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ORIGINAL REPORT

Carboplatin and Etoposide With or Without Palifosfamide in Untreated Extensive-Stage Small-Cell Lung Cancer: A Multicenter, Adaptive, Randomized Phase III Study (MATISSE)

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A B S T R A C T

Purpose

To evaluate the efficacy of the addition of palifosfamide to carboplatin and etoposide in extensive stage (ES) small-cell lung cancer (SCLC).

Patients and Methods

MATISSE was a randomized, open-label, adaptive phase III study. Previously untreated patients with ES SCLC were randomly assigned in a 1:1 fashion to receive carboplatin at area under the serum concentration-time curve 5 on day 1 plus etoposide 100 mg/m^2 per day on days 1 to 3 every 21 days (CE) or carboplatin at area under the serum concentration-time curve 4 on day 1 plus etoposide 100 mg/m^2 per day plus palifosfamide 130 mg/m^2 per day on days 1 to 3 every 21 days (PaCE). The primary end point was overall survival.

Results

In all, 188 patients were enrolled; 94 patients received CE and 94 patients received PaCE. The median age on both arms was 61 years. Six cycles of chemotherapy were completed on both arms of the study by approximately 50% of the patients. Serious adverse events were documented and did not differ significantly between patients receiving PaCE and those receiving CE. Median overall survival was similar between both arms with 10.03 months on PaCE and 10.37 months on CE (P = .096).

Conclusion

The addition of palifosfamide to CE failed to improve survival in ES SCLC.

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INTRODUCTION

Platinum doublet chemotherapy has been the standard of care first-line regimen in patients with extensive stage (ES) small-cell lung cancer (SCLC) for the last three decades.[1] Cisplatin in combination with irinotecan is the more frequently used regimen in Japan, but cisplatin with etoposide or carboplatin with etoposide (CE) is used in the United States.[2] Objective response rates in the first-line setting are 67% to 80%, and median overall survival (OS) is 8 to 13 months.[3] Unfortunately, disease relapse occurs in all patients, and second-line chemotherapy options lead to short responses.[4] Novel first-line therapies continue to be urgently needed.

A previous Hoosier Oncology Group phase III study demonstrated an improvement in OS with the addition of ifosfamide to cisplatin and etoposide.[5,6] Ifosfamide, an alkylating agent, in combination with cisplatin and etoposide (VIP) increased median OS to 9 months compared with 7.3 months with cisplatin and etoposide alone. In addition, the 2-year OS was improved from 5% to 13% in favor of VIP. However, the increased toxicity and inconvenience of the addition of ifosfamide, including the need for hospitalization and intravenous fluids, precluded the adoption of VIP as the standard first-line regimen for the treatment of ES SCLC. Ifosfamide is a prodrug whose cytotoxic effects are largely exerted by its active metabolite isophosphoramide mustard.[6] However, the clinical utility of ifosfamide is limited by a number of toxic metabolites such as acrolein and chloracetaldehyde, which are associated with hemorrhagic cystitis and neurotoxicity, respectively.

ASSOCIATED CONTENT

Appendix
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Data Supplement
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Palifosfamide (Zymafos, ZIO-201; ZIOPHARM Oncology, Boston, MA) is a salt formulation of isophosphoramide mustard, the active metabolite of ifosfamide that was developed by ZIOPHARM Oncology.[7,8] Preclinical activity demonstrated that palifosfamide was active in a number of tumor models, including sarcoma and lung cancer.[9] Palifosfamide was previously combined with CE in a phase I trial in patients with advanced solid malignancies.[10] Carboplatin at an area under the serum concentration-time curve (AUC) 4 on day 1 combined with etoposide at 100 mg/m^2 on days 1 to 3 and palifosfamide at 100, 130, or 150 mg/m^2 on days 1 to 3 were evaluated for safety in a standard 3 + 3 dose-escalation design. The dose-limiting toxicity reported was febrile neutropenia. Carboplatin at an AUC of 4 on day 1, etoposide at 100 mg/m^2 on days 1 to 3, and palifosfamide at 130 mg/m^2 on days 1 to 3 was shown to be a safe combination. By using that dosing schedule, we conducted a trial that evaluated the addition of palifosfamide to CE in patients with untreated ES SCLC.

