

Reviewer's Discussion:

Prior to discussing the design of the protocol, it is necessary to comment on the history of the protocol and the multiple amendments that were made. This study originated in December of 1996 and was completed in December of 1997. The original protocol was very vague with respect to details and was altered significantly over the course of its institution. Significant changes were made to the objectives, CT imaging procedure, histopathology diagnosis details, efficacy analysis and statistical analyses sections. This developmental progression seen taking place during the course of the protocol suggests that a hypothesis was being generated, as well as proven, during the course of the Phase 3 trial. Therefore, confirmation as to the integrity of the blind needs verification.

The intent of this protocol was to enroll patients with suspicion of lung cancer in order to determine the ability of the test drug to detect and localize primary and metastatic sites of lung tumor using histopathologic diagnosis as the standard of truth. The criteria for patient inclusion were at times vague with respect to details resulting in questions regarding the actual patient population under study. Specific questions that came to mind when reviewing this protocol were the following:

- Was the intent of the trial to study newly diagnosed patients with lung cancer or to study patients that had been previously diagnosed and were enrolled for recurrence or both? This question is important because the probability of a lesion being malignant will be dramatically different depending the type of population studied. If patients with a history of lung cancer present with a lung lesion, the chance of that lesion being malignant are greater than for a patient presenting for the first time with a lung lesion. If the intent of this study is to prove this diagnostic test for screening purposes, then this information will become important.

- What test or tests were used to define suspicion of lung cancer? Was this suspicion based solely on a diagnostic test (CT) or did it include patient history and symptoms. This information can influence efficacy if patients with a high level of suspicion of cancer are enrolled. Again, this is a factor if the intent of the test drug is to be a screening tool for lung cancer. In this case, representation of all disease states would need to be enrolled.

- Is the patient population strictly those patients with tumor originating in the lung or those patients with other primary tumors that have metastasized to the lung? The secondary endpoint which looks at staging, implies that we are dealing with a patient population presenting with primary lung tumor rather than a patient presenting with another known primary that has metastasized to the lung.

All of these points may seem arbitrary after the study is complete because this information can be found but the purpose of a prospective study design is to test a hypothesis and to do this, a pre-defined population must be provided. The second point in particular is needed to be prospectively defined because it is the source of information which defines the "primary lesion" that the Sponsors follows throughout the study to prove the test drugs efficacy. Given the uncertainty of this point, the Division requested further clarification by the Sponsor on 7/8/1998.

The Sponsor stated that the main presenting lesion was identified by the referring patient care provider prior to entry into the study. The appearance of the lesion on CT or chest x-ray as suspicious for lung cancer provided the basis for biopsy. The physician performing the biopsy was instructed as to the identity of the lesion of interest with the surgeon providing the precise anatomical location of the lesion following the biopsy procedure (Source: Fax dated 7/10/1998). All of the information provided by the Sponsor in the fax was not self evident by reading the study protocol. The Sponsor's response adequately addressed the issues in question.

The largest shortcoming foreseen regarding the design, is the lack of a lesion tracking system which would allow for accurate correlation of the primary lesion for all diagnostic modalities used. Initial identification of the "primary lesion" is, as per the Sponsor and not the protocol, performed prior to entry into the protocol. How this lesion was identified, as reported above, was by a suspicious lesion seen on CT or chest x-ray. However, the inclusion criteria allows for the CT and or chest X-ray to be performed within 6 weeks pre or post-enrollment, therefore, the "primary lesion" wouldn't always be identified at the time of enrollment unless the CT or chest X-ray was done prior to enrollment. Therefore, as patients proceed in this study, it is not totally clear when and by what modality the primary lesion was identified and tracked.

The Sponsor defined 9 potential localization regions in the chest to be used for all blinded readers for both Tc-99m P829 and CT images. These regions being each lung lobe, hilum and mediastinum per body side appear to be non-specific for tracking purposes. There was no provisions made for those cases where multiple lesions were identified within the same region. The results, therefore are highly dependent on the precision of the localization of the presenting lesion and other lesions that may be present near the main presenting lesion.

Other factors identified that could confound the study results include:

- Biopsy performed prior to imaging which could lead to altered anatomy or Tc-99m uptake as a result of the procedure itself. In the latter case, timing between biopsy and P829 imaging and type of biopsy would be relevant to this review. These factors would need to be analyzed to show that they do not influence imaging results.
- No analysis plan was predefined for patients who received treatment between diagnostic modalities to look at the affect of treatment on Tc-99m P829 uptake. This is of particular importance in patients who have had previously diagnosed disease or in those patients who had biopsy prior to imaging where the imaging was performed at a latter timepoint and the clinician treated the patient in the interim.

The Sponsor proposes diagnostic accuracy as the efficacy endpoint for comparing the Tc99m P829 images with histopathologic results. This analysis will be further supported with calculations of sensitivity and specificity. To really provide clinically meaningful results, additional lesions identified should have been followed for their concordance or discordance with CT imaging. Realizing that it is not practical to biopsy all lesions identified, additional lesions could have been followed with diagnostic imaging to confirm regression after treatment, thus indirectly confirming the presence of tumor.

The Safety analysis for this test drug should take into account the physiologic affects of native somatostatin to adequately assess Depreotide's safety. The current protocol calls for a limited serum chemistry panel, hematology panel and vital sign assessments, as well as, adverse event reporting. These measures may afford an adequate safety assessment only if earlier studies support the safety of this drug in healthy subjects and diseased patients when a full chemistry panel, urinalysis testing, immunogenicity testing and glucose physiology testing prove to be unaffected.

