Pergamon

European Journal of Cancer, Vol. 34, No. 5, pp. 654–658, 1998

Printed in Great Britain
0959-8049/98 $19.00+0.00

PII: S0959-8049(97)10103-4

Original Paper

One-hour Paclitaxel Plus Carboplatin in the Treatment of Advanced Non-small Cell Lung Cancer: Results of a Multicentre, Phase II Trial

J.D. Hainsworth,[1] W.J. Urba,[2] J.K. Hon,[3] K.A. Thompson,[4] M.P. Stagg,[5] L.G. Hopkins,[1] M. Thomas[1] and F.A. Greco[1]

[1]Sarah Cannon–Minnie Pearl Cancer Center, 250 25th Avenue North, Suite 412, Nashville, Tennessee 37203; [2]Earle A. Chiles Research Institute, Portland, Oregon 97213; [3]Comprehensive Cancer Institute, Huntsville, Alabama 35801; [4]Montgomery Cancer Center, Montgomery, Alabama 36106; and [5]Mary Bird Perkins Cancer Center, Baton Rouge, Louisiana 70809, U.S.A.

The aim of this phase II study was to determine the activity and toxicity of paclitaxel (administered by 1-h infusion) and carboplatin in advanced non-small cell lung cancer when used in a multicentre, community-based treatment setting. 100 chemotherapy-naive patients with stage IIIB or IV non-small cell lung cancer were treated between March 1995 and February 1996. All patients had Karnofsky performance status 70–100, measurable disease and adequate bone marrow, kidney and liver function. All patients received intravenous (i.v.) paclitaxel 225 mg/m^2 by 1-h infusion followed immediately by carboplatin at a targeted area under the concentration time curve (AUC) of 6.0 using the Calvert formula. Courses were repeated every 21 days. Colony stimulating factors were not used routinely. 38 of 94 evaluable patients (40%) had objective responses to treatment (3 complete responses, 35 partial responses). An additional 32 patients had stable disease at initial re-evaluation. Weight gain during treatment was experienced by 47% of patients with objective response or stable disease. The median survival in this group of 100 patients was 8 months, with an actuarial 1-year survival of 42%. Leucopenia was common, but hospitalisation for treatment of neutropenia and fever occurred in only 3% of courses. Cumulative peripheral neuropathy was common, but usually appeared after the third or fourth course and was severe (grade 3) in only 15% of patients. Other grade 3 and 4 toxicity was uncommon. There was one treatment-related death due to sepsis. This large multicentre community-based phase II trial demonstrated the efficacy of paclitaxel and carboplatin combination chemotherapy in advanced non-small cell lung cancer. When paclitaxel is given by 1-h infusion, this regimen is easily administered in the outpatient setting. © **1998 Elsevier Science Ltd. All rights reserved.**

Key words: paclitaxel, non-small cell lung cancer, carboplatin, chemotherapy
Eur J Cancer, Vol. 34, No. 5, pp. 654–658, 1998

INTRODUCTION

THE RECENT introduction of several active new agents has increased the possibility of developing effective combination chemotherapy regimens for the treatment of patients with non-small cell lung cancer. Paclitaxel has been of great interest because of its novel mechanism of action and demonstrated single agent activity in non-small cell lung cancer (NSCLC). Several phase II studies have documented response rates of approximately 25% when paclitaxel was administered as a single agent, and surprisingly good 1-year survival rates of 35–40% [1–3].

Although several paclitaxel-containing combination regimens are being evaluated, preliminary evidence has shown

Correspondence to J.D. Hainsworth.
Received 25 May 1997; revised 8 Oct. 1997; accepted 30 Oct. 1997.

the combination of paclitaxel and carboplatin to be active and well tolerated. In two single institution phase II studies performed at Fox Chase Cancer Center and the University of Southern California, response rates in excess of 50% were achieved, with median survivals of approximately 12 months [4, 5]. In addition, full doses of both drugs could be used, with less myelosuppression than anticipated and surprisingly good patient tolerance.

The optimum dose and schedule of paclitaxel administration continues to be the subject of clinical investigation; however, no clinical evidence currently suggests that its activity against NSCLC is schedule dependent. A 1-h infusion schedule of paclitaxel has been found to be safe and easily administered [6, 7]. In a phase II study in non-small cell lung cancer, a 25% response rate was achieved and responses in patients previously treated with cisplatin-based regimens were demonstrated [3]. Because of the ease of outpatient administration, the 1-h infusion of paclitaxel has continued to be explored and the preliminary results of a large phase II, multicentre study combining 1-h paclitaxel and carboplatin in the treatment of patients with advanced NSCLC are reported here.