PATIENTS AND METHODS

Eligible patients had histologic or cytologic diagnosis of ES SCLC defined as disease beyond the ipsilateral hemithorax, including contralateral mediastinum in the supraclavicular area and malignant pleural or pericardial effusion or hematogenous spread. Eligibility criteria included Eastern Cooperative Oncology Group performance status (ECOG PS) of 0 to 2. No prior chemotherapy or radiotherapy was allowed except prior radiotherapy for brain metastases as long as the patient had recovered from all acute radiation-related toxicities. Adequate bone marrow (hemoglobin $\geq$ 10.0 g/dL, absolute neutrophil count $\geq$ 1,500/μL, platelet count $\geq$ 100,000/μL), liver (total bilirubin $\leq$ 1.5 $\times$ upper limit of normal, ALT and AST $\leq$ 2.5 $\times$ upper limit of normal or $\leq$ 5 if documented liver metastases), and renal function (estimated glomerular filtration rate $\geq$ 60 mL/min per 1.73 m^2) were required. Patients were defined as active smokers if they had smoked 100 cigarettes in their lifetime and continue to smoke, former smokers if they currently do not smoke, and never smokers if they have never smoked or have smoked fewer than 100 cigarettes in their entire lifetime. Patients were excluded if they had significant concurrent medical conditions that would impact the safety of the patient or if they had a clinically significant infection within 7 days of random assignment. In addition, patients were excluded if they had symptomatic, untreated brain metastases but were allowed if their brain metastases were asymptomatic. Each patient signed an institutional review board–approved, protocol-specific informed consent in accordance with institutional guidelines (Fig 1).

Study Treatments

A minimum of four and maximum of six cycles were allowed on the trial. The use of growth factors such as erythropoietin or granulocyte colony-stimulating factor was allowed at the discretion of the investigator. Carboplatin was administered at AUC 4 on day 1, etoposide at 100 mg/m^2 on days 1 to 3, and palifosfamide at 130 mg/m^2 on days 1 to 3 every 21 days.

Study design and statistical considerations. MATISSE (Multicenter Adaptive Trial Investigating Small Cell Lung Cancer Survival Endpoints) was a multicenter, multinational, randomized, controlled, open-label phase III trial with an adaptive design. The primary end point of the study was OS defined as the time from random assignment to the date of death. Initial secondary end points included progression-free survival (PFS), objective response rates, duration of response, and safety, including all adverse events (AEs). Tumor-related end points were to be assessed according to Response Evaluation Criteria in Solid Tumors (RECIST 1.1). The study used an adaptive group sequential design that allowed early stopping for efficacy or futility and sample size re-estimation on the basis of the results of the interim analysis. The original sample size was estimated on the basis of 8.4- and 11.2-month median survivals for the control and treatment arms, respectively. Eligible patients were stratified according to age, sex, and ECOG PS and were allocated to treatment in a 1:1 ratio. With one-sided 2.5% type I error and an O'Brien-Fleming boundary at 0.5 for early efficacy, the power of the trial was 87%. Proportional hazards assumptions were checked by using the Schoenfeld method. On the basis of

