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ORIGINAL REPORT

Pivotal Study of Iodine-131–Labeled Chimeric Tumor Necrosis Treatment Radioimmunotherapy in Patients With Advanced Lung Cancer

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ABSTRACT

Purpose
Tumor necrosis treatment (TNT) uses degenerating tumor cells and necrotic regions of tumors as targets for radioimmunotherapy. Previous studies in animal tumor models and clinical trials have demonstrated that when linked to the therapeutic radionuclide iodine-131, recombinant chimeric TNT antibody (^{131}I-chTNT) can deliver therapeutic doses to tumors regardless of the location or type of malignancy. Therapeutic efficacy and toxicity of ^{131}I-chTNT in advanced lung cancer patients were studied in this pivotal registration trial.

Patients and Methods
Patients with advanced lung cancer were treated with systemic or intratumoral injection of ^{131}I-chTNT in eight oncology centers in China. The objective response rate (ORR) was assessed as the primary end point.

Results
All 107 patients who were entered onto the study and completed therapy had experienced treatment failure after prior radiotherapy or chemotherapy a mean of three times. The results showed an ORR of 34.6% (complete response, 3.7%; partial response, 30.8%; no change, 55.1%; and progressive disease, 10.3%) in all patients and 33% in 97 non–small-cell lung cancer patients. A biodistribution study demonstrated excellent localization of the radioactivity in tumors in both systemically and intratumorally injected patients. The most obvious adverse side effect was mild and reversible bone marrow suppression.

Conclusion
Radioimmunotherapy with ^{131}I-chTNT was well tolerated and can be used systemically or locally to treat refractory tumors of the lung.

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INTRODUCTION

Lung cancer has a worldwide incidence of 12.3% of all cancers, with an estimated 1.2 million new cases in 2000.[1] As such, it is the most common form of cancer in the world. Etiologically, tobacco smoking is responsible for 80% to 90% of the incidence of lung cancer.[2] Although the prevalence of smoking is decreasing in the United States, in China and East Europe there is an epidemic of smoking which will result in tens of millions of new cases of lung cancer in the future.[1,3,4] Despite improvements in therapy, approximately 90% of lung cancer patients will die from their disease. In 2000, it was estimated that lung cancer resulted in 1.1 million deaths worldwide, or 17.8% of all cancer deaths.[1] Because chemotherapy has added little to improve these grim statistics, only surgery with or without extended-field radiotherapy is a viable treatment option if warranted by the stage of the disease.

In recent years, targeted radiotherapy using radiolabeled monoclonal antibodies has emerged as a new treatment option, especially for the treatment of radiosensitive lymphomas.[5-10] For solid tumors, however, which tend to be more radioresistant in nature, radioimmunotherapy has not yielded significant results largely due to insufficient dosing to the tumor.[11-13] In the last several years, a new antibody targeting methodology has been developed for the targeting of solid tumors. Designated tumor necrosis therapy (TNT), this approach targets necrotic regions found in tumors but absent from normal tissues and organs.[14-17] Unlike other antibody targeting approaches that bind to cell surface antigens expressed on viable tumor cells, TNT antibodies recognize nonviable zones found principally in hypoxic areas of the tumor, regions that represent 30% to 80% of the tumor mass.[18,19] Normal tissues, which are policed by the reticuloendothelial system consisting of fixed tissue and circulating phagocytic cells, do not contain necrotic areas and hence cannot bind TNT antibodies, as shown by tissue biodistribution studies,[14,20] autoradiography,[21] and imaging studies[15,22] performed in both experimental animals and humans.[14,15]

From 1999 to 2001, 62 patients with lung cancer, glioblastoma, lymphoma, head and neck cancer, colorectal carcinoma, hepatocellular carcinoma, and other malignant solid tumors were treated with iodine-131–labeled recombinant chimeric TNT monoclonal antibody (^{131}I-chTNT). From these initial studies, it became clear that lung cancer was an excellent candidate to study the clinical efficacy of TNT radioimmunotherapy. From 2001 to 2002, these clinical trials were continued in an additional 45 patients. The results of this pivotal registration clinical trial were presented to the Chinese State Food and Drug Administration and on June 13, 2003, ^{131}I-chTNT was approved for the treatment of advanced lung cancer in China, making it the second of three approved radiolabeled antibodies (ibritumomab [Zevalin; Biogen Idec, San Diego, CA] and tositumomab [Bexxar; GlaxoSmithKline, Philadelphia, PA]) and the first for the treatment of solid tumors worldwide. Currently, additional trials are ongoing in China to expand the utility of this product for the treatment of brain cancer, hepatocellular carcinoma, and other solid tumors, and trials are ongoing in the United States for both systemic (gastrointestinal tumors) and intratumoral use (recurrent glioblastoma). We report the clinical data obtained during this pivotal trial as part of an international collaboration that began in the late 1980s and early 1990s when TNT was originally developed as a new approach for the targeting of solid tumors.

PATIENTS AND METHODS

Patient Selection

This study enrolled 107 patients from January 1, 1999, to June 30, 2002. Eligible patients were required to have a histologically or cytologically confirmed diagnosis of lung cancer, to be between the ages of 18 and 80 years, and to have experienced treatment failure after chemotherapy or radiotherapy. In addition, patients were required to have an anticipated survival time of at least 3 months according to the judgment of the clinicians. Other entry criteria included no radiotherapy for 2 months or chemotherapy for 1 month before study entry, and all patients had to demonstrate progressing and measurable disease as shown by thoracic radiograph or computed tomography (CT) scans. Finally, patients were required to have a WBC count more than 4,000/μL, an absolute neutrophil count more than 2,000/μL, a platelet count more than 100,000/μL, normal hepatic and renal function, a Karnofsky performance score of at least 60, no serum human antimouse antibodies (HAMA) or human antichimeric antibodies (HACA), and no serious concomitant illnesses. Follow-up was assured to the extent of allowing assessment of the short-term effects of the treatment.