PATIENTS AND METHODS

In March 1995, this phase II trial was initiated in The Minnie Pearl Cancer Research Network. Patients were enrolled by 17 community-based oncology groups; data management was co-ordinated at The Sarah Cannon–Minnie Pearl Cancer Center. The groups participating in this trial are listed in the Appendix.

Patients with histologically documented stage IV NSCLC were eligible for this trial. In addition, patients with stage IIIB disease who were not candidates for radiation therapy were eligible. Previous systemic therapy was not permitted. Patients who had previously received radiation therapy were eligible, as long as they had measurable disease outside the previous radiation therapy portal and treatment had been completed more than 4 weeks prior to initiation of chemotherapy. All patients were required to have uni- or bi-dimensionally measurable disease by chest radiograph or computerised tomography (CT). Additional eligibility requirements included: age >18 years, Karnofsky performance status ≥ 70, life expectancy ≥ 12 weeks, adequate bone marrow function (white blood cells $\geq 3500/\mu l$, platelets $\geq 100\,000/\mu l$), adequate liver function (bilirubin $\leq 1.25\times$ upper normal limit, serum glutamic oxalotransferase (SGOT) $\leq 2.5\times$upper normal limit), adequate renal function (serum creatinine $\leq 1.5\times$upper normal limit or calculated glomerular filtration rate [GFR] >50 ml/min). The following patients were also excluded: patients treated for another type of cancer during the previous 5 years, patients with brain metastases, patients with serious co-existing medical illnesses and pregnant or lactating females. This study was approved by the Investigational Review Board of Centennial Medical Center prior to its initiation. All patients gave written informed consent prior to beginning treatment.

The following pretreatment laboratory and radiological studies were performed on all patients: complete blood count, differential, platelet count, electrolytes, chemistry profile, chest X-ray, electrocardiogram and CT of the chest. Abdominal and brain CT scans were performed if clinically indicated. A pregnancy test was required in women of childbearing potential.

All patients received the following chemotherapy regimen: paclitaxel 225 mg/m^2 administered by 1-h intravenous (i.v.) infusion and immediately followed by carboplatin at an area under the concentration time curve (AUC) of 6.0 given i.v. over 30–60 min. Treatment courses were repeated every 21 days.

The carboplatin dose was calculated using the Calvert formula to achieve an estimated AUC of 6.0 as follows: carboplatin dose $= 6.0\times(\text{GFR} + 25)$. The GFR was calculated using the formula

$$\text{GFR} = \frac{(140 - \text{age}) \times \text{weight (kilograms)}}{72 \times \text{serum creatinine}} \quad \begin{matrix}\times 0.85 \text{ (female)} \\ \times 1.00 \text{ (male)}.\end{matrix}$$

Before receiving paclitaxel, all patients were premedicated with dexamethasone 20 mg given orally 12 h and 4 h before therapy. Thirty minutes prior to paclitaxel infusion, the following drugs were administered i.v.: dexamethasone 20 mg, diphenhydramine 50 mg and cimetidine 300 mg. Paclitaxel was mixed in normal saline at a concentration not exceeding 1.2 mg/ml.

After the initiation of therapy, all patients had complete blood counts measured weekly. The response to therapy was determined at week 6 (after two courses had been received). Therapy was discontinued in patients with progressive disease. Patients with stable disease or objective response continued treatment, with response reassessed after every two courses of treatment. Responding or stable patients received a minimum of six and a maximum of 10 courses of treatment.

Dose reductions were made for myelosuppression and other toxicities, as shown in Table 1. In addition to dose reductions, patients who had a neutrophil count $<1500/\mu l$ or platelets $<100\,000/\mu l$ on the day of scheduled treatment had treatment delayed by 1 week, or up to a maximum of 2 weeks, until the counts rose above these levels. Colony stimulating factors were not used during the first course of therapy in any patient. The subsequent use of cytokines was not prohibited, but could not substitute for a required dose reduction as outlined in Table 1. Patients who experienced moderate or severe hypersensitivity reactions to paclitaxel were removed from the study; subsequent treatment was at the discretion of the treating physician.