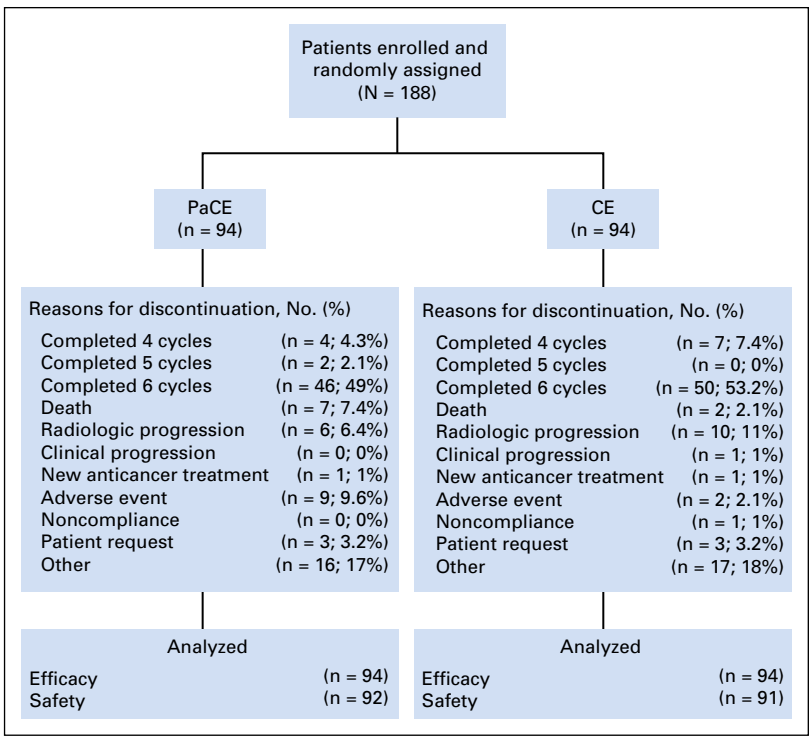

Fig 1. CONSORT diagram. CE, carboplatin and etoposide; PaCE, palifosfamide plus CE.

the number of events required, the expected number of patients to be enrolled on the study was 464 with a maximum number of 548 patients (274 per arm). The interim analysis by an independent data monitoring committee was planned after 125 OS events. The intention-to-treat population was defined as all randomly assigned patients. The safety population was defined as all randomly assigned patients who were treated with any study therapy. Patients were randomly assigned in a 1:1 ratio by using an interactive response system and were stratified on the basis of age, sex, and initial PS.

The development plans for palifosfamide changed after analysis showed negative phase III data regarding the addition of palifosfamide to doxorubicin in metastatic soft tissue sarcomas.[11,12] This led to an amendment that closed the study to enrollment after 188 patients of the planned 464 patients were randomly assigned. The primary objective remained OS. The secondary objectives were amended to include serious AEs (SAEs) only as compared with all AEs. An event was considered an SAE if it resulted in death, was life-threatening, required in-patient hospitalization or prolongation of existing hospitalization, was a persistent or significant disability/incapacity, or was a congenital anomaly/birth defect. Treatment-emergent adverse events (TEAEs) were reported and defined AEs that started on or after the date of the first dose of any study drug. The maximum intensity of events was recorded by using the National Cancer Institute Common Terminology Criteria for Adverse Events 4.03. The investigator determined the potential relationship of events to the study drugs. In addition, as part of the amendment, response assessments and PFS were no longer required. The amended statistical post hoc power was 80% and a two-sided 0.05 type I error was used to detect a 0.64 hazard ratio (HR) in OS with 94 patients on each treatment arm observed for up to 40 months.

RESULTS

Patient Characteristics

This study was a multicenter, multinational study that enrolled patients in 13 countries and 70 (of 109) study sites. From June 8, 2012, through April 22, 2013, 188 patients were randomly assigned (94 per arm). Among the 188 patients randomly assigned, there were 159 deaths; 29 patients were alive at the time of this analysis. The last patient follow-up was performed on December 2, 2014. Baseline characteristics of patients are summarized in Table 1 with no major differences between arms. Median age on both arms was 61 years, with 70% of patients being males as is expected in SCLC. Two thirds of patients were treated outside the United States with Russia enrolling the most patients outside the United States, followed by Ukraine and France. Sixty patients were treated in the United States, five in Australia, 14 in Canada, 15 in France, one in Germany, three in Hungary, and five each in Israel, Italy, and Poland, 45 in Russia, three in Taiwan, 17 in Ukraine, and 10 in the United Kingdom (for a list of all study sites, see Appendix Table A1 [online only]). All 188 patients were evaluable for OS and were included in the intention-to-treat population. Because of the amendment, response assessments were left to the discretion of investigators and were collected in only 45% of patients on each treatment arm.