The study was approved by the Chinese State Food and Drug Administration and the Research Ethics Committee of Zhongshan Hospital, Fudan University, Shanghai. Informed consent was obtained for all of the enrolled patients.

Preparation of ^{131}I-chTNT

^{131}I-chTNT was provided by Shanghai MediPharm Biotech Co Ltd (Zhangjiang HiTech Park, Shanghai, China). Recombinant human and mouse chimeric TNT antibody was produced in NS0 murine myeloma cells cultured in a bioreactor and was purified by a series of steps including protein A chromatography and measures to inactivate and remove viruses. The purified chTNT antibody with purity of at least 98% was radiolabeled with Na^{131}I (Syncor International, Shanghai, China) using chloramine T as the oxidant, and the products were purified and tested for radioactivity and pathogen contamination as previously described.[15] The purity of ^{131}I-chTNT was more than 95% and the specific radioactivity of the radiolabeled product was between 8 and 12 mCi/mL.

Therapeutic Regimen

All patients received a saturated solution of potassium iodine (10 drops orally tid) 3 days before the initiation of radioimmunotherapy and continued until 7 days after completion of therapy to block uptake of free ^{131}I by the thyroid. All patients received dexamethasone and diphenhydramine 30 minutes before each treatment to prevent allergic reactions. The 107 patients in eight clinical oncology centers were injected with ^{131}I-chTNT intravenously or intratumorally. In all cases, the patients received two doses of ^{131}I-chTNT administered 2 to 4 weeks apart. For intravenous injection, ^{131}I-chTNT at a dose of 0.8 mCi/kg of body weight was diluted in normal saline and administered through a free-flowing intravenous line during a 1-hour period. Patients were monitored for symptoms and vital signs were measured every 15 minutes. For intratumoral injection, ^{131}I-chTNT at a dose of 0.8 mCi/cm^3 of tumor size was injected directly into the tumor mass using thoracic CT or x-ray guidance and a fine core needle (Dr Japan Co, Tokyo, Japan). CT scans or x-rays clearly showed the location of the tumor and the pathway of the needle. In this way, the proper placement of the needle and the extent of dissemination of the radiolabeled antibody into the tumor mass were monitored. Patients remained in radiation isolation until their whole-body radiation had reached acceptable limits ($\leq$ 5 mR/h at 1 m).

Response Criteria and Evaluation

Efficacy was assessed as the objective response rate to treatment, which was the primary end point of the study. Responses were defined according to WHO criteria for measuring solid tumors as a complete response (CR), a partial response (PR), no

Table 1. Patient Characteristics and Disease Status

Characteristic	No. of Patients	%
Sex		
Male	74	69.2
Female	33	30.8
Age, years		
Mean	58.4	
Median	60.0	
Range	30-77	
Stage at study entry		
II	14	13.1
III	62	57.9
IV	31	29.0
Histology		
Small-cell lung cancer	10	9.3
Non–small-cell lung cancer	97	90.7
Squamous	39	40.2
Adenocarcinoma	50	51.5
Adenosquamous carcinoma	2	2.1
Low-grade lung cancer	3	3.1
Not specified	3	3.1

Table 2. Objective Response Data

Characteristic	No. of Patients	ORR	%	CR	PR	NC	PD
Overall	107	37	34.6	4	33	59	11
Histology							
Small-cell lung cancer	10	5	50	1	4	5	1
Non–small-cell lung cancer	97	32	33	3	29	54	11
Squamous	39	18	46.2	1	17	18	3
Adenocarcinoma	50	12	24	2	10	31	7
Stage at study entry							
Stage II	14	6	42.8	0	6	7	1
Systemic	11	5	45.5	0	5	5	1
Intratumoral	3	1	33.3	0	1	2	0
Stage III	62	23	37.1	3	20	33	6
Systemic	39	14	35.9	2	12	21	4
Intratumoral	23	9	39.1	1	8	12	2
Stage IV	31	8	25.8	1	7	19	4
Systemic	12	3	25	0	3	6	3
Intratumoral	19	5	26.3	1	4	13	1
Route of administration							
Systemic	62	22	35.5	2	20	32	8
Intratumoral	45	15	33.3	2	13	27	3

Abbreviations: ORR, objective response rate; CR, complete response; PR, partial response; NC, no change; PD, progressive disease.

change (NC), or progressive disease (PD). Objective response rate (ORR) was defined as CR plus PR.[23] Tumor growth was monitored by the same imaging method used to establish baseline tumor measurements and was performed after each administration. Confirmation of response required a repeated imaging study 10 weeks after treatment using thoracic x-rays and CT.

Imaging and Biodistribution

All radionuclide imaging was performed to document the biodistribution of the ^{131}I radioactivity in the tumor sites and the whole body. A series of anterior and posterior images were obtained at different time points after systemic or intratumoral administration of ^{131}I-chTNT (scan speed of 5 to 10 cm/min). Regions of interest were drawn to calculate the ratio of tumor to nontumor (normal lung) uptake. MIRDOSE 3.0 (Medical Internal Radiation Dose Committee, Society of Nuclear Medicine, Reston, VA) was used for the estimation of the radiation-absorbed organ doses.