All patients who received at least two courses of treatment were assigned a response category. A complete response required the disappearance of all clinical evidence of tumour, determined by two observations not less than 4 weeks apart. A partial response required a 50% or greater decrease in the tumour size (the sum of the products of measured lesions), determined by two observations not less than 4 weeks apart, with no appearance of any new lesions and non-measurable lesions remaining stable or regressing. Stable disease was defined as a response less than a partial response (i.e. less than a 50% decrease in the sum of the products of measured lesions) or progression less than that defined as progressive disease, of at least 4 weeks' duration. Progressive disease was defined as an increase of at least 25% in the product of measured lesions, or the appearance of new lesions.

All patients registered on this study were included in the survival analysis. Actuarial survival curves were constructed using the method of Kaplan and Meier [8]. All patients who received at least one course of treatment were included in the analysis of treatment-related toxicity. Although formal quality

Table 1. *Required dose reductions*

Toxicity	Paclitaxel	Carboplatin
Myelosuppression		
Neutrophil nadir $\geq$ 500/μl and platelets $\geq$ 50 000/μl	No change	No change
Neutrophil nadir < 500/μl or platelets < 50 000/μl	No change	↓ 1 dose level
Mucositis		
Grade 3 or 4	↓ 1 dose level	↓ 1 dose level
Neuropathy or arthralgias/myalgias		
Grade 1	No change	No change
Grade 2	↓ 1 dose level	No change
Grade 3	↓ 2 dose levels	No change
Other toxicity (except nausea/vomiting)		
Grade 2	↓ 1 dose level	↓ 1 dose level
Grade 3 or 4	↓ 3 dose levels	↓ 3 dose levels
Dose modification		
Dose level	Paclitaxel (mg/m^2)	Carboplatin (AUC)
0 (starting dose)	225	6
−1	200	5
−2	175	4
−3	150	3

AUC, area under the concentration time curve.

of life assessments were not included in this trial, serial changes in weight, disease-related symptoms and performance status were recorded in all patients. The duration of response was calculated from the first day of treatment until the day that disease progression was documented.

RESULTS

Between March 1995 and January 1996, 100 patients entered the study. Patient characteristics are summarised in Table 2. Patient demographics with regard to age, gender and histology were typical of the NSCLC population. 37 patients were treated at the Sarah Cannon Cancer Center and 63 were entered at the 16 other co-operating centres. 70% of patients had stage IV disease.

88 of 100 patients received at least two courses of therapy and were evaluated for response. An additional 6 patients received only one course of treatment due to rapid progression of lung cancer and are categorised as non-responders.

Table 2. *Patient characteristics* (n = 100)

Characteristic	Number of patients
Median age (range)	62 (36–82)
Gender (male/female)	70/30
Histology	
Adenocarcinoma	47
Squamous cell carcinoma	27
Large cell carcinoma	26
Karnofsky performance status	
90–100	58
70–80	42
Stage	
IIIB	30
IV	70
Institution	
Sarah Cannon Cancer Center	37
Affiliated institutions	63
Weight loss	
< 10%	85
$\geq$ 10%	15

6 patients received only one course of therapy and were inevaluable for response for the following reasons: treatment-related death (1 patient), intercurrent events (postobstructive pneumonia, massive haemoptysis, bronchopleural fistula (3 patients); inadvertently received concurrent radiation therapy (1 patient), moved out of State (1 patient). All 100 patients were evaluated for treatment-related toxicity and all were included in survival analyses.

The 100 patients in this study received a median of four courses of paclitaxel and carboplatin. Of the 70 patients who had an objective response or stable disease after two courses of therapy, 36 received between 6 and 10 courses of treatment as planned. 34 patients received fewer than six courses for the following reasons: progression of disease (20 patients), removed due to treatment-related toxicity (2 patients), removed at the discretion of the treating physician (2 patients).

Efficacy

38 of 94 evaluable patients (40%) had major responses to therapy (complete response 3, partial response 35). An additional 32 patients (34%) had stable disease after two courses of treatment and 24 (26%) had progressive disease. 26 of 38 responders have progressed after a median response duration of 5.5 months (range 3–12 months). 12 responders are free from progression at a median of 8 months (range 4–13.5 months). 25 of 32 patients with stable disease progressed after a median 3 months (range 2–10 months); 7 are free from progression at a median 8.5 months.