Treatment Delivered

Approximately half the patients on each arm received six cycles of chemotherapy. The main reason for death was disease progression in 82% of patients on either the CE or PaCE arm. Dose delays and reductions were not collected from enrolling sites.

Table 1. Demographic and Clinical Characteristics

Characteristic	PaCE (n = 94) No.	PaCE (n = 94) %	CE (n = 94) No.	CE (n = 94) %
Median age, years (range)	61 (42-82)		61 (32-88)	
Sex				
Male	66	70	66	70
Female	28	30	28	30
ECOG PS				
0	24	25	21	22
1	60	64	62	66
2	10	11	9	10
Metastases				
Liver	39	42	37	39
Brain	14	15	17	18
Bone	14	15	16	17
Country				
US	31	33	29	31
Other	63	67	65	69
Smoking status				
Current	46	49	44	47
Former	36	38	33	35
Unknown	7	7.4	10	10.6
Never	5	5.3	7	7.4

Abbreviations: CE, carboplatin and etoposide; ECOG PS, Eastern Cooperative Oncology Group performance status; PaCE, palifosfamide plus CE.

Toxicity

The safety population included 92 patients on the PaCE arm and 91 patients on the CE arm; five patients were not evaluable for toxicity. Safety population patients had received at least one dose of the study therapy. There were no significant differences between the two treatment arms in the number of patients who experienced SAEs ($P > .99$). Twenty-six patients (28.3%) on the PaCE arm and 25 patients (27.5%) on the CE arm had at least one SAE as defined per protocol. SAEs reported in three or more patients on either arm are listed in Table 2. Approximately 20% of patients on both treatment arms experienced at least one TEAE. Dizziness was the

Table 2. SAEs Reported in Three or More patients on Each Arm

Toxicity	PaCE (n = 92) No.	PaCE (n = 92) %	CE (n = 91) No.	CE (n = 91) %
Hematologic				
Febrile neutropenia	4	4.3	5	5.5
Pancytopenia	4	4.3	0	0
Neutropenia	1	1.1	3	3.3
Nausea	3	3.3	1	1.1
Dehydration	3	3.3	2	2.2
Hyponatremia	0	0	3	3.3
Dyspnea	3	3.3	2	2.2
Infection	5	5.4	9	9.9

Abbreviation: CE, carboplatin and etoposide; PaCE, palifosfamide plus CE; SAE, serious adverse event.

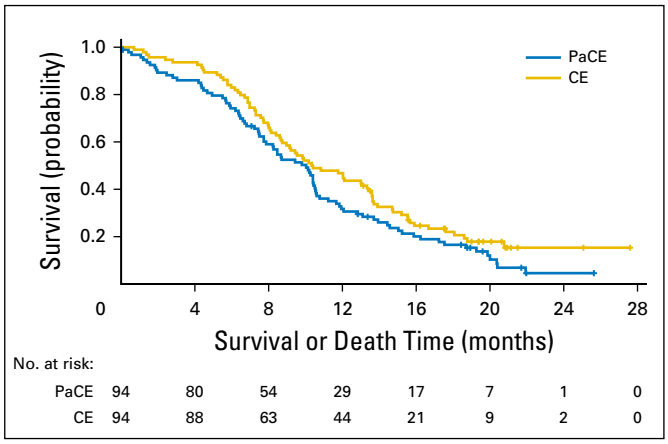

Fig 2. Kaplan-Meier curves for overall survival for intention-to-treat population. CE, carboplatin and etoposide; PaCE, palifosfamide plus CE.

only statistically significant TEAE in both treatment arms and was noted in 11% of patients on the CE arm compared with 3.3% of patients on the PaCE arm (P = .048).

Efficacy

The median OS for the PaCE patients was 10.03 months (95% CI, 7.7 to 10.5 months) compared with 10.37 months (95% CI, 8.7 to 13.4 months) for the CE patients (P = .096). The HR of 1.30 (95% CI, 0.95 to 1.78) is shown in Figure 2. The median OS follow-up was 10.7 months overall and 18.2 months for those 29 patients who were alive at the last assessment. There were no statistically significant differences in OS with PaCE versus CE patients according to age, sex, ECOG PS, or region of treatment except for patients age 65 years or older receiving CE who had a superior survival compared with those receiving PaCE (9.7 *v* 6.8 months; P = .044). Results are presented in the forest plot in Figure 3.