Evaluation of Toxicity

Adverse experiences were graded using the WHO toxicity criteria. Lung cancer patients underwent a complete physical examination, blood counts, and a battery of laboratory tests including radiological studies, ECG, CBC, and chemistry panels to evaluate the status of liver and renal functions at baseline and 2, 3, 4, 5, 6, and 10 weeks after the first administration. In addition, blood HACA and HAMA determinations were performed in all patients before the initiation of the therapy and 4 and 10 weeks after the start of therapy. Samples were assayed for HAMA using murine immunoglobulin G–coated enzyme-linked immunosorbent assay plates and for HACA using chTNT-coated plates followed by horseradish peroxidase–labeled antihuman Fc antibody and colorimetric agent.[15] Thyroid function tests were performed at baseline and at 4 and 10 weeks after the start of therapy.

Statistical Analysis

This was a purely observational registration clinical trial, even though by design there were two parallel injection methods—systemic and intratumoral. No attempt was made to assign the 107 participating patients randomly into systemic or intratumoral groups. The authors did not compare statistical outcomes between the two administration methods.

RESULTS

Patient Characteristics

A total of 107 patients with advanced lung cancer were entered onto the trial and completed treatment from January 1999 to June 2002. The main demographic and clinical characteristics of the cohort are listed in Table 1. All patients had experienced treatment failure after prior therapies (mean, three times; range, 1 to 5 times). These prior therapies included

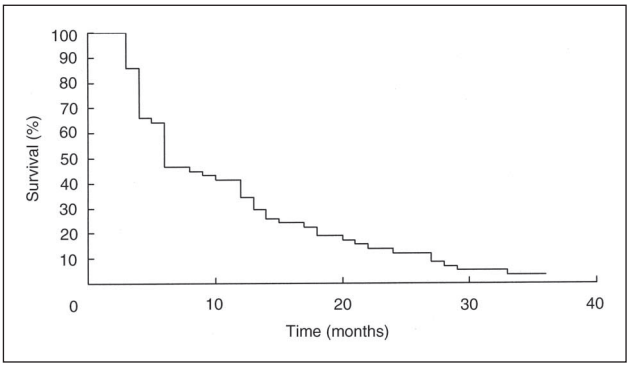

Fig 1. Overall survival of 58 assessable patients with advanced lung cancer after systemic or intratumoral administration of ^{131}I-chTNT.