An improvement in subjective symptoms, including weight gain, was common in patients responding to treatment with this regimen. 33 of 70 patients (47%) with an objective response or stable disease gained a median of 10 lb in weight during treatment (range 2–40 lb). 14 of 27 responders (52%) who had tumour-related symptoms improved during therapy and 37% of responding patients had an improvement in Karnofsky performance status.

Figure 1 shows the actuarial survival curve for this group of 100 patients. Median survival was 8 months and the actuarial 1-year survival was 42%. 47 of 100 patients remain alive after a median follow-up of 9.5 months (range 3.7–14.9 months).

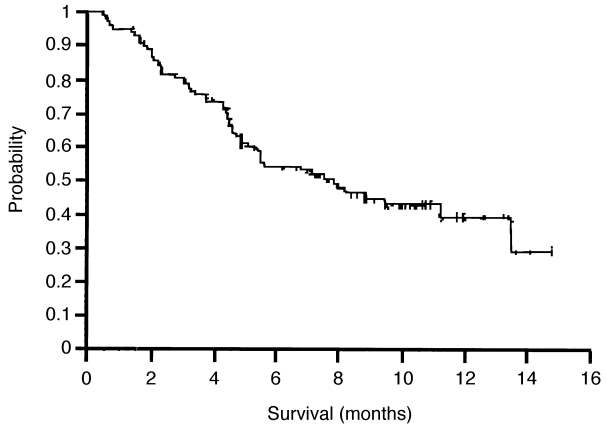

Figure 1. Actuarial survival curve for 100 patients entering the study. Median survival is 8 months, with a 42% 1-year survival.

The effects of various demographic and prognostic factors on response rate for patients treated with this regimen are shown in Table 3. Statistically significant differences in response rate were not observed based on gender, performance status, stage, or previous weight loss in this group of patients.

Toxicity

This treatment regimen was well tolerated by most patients. Myelosuppression was the most common toxicity (Table 4). Grade 3 or 4 leucopenia occurred in 32 patients (10% of courses). 15 patients required dose reductions due to leucopenia at some time during their treatment course. Anaemia and thrombocytopenia were less common, with grade 3/4 toxicities occurring in only 10 and 12% of patients, respectively. 11 patients were hospitalised for treatment of fever associated with neutropenia. There was one treatment-related death due to sepsis.

Toxicity other than myelosuppression is summarised in Table 5. The arthralgia/myalgia syndrome was common, but was only severe (grade 3 or 4) in 5 patients (5%). Peripheral neuropathy was also frequent and generally became manifest after the third or fourth course. Grade 3 peripheral neuropathy was only encountered in 15 patients, but, an additional 12 patients were electively removed from treatment after four to eight courses due to mild to moderate neuropathy (grade 2). Other grade 3 and 4 toxicity was uncommon. 1 patient developed a severe bullous skin reaction involving his entire arm within 1 h of receiving chemotherapy. He eventually required skin grafts and was withdrawn from therapy. 1 patient had an acute myocardial infarction within 1 h of completing her first course of treatment (no arrhythmia documented); she recovered from this cardiac event but died 2 weeks later of sepsis while neutropenic.

Table 3. Treatment response in patient subgroups

Patient characteristic	Number of patients	Number of responders (%)
Gender		
Male	70	29 (41)
Female	30	9 (30)
Performance status		
90–100	59	26 (44)
70–80	41	12 (29)
Weight loss		
$< 10\%$	85	31 (36)
$\geq 10\%$	15	7 (47)
Stage		
IIIB	30	10 (33)
IV	70	28 (40)

Table 4. Myelosuppression (100 patients/414 courses)

	Percentage of patients		Number of courses (%)	
Toxicity	Grade 3	Grade 4	Grade 3	Grade 4
Leucopenia	22	10	38 (9)	14 (3)
Thrombocytopenia	9	3	12 (3)	3 (1)
Anaemia	10	—	16 (4)	—

DISCUSSION

In this large, multicentre, community-based trial we confirm the efficacy of paclitaxel and carboplatin in the treatment of advanced NSCLC. In 94 evaluable patients treated at 17 centres, a 40% overall response rate was obtained and the actuarial 1-year survival was 42%. In addition, most responding patients and some with stable disease experienced improvement in one or more symptoms and 47% of these patients gained weight during therapy. Using a 1-h paclitaxel infusion, this regimen was easily administered and well tolerated in the outpatient setting.