DISCUSSION

This randomized, controlled, open-label trial with an adaptive design failed to meet its primary end point of improving OS with the addition of palifosfamide to CE in patients with ES SCLC. The median OS with the addition of palifosfamide (PaCE) was numerically inferior to that observed on the CE arm. The addition of palifosfamide was not associated with an increase in SAEs; however, with the lack of documentation for all AEs, dose delays, or dose reductions on our study, it is difficult to make firm conclusions regarding the overall toxicity of PaCE compared with CE. The study did not meet its accrual goal and was underpowered, but it is extremely unlikely that this would have been a positive study with full accrual. Carboplatin was given at a lower dose on the PaCE arm because this was found to be the safe dose in the phase I study, and it is unlikely that this lower dose had an impact on OS with the PaCE regimen. This study failed to confirm or reproduce the small improvement in OS observed on the Hoosier Oncology Group study that tested the addition of ifosfamide to CE.[5] Further chemotherapy strategies are being evaluated in the first-line setting of ES SCLC, but it remains unknown whether any will improve outcomes over platinum doublet chemotherapy. Other strategies being evaluated in the maintenance setting after platinum doublet therapy in ES SCLC include maintenance sunitinib, which improved PFS by 1.5 months but not OS.[13] In addition, pembrolizumab and nivolumab (humanized antibodies targeting the programmed cell death-1 [PD-1] receptor) are undergoing evaluation in the maintenance setting. In addition, PD-1 inhibitors are