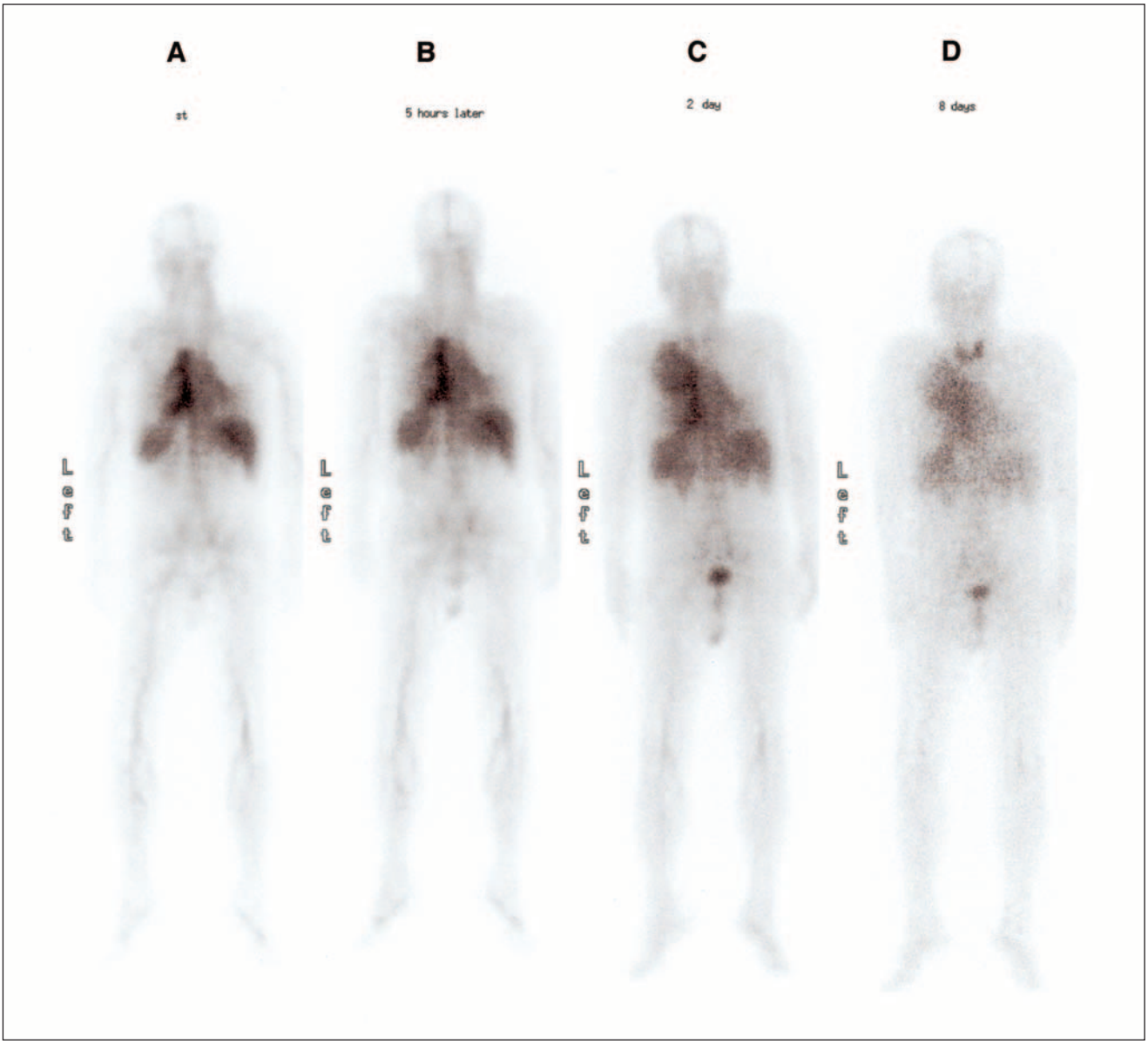

Fig 2. Whole-body single-photon emission computed tomography (SPECT) scans of patients with non–small-cell lung cancer. SPECT scans performed at (A) 0.5 hours, (B) 5 hours, (C) 2 days, and (D) 8 days after systemic administration of iodine-131–labeled chimeric tumor necrosis treatment (^{131}I-chTNT). Whole-body scintigraphy of lung cancer patient at (E) 5, (F) 15, and (G) 25 days after intratumoral administration of ^{131}I-chTNT. Note minimal diffusion of radiolabel from site of injection. Five days after intratumoral radioimmunotherapy, computed tomography (CT) and SPECT images were performed including (H) transaxial, coronal, and sagittal CT scans of lung tumor; (I) transaxial, coronal, and sagittal SPECT of lung tumor after intratumoral injection of ^{131}I-chTNT; (J) fusion images of transaxial, coronal, and sagittal CT and SPECT; and (K) x-ray (scout view) and SPECT of lung tumor.

radiotherapy, irinotecan-based chemotherapy, platinum-containing regimen, or other combined chemotherapy regimens. The median age was 60 years (range, 30 to 77 years). Ninety-three of the patients (86.9%) had stage III or IV disease. Ten of the patients (9.3%) had a diagnosis of small-cell lung carcinoma and 97 of the patients (90.7%) had a diagnosis of non–small-cell lung cancer.

Clinical Efficacy

Eight different oncology centers in China participated in the pivotal study. All patients received two doses of TNT radioimmunotherapy either by systemic (0.8 mCi/kg of body weight) or intratumoral (0.8 mCi/cm^3 of tumor size) administration at 2- or 4-week intervals. Assessments of objective response used WHO criteria and responses were observed regardless of type or number of prior radiotherapy or chemotherapy regimens. As shown in Table 2, among the 107 patients, four patients (3.7%) achieved a CR, 33 patients (30.8%) had a PR, 59 patients (55.1%) had NC, and 11 patients (10.3%) had PD. The overall therapeutic efficacy ORR (CR plus PR) was therefore 34.6%.

For the 10 patients with small-cell lung cancer, the ORR was 50%, with one CR and four PRs. For the 97 patients with non–small-cell lung cancer, the ORR was 33%, with three CRs and 29 PRs. Among the 39 non–small-cell lung cancer patients with squamous cancer, one patient had a CR and 17 patients had a PR, with an ORR of 46.2%. For the 50 non–small-cell lung cancer patients with adenocarcinoma, the ORR was 24%, with two CRs and 10 PRs. Patients with different stages of disease at entry onto the study had different therapeutic responses. In 14 patients with stage II disease, the ORR for six patients was 25%, and in 62 patients with stage III disease, the ORR was 37.1%. In contrast, in 31 patients with stage IV disease, one patient achieved a CR and seven patients achieved a PR, with an ORR of 25.8%. Sixty-two patients received systemic administration of ^{131}I-chTNT; two of the systemically treated patients achieved a CR and 20 patients achieved a PR, with an ORR of 35.5%. Forty-five of the cancer patients were treated with intratumoral injection of ^{131}I-chTNT, and in this group two patients achieved a CR and 13 patients achieved a PR, with an ORR of 33.3%. In 58 patients evaluated for overall