Several other phase II studies have documented a high level of activity for the combination of paclitaxel and carboplatin, although the doses and schedules of administration have varied among the other studies [4, 5, 9–11]. Langer and colleagues documented a 62% response rate in 53 patients receiving carboplatin at AUC 7.5 and an escalating paclitaxel dose administered by 24-h infusion [4]. In a subsequent phase II study, response rates remained high (55%) when the schedule of paclitaxel was changed to a 1-h infusion, while maintaining the same dose of carboplatin [9]. Using lower doses of paclitaxel (135 or 175 mg/m^2) with carboplatin (AUC 6.0), Johnson and associates obtained a response rate of 27% with 32% 1-year survival; the duration of paclitaxel infusion was changed from 24 h to 1 h during the study, with no obvious effect on response rate [12].

The regimen reported here was modelled after the regimen developed at the University of Southern California (USC) in

Table 5. Other toxicity

	Percentage of patients		
Toxicity	Grade 1–2	Grade 3	Grade 4
Arthralgia/myalgia	63	5	0
Peripheral neuropathy	46	15	0
Mucositis	10	1	0
Nausea/vomiting	38	7	0
Cardiac toxicity	0	0	1
Skin toxicity	0	0	1
Hypersensitivity reactions	7	0	0
Dizziness	6	0	0
Diaphoresis	3	0	0
Confusion	2	0	0
Anxiety	1	0	0
Chest pain	1	0	0
Syncope	1	0	0
Ataxia	1	0	0

which paclitaxel, 225 mg/m^2 by 3-h infusion, was administered with carboplatin at AUC 6.0 [5]. Preliminary results with this regimen reported by Vafai and colleagues documented a 63% response rate in the first 27 patients treated [5]. The doses of both drugs used in the present study were identical to the USC regimen, with the only change being the administration of paclitaxel by 1-h rather than 3-h infusion. Although this 2-h difference in the duration of paclitaxel infusion may seem trivial, it enables the regimen to be administered easily as an outpatient (2 h versus 4 h total administration time). The response rate, median survival and 1-year survival achieved with this regimen in a large number of patients are similar to those reported with other regimens using longer paclitaxel infusions and, in some instances, higher carboplatin doses.

Cumulative peripheral neuropathy has emerged as the most bothersome treatment-related toxicity when paclitaxel is administered by short infusion and is accentuated in regimens also containing a platinum analogue. Grade 3 neuropathy occurred in 15% of patients in the present study and another 12% discontinued therapy prematurely after developing grade 2 neuropathy. Similar problems with neuropathy were reported by Vafai and colleagues with a 3-h paclitaxel infusion and also by Langer and associates when the duration of paclitaxel infusion was decreased from 24 h to 1 h [9]. However, the markedly reduced myelosuppression and the ease of administration makes the short paclitaxel infusions preferable to a 24-h infusion in the treatment of NSCLC. Based on our experience with similar combination regimens in other malignancies, it seems likely that a modest reduction in the paclitaxel dose (i.e. from 225 to 200 mg/m^2) would partially alleviate the development of neuropathy.

Ongoing randomised trials are comparing the combination of paclitaxel and carboplatin to other standard regimens employed in NSCLC, including cisplatin/etoposide, cisplatin/vinorelbine and paclitaxel as a single agent. However, results of a recently reported randomised three-arm Eastern Cooperative Oncology Group (ECOG) trial demonstrated that two different combinations of paclitaxel (administered by 24-h infusion) and cisplatin produced superior response rates and survival when compared with a standard cisplatin/etoposide regimen [13]. Response rates for the paclitaxel/cisplatin regimens were 26.5% (paclitaxel 135 mg/m^2) and 32.1% (paclitaxel 250 mg/m^2), both similar to the response rate of 40% using 1-h paclitaxel and carboplatin. As data accumulate, it seems likely that regimens containing paclitaxel and a platinum agent will be accepted as standard treatment for advanced NSCLC. Of the various regimens employed, the 1-h paclitaxel and carboplatin regimen is the easiest to administer in the outpatient setting and provides a useful and widely applicable option.

The introduction of additional active agents offers further possibilities for the improvement of therapy of NSCLC. Gemcitabine, vinorelbine, topotecan, irinotecan and docetaxel have demonstrated single agent activity in advanced NSCLC. Although only limited data regarding these drugs in combination are available, it seems probable that novel combinations of these agents will further improve treatment results for patients with advanced NSCLC.

