of thalidomide might have been more effective, but this would be associated with a higher risk of developing a thrombotic event. In addition, there is currently no clinical evidence to support a dose response relationship for thalidomide in multiple myeloma,[28] small-cell lung cancer,[26,29,30] or other solid tumors.[31] The results of the ongoing ECOG 3598 randomized trial of 400 mg thalidomide in combination with carboplatin and paclitaxel for patients with stage IIIA NSCLC are awaited with interest.[32]

We considered whether any possible benefit of thalidomide was outweighed by a negative effect on chemotherapy dose intensity. There was no difference in the number of cycles or dose modifications in the thalidomide and placebo groups. Furthermore, there was no increase in chemotherapy-associated adverse effects, including myelosuppression and febrile neutropenia. Although thalidomide did not adversely impact on overall quality of life or tumor response, the reduced compliance with thalidomide compared with placebo suggested poorer tolerability.

In contrast to other studies of antiangiogenic agents, our trial suggested that patients with nonsquamous histology had a poorer survival in the thalidomide group (2-year risk difference of 10%; 95% CI, 4% to 16%; $P < .001$). Although, there was also an indication that thalidomide might have benefitted those with squamous histology (HR, 0.84; 95% CI, 0.64 to 1.09), this was an unplanned and retrospective analysis, so these data cannot be used to claim effectiveness in this subgroup, but rather generate hypotheses for further studies. The basis for undertaking this analysis was

the accruing evidence of differential sensitivity to treatments according to histology. In addition, many recent randomized trials of antiangiogenic agents in NSCLC excluded patients with squamous NSCLC because of the observation of increased life-threatening and fatal pulmonary hemorrhages in a phase II study.[12,33,34] NSCLC patients with squamous tumors appeared to have responded better to hyperfractionated radiotherapy,[35] while those with nonsquamous tumors have responded better to chemotherapy with pemetrexed.[36,37] Survival of patients with adenocarcinoma or large-cell carcinoma was improved when given cisplatin plus pemetrexed compared with those given cisplatin plus gemcitabine (HR, 0.81; 95% CI, 0.70 to 0.94).[38] However, those with squamous cell carcinoma had an improved survival when given cisplatin plus gemcitabine (HR, 0.81; 95% CI, 0.66 to 1.00).[38] Although there is considerable interest in studying novel predictive biomarkers in NSCLC, the effect of histologic subtype has not yet been fully evaluated. Ongoing trials of lung cancer should investigate potential differential treatment effects according to histology.

Our data add to a growing body of evidence that antiangiogenic strategies in advanced NSCLC may not be as effective as originally hoped. The lack of an effect associated with thalidomide was also observed in a large trial of 724 patients with small-cell lung cancer, conducted by our group. The HR was 1.09 (95% CI, 0.93 to 1.27).[39] The ECOG 4599 trial showed that bevacizumab improved median survival from 10.3 to 12.3 months ($P = .003$) in patients with NSCLC receiving carboplatin and paclitaxel, but the AVAiL trial (bevacizumab with cisplatin and gemcitabine) reported no survival advantage, and an improvement of PFS of shorter than 1 month.[12,34] In addition, Bayer/Onyx and AstraZeneca recently announced the early stopping of their clinical trials in advanced NSCLC with two other potent oral angiogenesis inhibitors, sorafenib and cediranib, respectively.[40,41] The phase III ESCAPE trial of 926 patients, using sorafenib in combination with chemotherapy, was stopped early because the independent data monitoring committee found that mortality was higher in patients receiving sorafenib at the interim analysis. The phase II/III BR.24 trial with cediranib was stopped early because of excessive toxicity. It is possible that antiangiogenic may only work with certain chemotherapy regimes or histological subtypes as suggested in our trial here.[42] The AVAiL (Avastin in Lung) study used a similar regimen to our trial. However, both the ECOG 4599 and ESCAPE (Evaluation of Sorafenib, Carboplatin and Paclitaxel Efficacy in NSCLC) studies used carboplatin and paclitaxel, and only one reported a benefit.

Although the precise antiangiogenic or resistance mechanism of thalidomide is not fully understood, it is possible that for advanced late-stage IIIB/IV NSCLC, where tumor blood vasculature are already established, VEGF may be superfluous and angiogenesis is affected by other proangiogenic factors. Targeting VEGF or VEGF receptors may be insufficient, and success may come only from treating the disease at an earlier stage or targeting multiple angiogenic pathways for late stage disease. There is emerging evidence suggesting that antiangiogenic agents may work better with some chemotherapy agents than others.[42,43]

Unlike the results reported with a VEGF-targeted approach, we did not observe an increase in response rates. It is possible that the 200 mg dose used in our study was too low compared with the trial reported by Pujol et al,[26] which used 400 mg. The ESCAPE trial, examining sorafenib combined with chemotherapy, stopped early because of an increased risk of early death, predominantly in squamous cell patients. It is possible that for squamous patients, deaths may occur early in treatment before the late beneficial effect is observed. Interestingly, patients with squamous histology were excluded from the ECOG 4599 and AVAiL trials because of the paradoxical observation of marked tumor necrosis and central cavitation leading to increased hemorrhage and deaths.[33]

In conclusion, our data showed that thalidomide was not associated with a survival benefit in the whole group of patients with NSCLC, but survival was possibly worse in those with nonsquamous histology.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a "U" are those for which no compensation was received; those relationships marked with a "C" were compensated. For a detailed description of the disclosure categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

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AUTHOR CONTRIBUTIONS

Conception and design: Siow Ming Lee
Administrative support: Nicole Gower
Provision of study materials or patients: Siow Ming Lee, Robin Rudd, Penella J. Woll, Christian Ottensmeier, David Gilligan, Allan Price
Collection and assembly of data: Siow Ming Lee, Nicole Gower, Mark Jitlal, Allan Hackshaw
Data analysis and interpretation: Siow Ming Lee, Robin Rudd, Christian Ottensmeier, David Gilligan, Allan Price, Stephen Spiro, Mark Jitlal, Allan Hackshaw
Manuscript writing: Siow Ming Lee, Robin Rudd, Penella J. Woll, Christian Ottensmeier, David Gilligan, Allan Price, Stephen Spiro, Nicole Gower, Allan Hackshaw
Final approval of manuscript: Siow Ming Lee, Robin Rudd, Penella J. Woll, Christian Ottensmeier, David Gilligan, Allan Price, Stephen Spiro, Nicole Gower, Mark Jitlal, Allan Hackshaw

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