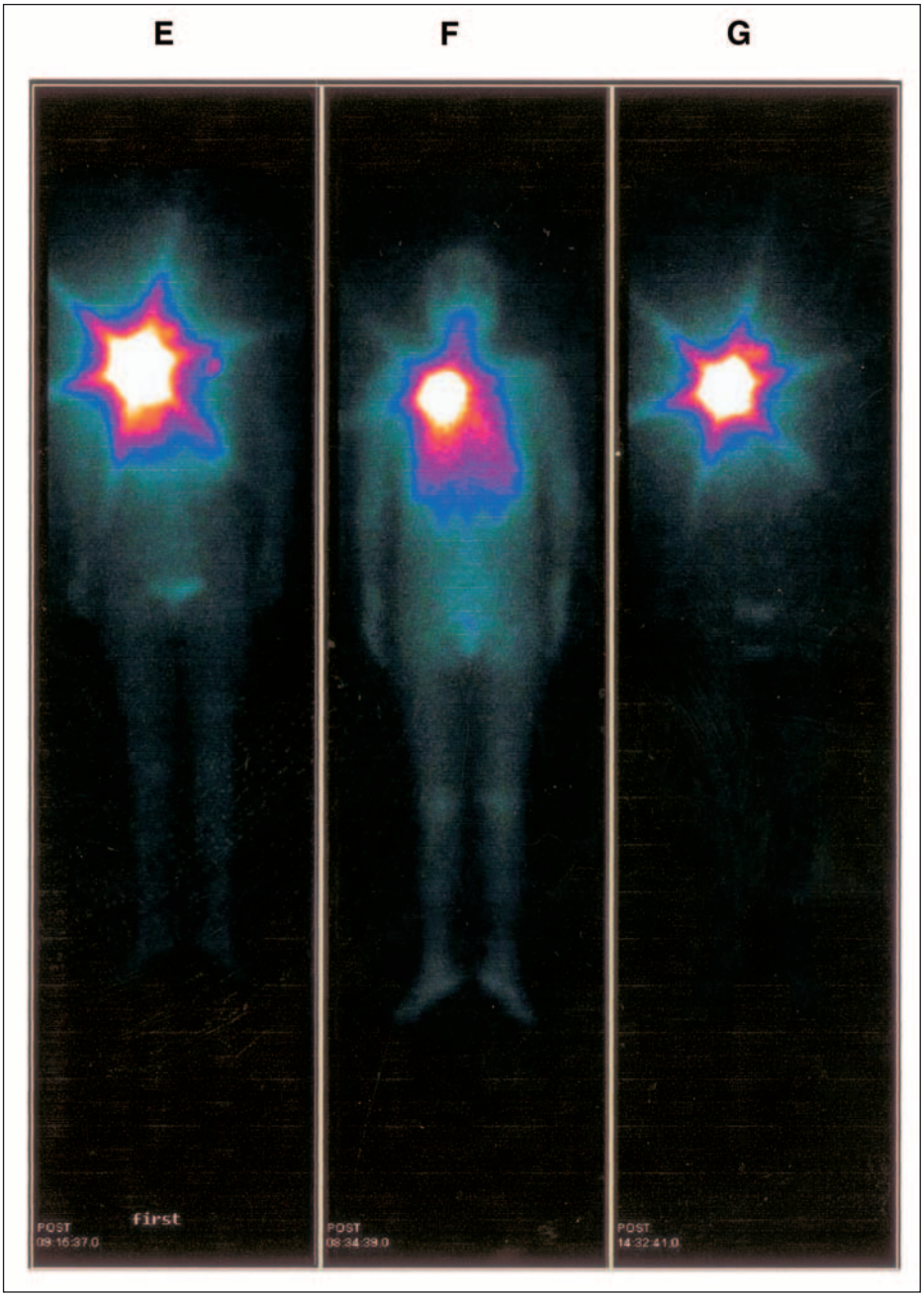

Fig 2. (continued)

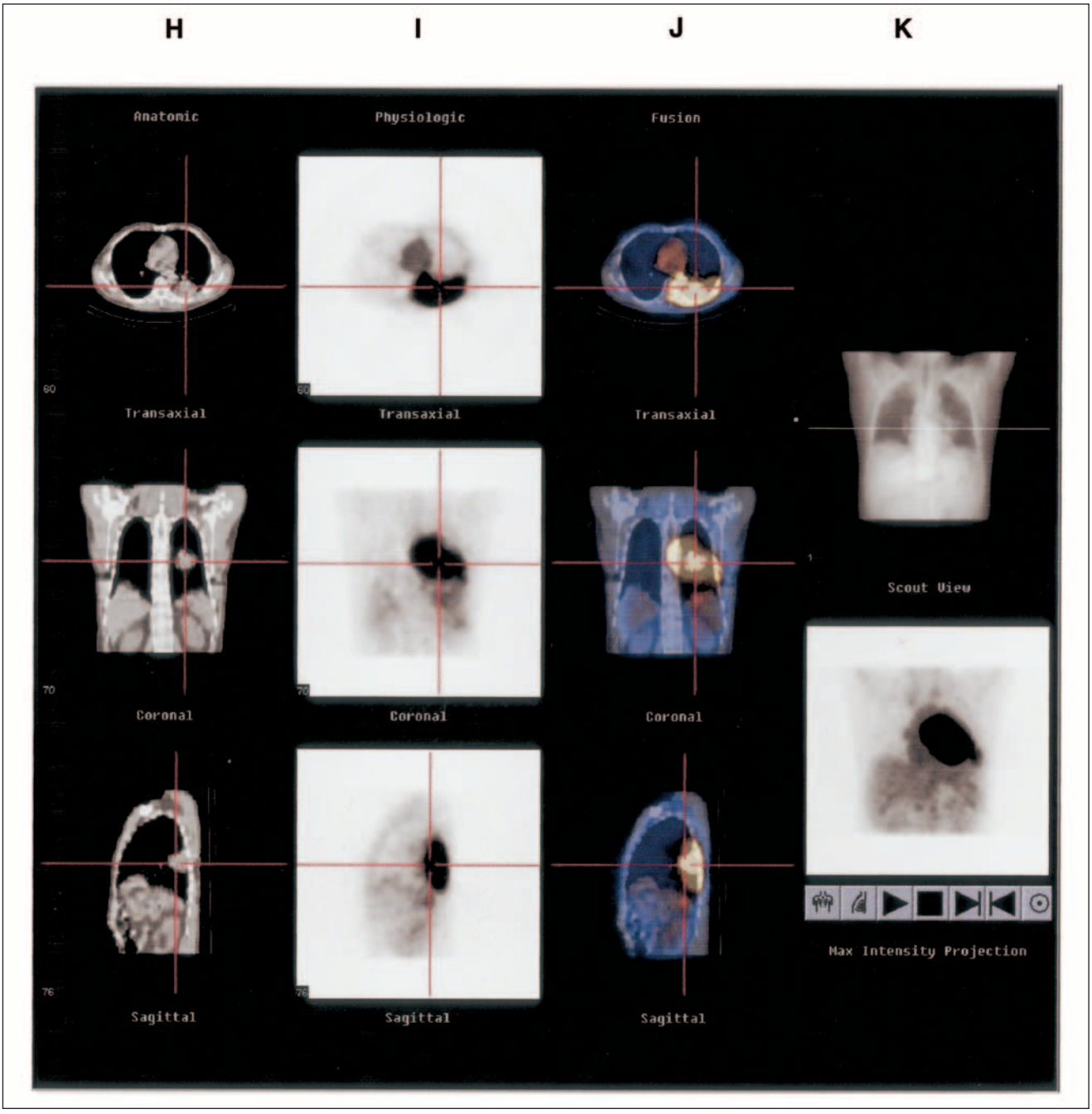

Fig 2. (continued)