1. Murphy WK, Fossella FV, Winn RJ, *et al.* Phase II study of Taxol in patients with untreated advanced non-small cell lung cancer. *J Natl Cancer Inst* 1993, **85**, 384–388.
2. Chang AY, Kim K, Glick J, *et al.* Phase II study of Taxol, merbarone, and piroxantrone in stage IV non-small cell lung cancer: the Eastern Cooperative Oncology Group results. *J Natl Cancer Inst* 1993, **85**, 388–394.
3. Hainsworth JD, Thompson DS, Greco FA. Paclitaxel by 1-hour infusion: an active drug in metastatic non-small cell lung cancer. *J Clin Oncol* 1995, **13**, 1609–1614.
4. Langer CJ, Leighton JC, Comis RL, *et al.* Paclitaxel and carboplatin in combination in the treatment of advanced non-small cell lung cancer: a phase II toxicity, response, and survival analysis. *J Clin Oncol* 1995, **13**, 1860–1870.
5. Vafai D, Israel V, Zaretsky S, Natale RB. Phase I/II trial of combination carboplatin and Taxol in non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1995, **14**, 352 (Abstr.).
6. Hainsworth JD, Greco FA. Paclitaxel administered by 1-hour infusion: preliminary results of a phase I/II trial comparing two schedules. *Cancer* 1994, **74**, 1377–1382.
7. Hainsworth JD, Raefsky EL, Greco FA. Paclitaxel administered by a 1-hour infusion: a phase I–II trial comparing two schedules. *Cancer J Sci Am* 1995, **1**, 281–287.
8. Kaplan EL, Meier P. Non-parametric estimation from incomplete observations. *J Am Stat Assoc* 1958, **53**, 457–481.
9. Langer C, Kaplan R, Roswald E, *et al.* Paclitaxel by 1-hour infusion combined with carboplatin in advanced non-small cell lung carcinoma (NSCLC): a phase II study. *Proc Am Soc Clin Oncol* 1996, **15**, 396 (Abstr.).
10. Schutte W, Bork I, Sucker S. Phase II trial of paclitaxel and carboplatin as firstline treatment in advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1996 **15**, 398 (Abstr.).
11. Ros V, Conner A, Mitchell RB. Carboplatin and paclitaxel for chemotherapy-naive patients with advanced non-small cell lung cancer. *Proc Am Soc Clin Oncol* 1996, **15**, 404 (Abstr.).
12. Johnson DH, Paul DM, Hande KR, *et al.* Paclitaxel plus carboplatin in advanced non-small cell lung cancer: a phase II trial. *J Clin Oncol* 1996, **14**, 2054–2060.
13. Bonomi P, Kim K, Chang A, *et al.* Phase III trial comparing etoposide (E) cisplatin (C) versus taxol (T) with cisplatin-GCSF (G) versus taxol–cisplatin in advanced non-small cell lung cancer: an Eastern Cooperative Oncology Group trial. *Proc Am Soc Clin Oncol* 1996, **15**, 382 (Abstr.).

Acknowledgements—Supported in part by grants from Bristol-Myers Squibb and The Minnie Pearl Cancer Research Network.

APPENDIX

Minnie–Pearl Cancer Research Network

Tennessee Oncology, P.C., Nashville, Tennessee
Comprehensive Cancer Institute, Huntsville, Alabama
Montgomery Cancer Center, Montgomery, Alabama
Earle A. Chiles Research Institute, Portland, Oregon
Mary Bird Perkins Cancer Center, Baton Rouge, Louisiana
Medical Oncology Associates, Pittsburgh, Pennsylvania
Oncology/Hematology Group of South Florida, Miami, Florida
Grand Rapids CCOP, Grand Rapids, Michigan
The West Clinic, Memphis, Tennessee
McLeod Cancer and Blood Center, Johnson City, Tennessee
Mid-State Oncology and Hematology, Nashville, Tennessee
Clarksville Memorial Hospital, Clarksville, Tennessee
Graves-Gilbert Clinic, Bowling Green, Kentucky
Oncology Associates of Western Kentucky, Paducah, Kentucky
Northwest Alabama Cancer Center, Muscle Shoals, Alabama
Forsyth Hematology and Oncology Associates, P.A., Winston Salem, North Carolina
Northwest Oncology, Marietta, Georgia.