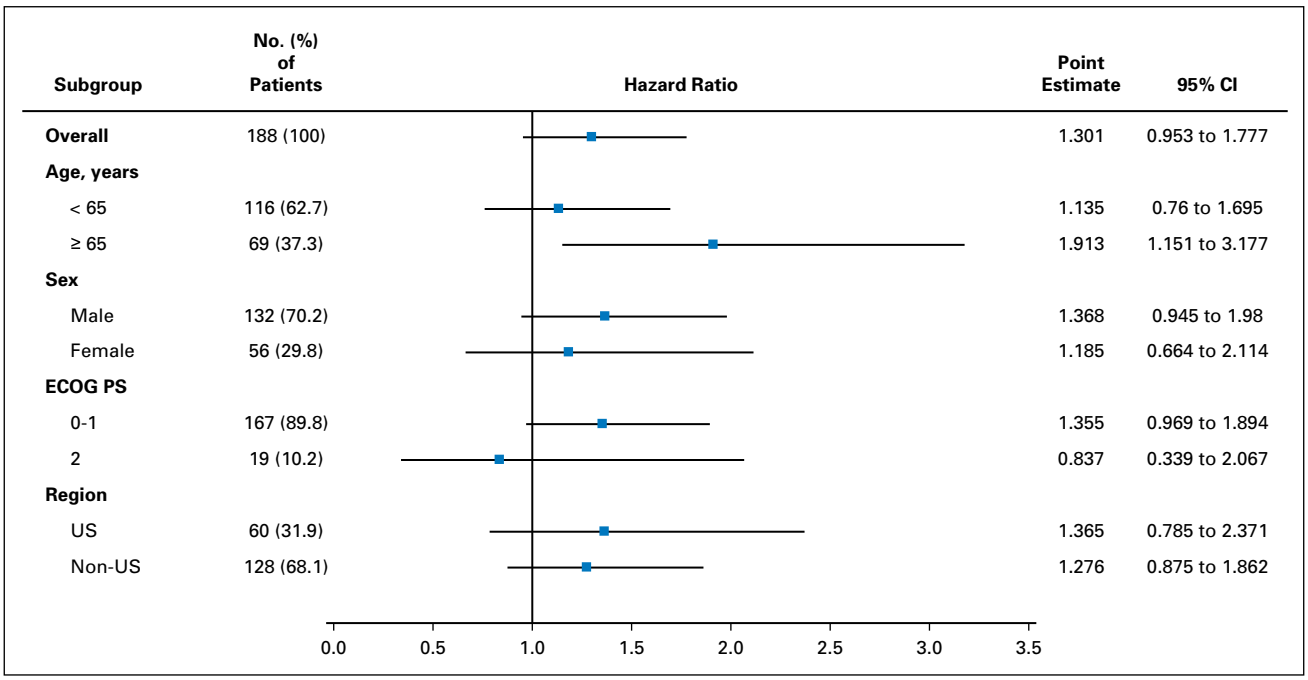

Fig 3. Forest plot of overall and subgroup hazard ratios including interactions. ECOG PS, Eastern Cooperative Oncology Group performance status.

being combined with CE in the first-line setting in patients with limited-stage disease and also in the second-line setting.[14]

Our understanding of the biology of SCLC has significantly increased, but translating that knowledge into new clinical therapeutic options that have an impact on the care of patients with SCLC has yet to be achieved. SCLC has a high mutational burden resulting from decades of exposure to tobacco-induced carcinogens. A panel of several genes seems to be mutated or abnormal in almost all SCLCs, including p53, retinoblastoma gene, and Myc family gene members.[14,15] In addition, Nfib overexpression has been shown to accelerate tumorigenesis and promote metastases in SCLC. ASCL1 is a transcription factor that is pivotal for neuroendocrine differentiation and contributes to proliferation and migration of SCLC.[16] Targeting the abnormalities identified and assessing whether these approaches are effective in SCLC still need to be evaluated. Chemotherapy remains the only systemic therapy that has been shown to improve survival in ES SCLC compared with targeted therapies. Better first- and second-line treatment options for ES SCLC are necessary to transform the landscape of this bleak disease.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at jco.org.

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Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Appendix

Table A1. Sites for the MATISSE (Multicenter Adaptive Trial Investigating Small Cell Lung Cancer Survival Endpoints) Study

Country/State/Province	City	Institution
United States		
Alabama	Birmingham	Birmingham Hematology and Oncology Associates
California	Los Angeles	University of Southern California
	Santa Rosa	Redwood Regional Oncology Group
Delaware	Newark	Christiana Care Health Services
Florida	Jacksonville	Baptist Cancer Institute
	Port St. Lucie	Hematology Oncology Associates of the Treasure Coast
Georgia	Atlanta	Peachtree Hematology Oncology Consultants
Illinois	Chicago	Rush University Medical Center
	Galesburg	Medical and Surgical Specialists
	Niles	Illinois Cancer Specialists
Indiana	Fishers	Central Indiana Cancer Centers
	Goshen	Goshen Center for Cancer Care
	Indianapolis	Indiana University
	Lafayette	Horizon Oncology Center
	Muncie	Indiana University Health Ball Memorial Hospital
Kansas	Overland Park	University of Kansas Hospital
Kentucky	Lexington	Central Baptist Hospital
Louisiana	Baton Rouge	Medical Oncology
Maryland	Frederick	Frederick Memorial Hospital Regional Cancer Therapy Center
Michigan	Wyoming	Metro Health Cancer Center
Minnesota	Duluth	Saint Mary's Medical Center
	Minneapolis	Virginia Piper Cancer Institute
New Jersey	Hackensack	John Theurer Cancer Center at Hackensack University Medical Center
	Morristown	Hematology Oncology Associates of Northern New Jersey; Carol G. Simon Cancer Center
New Mexico	Albuquerque	University of New Mexico Cancer Center
New York	Albany	New York Oncology Hematology
	New York City	Montefiore Medical Center
Ohio	Cincinnati	The Christ Hospital
	Dayton	Greater Dayton Cancer Center, Medical Oncology Hematology Associates
Pennsylvania	Kingston	Medical Oncology Associates of Wyoming Valley
South Carolina	Charleston	Charleston Hematology Oncology Associates
Texas	Dallas	Texas Oncology-Medical City Dallas
	Dallas	Texas Oncology-Baylor, Charles A. Sammons Cancer Center
	Galveston	University of Texas Medical Branch at Galveston
	Houston	Oncology Consultants
	Wichita Falls	Texas Oncology
Vermont	Burlington	University of Vermont Medical Center
Virginia	Fairfax	Fairfax Northern Virginia Hematology-Oncology
Washington	Seattle	Swedish Medical Center
Wisconsin	Madison	Wisconsin Institutes for Medical Research
Australia		
New South Wales	Wollongong	Southern Medical Day Oncology Care Centre
Canada		
Manitoba	Winnipeg	CancerCare Manitoba
Ontario	Oshawa	R.S. McLaughlin Durham Regional Cancer Center at Lakeridge Health Oshawa
Quebec	Sainte-Foy	Hôpital Laval
France		
Normandie	Caen	Centre François Baclesse
Bretagne	Brest	Centre Hospitalier Universitaire-Hôpital Morvan
Centre-Val de Loire	Tours	Centre Hospitalier Universitaire, Hopital Bretonneau
Lorraine	Limoges	Hôpital du Cluzeau
Pays de la Loire	Saint-Herblain	Institut de Cancérologie de l'Ouest-René Gauducheau
Cote d'Azur-Corse	Marseille	Hôpital Saint Joseph
Rhône -Alpes	Pierre Bénité	Centre Hospitalier Lyon Sud
	Strasbourg	Centre Paul Strauss