survival, median survival time was 11.7 months and the 1-year survival rate was 41.4% (Fig 1). Determination of therapeutic efficacy of this radioimmunotherapy was based mainly on ORR without evidence of an effect on overall survival.

Imaging and Biodistribution of ^{131}I-chTNT in Patients

Imaging was conducted in all ^{131}I-chTNT–treated patients. Figures 2A to 2G show whole-body images of representative patients after systemic or intratumoral administration of ^{131}I-chTNT. Data in Figures 2A to 2D demonstrated visual uptake of ^{131}I activity in the tumor obtained at 0.5 and 5 hours, and 2 and 8 days after systemic administration of ^{131}I-chTNT. These images reveal the remarkable retention of radiolabeled antibody in the vicinity of the tumor mass over time. Figures 2E to 2G show whole-body scintigraphy of a lung cancer patient at 5 (Fig 2E), 15 (Fig

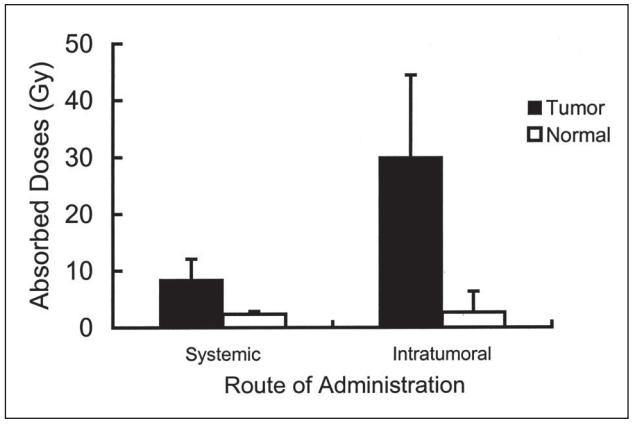

Fig 3. Absorbed doses of radioactivity by tumors and nontumor normal lung tissue after systemic or intratumoral administration of iodine-131–labeled chimeric tumor necrosis treatment.

2F), and 25 days (Fig 2G) after intratumoral administration of ^{131}I-chTNT, demonstrating minimal diffusion of radioactivity from tumor site of injection. To demonstrate that the location of the radiolabel coincides with the anatomic position of the tumor, fusion images consisting of transaxial, coronal, and sagittal CT and single-photon emission CT, and x-ray (scout view) and single-photon emission CT of the lung tumor were prepared (Figs 2H to 2K) in a patient receiving intratumoral injection of ^{131}I-chTNT 5 days previously. These images again demonstrated excellent localization of the radiolabel in the tumor, with little evidence of diffusion over time. The biodistribution of ^{131}I radioactivity in the tumor versus nontumor areas (normal lung fields, T-to-NT ratio) was measured in 11 patients in each group. As shown in Figure 3, the average absorbed doses for tumor and normal lung tissue were 8.45 and 2.35 Gy in patients receiving systemic radioimmunotherapy. For patients receiving intratumoral injection, the average absorbed doses for tumor and normal lung tissue were 30.0 and 2.65 Gy, respectively. The T-to-NT ratio was 3.8:1 for systemically administered antibody and 16.1:1 for intratumorally injected reagent.

Radiation-absorbed dose estimation for ^{131}I-chTNT was performed using sequential whole-body images and the MIRDOSE 3.0 software program. The data for both systemic and intratumoral administration are shown in Table 3. As expected, most organs except for the lungs (site of intratumoral injection), received about half of the dose of those patients receiving intratumoral injection compared with those administered systemic ^{131}I-chTNT.

Adverse Experiences

Toxicity was graded according to the WHO toxicity criteria. As listed in Table 4, the major site of adverse effects was the bone marrow. All-grade platelet toxicity was found in

Table 3. Estimated Radiation-Absorbed Organ Doses

Organ	Systemic (mGy/MBq)			Intratumoral (mGy/MBq)		
	Mean	SD	Range	Mean	SD	Range
Adrenals	0.48	0.09	0.34-0.64	0.28	0.18	0.15-0.58
Brain	0.24	0.06	0.15-0.37	0.12	0.06	0.06-0.20
Breasts	0.34	0.07	0.25-0.48	0.22	0.14	0.12-0.47
Gallbladder wall	0.47	0.09	0.32-0.63	0.22	0.11	0.11-0.38
Lower large intestinal wall	0.37	0.08	0.24-0.52	0.15	0.08	0.07-0.24
Small intestine	0.39	0.08	0.25-0.56	0.15	0.08	0.07-0.25
Stomach	0.42	0.08	0.29-0.58	0.20	0.12	0.10-0.40
Upper large intestinal wall	0.39	0.09	0.26-0.56	0.16	0.09	0.08-0.27
Heart wall	1.44	0.52	0.91-2.33	0.36	0.27	0.20-0.83
Kidneys	1.56	0.55	0.92-2.81	0.18	0.10	0.09-0.34
Liver	1.09	0.25	0.79-1.62	0.65	0.30	0.23-1.08
Lungs	1.69	0.47	1.46-2.31	2.49	2.87	0.53-7.57
Muscle	0.35	0.07	0.24-0.50	0.17	0.10	0.09-0.34
Ovaries	0.43	0.05	0.37-0.47	0.15	0.08	0.07-0.25
Pancreas	0.49	0.09	0.34-0.66	0.25	0.15	0.13-0.50
Red marrow	0.37	0.07	0.26-0.52	0.19	0.11	0.10-0.36
Bone surfaces	0.40	0.08	0.27-0.56	0.20	0.11	0.10-0.37
Skin	0.29	0.06	0.20-0.41	0.13	0.07	0.06-0.23
Spleen	1.93	0.62	0.51-2.73	0.22	0.14	0.11-0.45
Testes	0.31	0.08	0.21-0.47	0.10	0.07	0.05-0.19
Thymus	0.43	0.08	0.32-0.59	0.27	0.18	0.15-0.58
Thyroid	7.52	4.85	0.31-18.8	3.46	5.54	0.21-9.85
Urinary bladder wall	0.73	0.11	0.58-0.90	0.57	0.11	0.46-0.71
Uterus	0.43	0.05	0.37-0.47	0.19	0.09	0.08-0.25
Whole body	0.41	0.08	0.30-0.55	0.27	0.17	0.15-0.57

Abbreviation: SD, standard deviation.

Table 4. Bone Marrow Suppression in Advanced Lung Cancer Patients After Systemic or Intratumoral Administration of Iodine-131–Labeled Chimeric TNT Antibody

Hematologic Toxicity* (grade)	Systemic Administration		Intratumoral Administration	
	Incidence	%	Incidence	%
Platelets	37	59.7	11	24.4
1	17	27.4	9	20
2	8	12.9	0	0
3	7	11.3	2	4.4
4	5	8.1	0	0
Neutrophils	17	27.4	15	33.3
1	6	9.7	12	26.7
2	5	8.1	2	4.4
3	5	8.1	1	2.2
4	1	1.6	0	0
Hemoglobin	26	41.9	9	20
1	21	33.9	6	13.3
2	3	4.8	2	4.4
3	2	3.2	1	2.2
4	0	0	0	0

Abbreviation: TNT, tumor necrosis treatment.
*Evaluated according to WHO criteria for anticancer drugs.

Table 5. Adverse Reactions

Category	All Adverse Effects		Toxicity Grade	
	Incidence	%	1	2
Systemic				
Hemorrhage	1	1.6	1	0
Increased ALT	3	4.8	2	1
Nausea	4	6.5	4	0
Vomiting	4	6.5	4	0
Increased creatinine	1	1.6	1	0
Proteinuria	1	1.6	1	0
Hematuria	2	3.2	2	0
Arrhythmia	3	4.8	3	0
Somnolence	1	1.6	1	0
Weakness	1	1.6	1	0
Dyspnea	1	1.6	0	1
Constipation	1	1.6	1	0
Hair loss	2	3.2	2	0
Intratumoral				
Increased ALT	1	2.2	1	0
Nausea	1	2.2	1	0
Vomiting	1	2.2	1	0
Increased urea	1	2.2	1	0
Pericarditis	1	2.2	1	0
Fever	1	2.2	0	1
Cachexia	1	2.2	1	0

59.7% of systemically treated patients and 24.4% of intratumorally treated patients. For patients receiving systemic administration, 11.3% and 8.1%, respectively, experienced grade 3 or 4 platelet toxicity compared with 4.4% and 0% for patients receiving intratumoral injection. Grade 1 to 4 neutrophil toxicity was found in about one third of all patients, and for patients receiving systemic administration, 8.1% and 1.6%, respectively, had grade 3 and 4 neutrophil toxicity compared with 2.2% and 0% for those patients receiving intratumoral injection. All-grade hemoglobin toxicity was found in 41.9% of systemically treated patients and 20% of intratumorally treated patients. Only two patients receiving systemic therapy and one patient receiving intratumoral therapy had grade 3 hemoglobin toxicity, and no patient was reported with grade 4 hemoglobin toxicity.

Other adverse reactions are listed in Table 5 for patients receiving either systemic or intratumoral injection of ^{131}I-chTNT. In general, no adverse effects were detected in the liver or kidneys during the treatment and follow-up periods. Likewise, no patient developed a HACA or HAMA response during the time it was tested. Because absorption of released radionuclide was imaged in the thyroid of some patients undergoing ^{131}I-chTNT therapy, total T3, total T4, free T3, free T4, and thyroid-stimulating hormone before and after radioimmunotherapy were determined. The results demonstrated that total T3, total T4, free T3, and free T4 decreased slightly and thyroid-stimulating hormone increased significantly 1 and 2 months after ^{131}I-chTNT administration. These changes, however, were all within the normal range (data not shown).

DISCUSSION

To date, only tositumomab[6] (^{131}iodine-labeled murine anti-CD20 antibody) and ibritumomab[7] (yttrium-90–labeled murine anti-CD20 antibody), and two radiolabeled antibodies for the radioimmunotherapy of human malignant B-cell non-Hodgkin's lymphoma, are approved for use in the United States. Along with ^{131}I-chTNT, now approved for refractory advanced lung cancer in China, these reagents are important new biologics for the radioimmunotherapy of cancer that can lead the way to the identification of new methods to produce longer disease-free intervals and/or survival times for patients with these tumors. In this regard, the results of our study show that ^{131}I-chTNT can be an effective radioimmunotherapeutic reagent when given systemically or intratumorally in patients with resistant lung cancer. Adverse reactions to this therapy are essentially limited to bone marrow suppression due to the circulatory time of the radiolabeled product (passenger effect). As expected, intratumorally administered reagent, which enters the circulation at a slower rate over an extended time frame, has a lower severity of thrombocytopenia and neutropenia than when given intravenously. The results also show that small-cell and non–small-cell tumors are both good targets for this form of therapy.