(continued on following page)

Table A1. Sites for the MATISSE (Multicenter Adaptive Trial Investigating Small Cell Lung Cancer Survival Endpoints) Study (continued)

Country/State/Province	City	Institution
Hungary		
Hajdu-bihar	Debrecen	Debreceni Egyetem Orvos és Egészségtudományi Centrum
Heves	Mátraháza	Mátrai Gyógyintézet
Israel	Haifa	Rambam Medical Center
	Jerusalem	Hadassah Medical Organization, Ein Kerem
	Kfar Saba	Meir Hospital Sapir Medical Center
	Nahariya	Western Galilee Medical Center
	Petah Tiqwa	Rabin Medical Center, Beilinson Campus
Italy	Genova	Istituto Nazionale per la Ricerca sul Cancro
	Milano	Azienda Ospedaliera Ospedale Niguarda Ca' Granda
	Trento	Presidio Ospedaliero S. Chiara
Poland		
Mazowieckie	Warszawa	Centrum Onkologii-Instytut im. M. Sklodowskiej-Curie w Warszawie
Pomorskie	Gdansk	Uniwersyteckie Centrum Kliniczne
Pomorskie	Gdansk	Wojewódzkie Centrum Onkologii
Zachodniopomorskie	Szczecin	Specjalistyczny Szpital im. Alfreda Sokolowskiego
Russian Federation		
Bashkortostan	Ufa	Republic Clinical Oncology Dispensary of the Ministry of Healthcare of Republic of Bashkortostan
Moscow Region	Moscow	City Oncology Hospital # 62
Primorsky	Arkhangelsk	State Institution of Healthcare "Arkhangelsk Regional Clinical Oncology Dispensary"
Tatarstan	Kazan	Republican Clinical Oncologic Dispensary of Ministry of Health of Republic Tatarstan
	Chelaybinsk	State Budget Institution of Healthcare "Chelyabinsk Regional Clinical Oncology Dispensary"
	Ivanovo	Ivanovo Regional Oncology Centre
	Moscow	Cancer Research Center n.a. N.N. Blokhin
Nizhny Novgorod		Nizhnij Novgorod City Oncology Dispensary
	St. Petersburg	State Educational Institution "S.M. Kirov Military Medical Academy of Ministry of Defense of Russia"
	St. Petersburg	St. Petersburg State I.P. Pavlov Medical University
Yaroslavl		State Healthcare Institution of Yaroslavl region "Regional Clinical Oncologic Hospital"
Taiwan	Taichung	China Medical University Hospital
United Kingdom	Manchester	Wythenshawe Hospital