Although most prior studies with radiolabeled antibodies have been performed using systemic administration,[5,9] a number of investigators are now focusing on the locoregional use of these reagents to treat identifiable

lesions in solid tumor patients. Reasons for this include the low amount of uptake seen in tumors after intravenous injection, poor penetration into larger lesions, and heterogeneity of antibody uptake. Locoregional injection has been used most frequently in studies with malignant glioblastomas, which are tumors that are especially difficult to treat due to local extension of tumor tendrils into the white and gray matter of the brain. One such study by Riva et al[24] using radiolabeled antitenascin antibodies found that catheter-directed administrations of ^{131}I-antitenascin antibodies produced an increase in both the duration of remission and survival time in these difficult-to-treat patients, with little or no toxicity. In these studies, the results were dependent on the size of the tumor at the time of treatment. In addition, studies performed at multiple centers in the United States with ^{131}I-chTNT-1 plus biotin produced dramatic results despite the dismal prognosis of these patients. In these studies, an infusion pump was used to deliver the radiolabeled antibody into the tumor over a 20-hour period via a surgically implanted catheter (unpublished observation). The use of the infusion pump to deliver the radiolabeled antibody slowly and forcefully may have improved the effectiveness of locoregional delivery by ensuring a more homogeneous distribution of reagent into the substance of the tumor. Although this may be an important consideration for glioblastoma, the method used in our study appears to have successfully infiltrated the full substance of the tumor, as shown by images taken shortly after infusion of tumor by the radiolabeled antibody (Fig 2). Because of the lower toxicity of this approach and the ability of radiolabeled antibody to infiltrate even large tumor masses effectively, locoregional or intratumoral injection may be a useful method of treating individual lesions such as those seen in glioblastoma or lung cancer, as described in this report.

Despite these hopeful findings, the number of complete responders in all the above-described studies was small, indicating that radioimmunotherapy might require additional treatment modalities to be used in combination for this form of therapy to reach its full potential. For example, it may be possible to improve the clinical efficacy of ^{131}I-chTNT if it is used in combination with methods to increase the radiosensitivity of the tumor.[25] In addition, as demonstrated by Anderson et al,[26] prior treatment of tumors with ablative therapies increases the target size for TNT antibodies. In this study, it was demonstrated that prior radiofrequency ablation therapy of hepatic metastases, which generally produces a 1- to 5-cm zone of necrosis, significantly enhanced ^{131}I-chTNT-1/biotin uptake in the tumor lesions. Anderson et al is the first patient study to take advantage of the basic property of TNT; namely, its proclivity to bind to dead and dying cells. When used in this manner, ^{131}I-chTNT may become an adjuvant to other cytotoxic therapies. Chemotherapeutic drugs may also be used to generate larger areas of necrosis in tumors, and some of these drugs, such as doxorubicin, are also radiosensitizing because of their inhibition of DNA repair mechanisms. In addition, methods such as hormonal therapy used in prostate cancer patients can produce massive tumor destruction in a short period of time, thereby providing an excellent opportunity to test the adjuvant effects of ^{131}I-chTNT in this setting.

With the approval of ^{131}I-chTNT radioimmunotherapy for refractory lung cancer in China, it becomes possible for clinicians to study these more advanced concepts with ^{131}I-chTNT radioimmunotherapy. It is hoped that ongoing studies in the United States and China with ^{131}I-chTNT may provide new indications for its use or reveal its role as an adjuvant to current treatment approaches.

Authors' Disclosures of Potential Conflicts of Interest

The following authors or their immediate family members have indicated a financial interest. No conflict exists for drugs or devices used in a study if they are not being evaluated as part of the investigation. Employment: Qing Fu, Shanghai MediPharm Biotech Co Ltd; Qun Tao, Shanghai MediPharm Biotech Co Ltd; Dan Ye, Shanghai MediPharm Biotech Co Ltd; Dian Wen Ju, Shanghai MediPharm Biotech Co Ltd. Leadership Position: Peisheng Hu, Cancer Therapeutics Labs, MediBiotech Inc; Clive R. Taylor, Cancer Therapeutics Labs, MediBiotech Inc, Peregrine Pharmaceuticals; Alan L. Epstein, Cancer Therapeutics Labs, MediBiotech Inc. Consultant/advisory role: Peisheng Hu, Peregrine Pharmaceuticals; Leslie A. Khawli, Peregrine Pharmaceuticals; Alan L. Epstein, Peregrine Pharmaceuticals. Stock ownership: Peisheng Hu, Cancer Therapeutics Labs, Peregrine Pharmaceuticals; Leslie A. Khawli, Peregrine Pharmaceuticals; Clive R. Taylor, Cancer Therapeutics Labs, Peregrine Pharmaceuticals; Alan L. Epstein, Cancer Therapeutics Labs, Peregrine Pharmaceuticals. For a detailed description of these categories, or for more information about ASCO's conflict of interest policy, please refer to the Author Disclosure Declaration and Disclosures of Potential Conflicts of Interest found in Information for Contributors in the front of each issue.

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