Please see the Statistical Review for comments regarding the adequacy of the statistical analysis plan.

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Comment: The Sponsor identified 14 patients in Table 1.3.0 (Vol. 67, pg. 0129) as having been excluded due to lack of an evaluable histopathologic assessment. When the histopathologic information was reviewed, Appendix 16.2.10.3, Vol. 65 (part 3 of 6, page 0311), 4 patients that were excluded had histopathologic results listed in this appendix. Three of the 4 had a benign process and one patient had a malignant process identified. The reasoning behind the exclusion of these 4 patients is not understood.

Table 1. Patient Disposition at Study Completion For All Enrolled Patients

	Statistic	All Patients ¹
Total number of patients	n	128
Number of patients who completed the study per protocol	n (%)	103 (80%)
Number of patients who did not complete all study procedures: ²	n (%)	25 (20%)
Completed Technetium Tc 99m P829 imaging, but did not complete safety assessments	n (%)	13 (10%)
Completed safety assessments, but did not complete Technetium Tc 99m P829 imaging	n (%)	5 (4%)
Did not complete Technetium Tc 99m P829 imaging or safety assessments	n (%)	1 (1%)
Did not complete computed tomography imaging or histopathology	n (%)	1 (1%)
Did not have histopathology evaluation of lesion	n (%)	8 (6%)
Reason patients did not complete all study procedures		
Withdrew consent	n (%)	0
Adverse event	n (%)	0
Lost to follow-up	n (%)	0
Other	n (%)	25 (20%)

Data Source: Section 14.1, Table 1.1.0
 1 Percentages are based on the total number of patients.
 2 Three patients had more than one reason recorded.

Sponsor Text Table 10-A.

Table 2. Enrollment Per Study Site

STUDY SITE	NO. OF PATIENTS ENROLLED
Site 1	32 (25%)
2	3 (2%)
3	7 (5%)
5	17 (13%)
6	2 (2%)
7	1 (1%)
8	6 (5%)
10	10 (8%)
11	29 (23%)
12	15 (12%)
13	6 (5%)

Data Source: Vol. 61, Section 14.1, Table 1.0.0

Demographics: The Sponsor's table below (Table 3) compares demographic data between the Intent-to-Treat population and Efficacy Evaluable population. Height and weight demographic information can be found in Table 4. Among the 128 patients in the Safety population, the most common abnormalities or diseases reported were respiratory disease (88%); cardiovascular disease (62%); gastrointestinal disease (61%); and diseases of the eye, ear, nose, and throat (53%). Physical examinations were performed prior to injection of Technetium Tc 99m P829 and abnormalities were recorded by body system. Abnormalities of the lung were present in 45 of 128 patients (35%). Other body systems with abnormalities reported for 10% or more of patients were: head, eyes, ears, nose, and throat (22%); skin (20%); heart (16%); abdomen (15%); extremities (15%); general appearance (13%); and neck (10%).

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Table 3. Demographic and Background Characteristics For Safety and Evaluable Populations

Parameter	Statistic	Safety/ITT Population	Evaluable Population	
Total number of patients	n	128	112	
Age (years)	n	128	112	
	Mean	63.9	63.9	
	Median	65.5	65.0	
	SE	1.06	1.13	
	Min, Max	33, 86	33, 86	
Gender				
Male	n (%)	72 (56%)	61 (54%)	
Female	n (%)	56 (44%)	51 (46%)	
Race				
	Caucasian	n (%)	111 (87%)	99 (88%)
	Black	n (%)	10 (8%)	9 (8%)
	Hispanic	n (%)	6 (5%)	3 (3%)
	Native American	n (%)	0	0
	Asian/Oriental	n (%)	0	0
	Other	n (%)	1 (1%)	1 (1%)
Karnofsky Performance Status (%)	n	128	112	
	Mean	90.0	90.3	
	Median	90.0	90.0	
	SE	1.04	1.11	
	Min, Max	60, 100	60, 100	
Chest X-ray				
	Normal	n (%)	7 (5%)	3 (3%)
	Abnormal	n (%)	120 (94%)	109 (97%)
Missing	n (%)	1 (1%)	0	
CT Scan				
	Normal	n (%)	0	0
	Abnormal	n (%)	127 (99%)	112 (100%)
Missing	n (%)	1 (1%)	0	
Solitary Pulmonary Nodules ¹	n (%)	71 (55%)	65 (58%)	
	>0 to ≤3 cm diameter	n	53	48
	Non-calcified SPN >0 to ≤3 cm diameter	n	51	46
	>3 to ≤6 cm diameter	n	15	14
	Non-calcified SPN >3 to ≤6 cm diameter	n	14	13
Calcification Evident on Chest X-ray	n (%)	3 (2%)	3 (3%)	

Data Source: Section 14.1, Tables 2.0.0, 2.0.1

Note: Percentages are based on the total number of patients.

¹ Based on chest X-ray or CT measurement.

Data Source: Sponsor Text Table 11-A, Vol. 61, pg. 064.

Table 4. Height and Weight Demographics

Parameter	Intent to Treat	Efficacy Evaluable
Total Number of Patients	128	112
Weight (kg)		
Mean	75.5	74.5
Median	72.5	72.5
Std. Error	1.7	1.7
Range	43-163	43-133
Height (cm)		
Mean	169.4	168.9
Median	170.1	167.6
Std. Error	1.0	1.1
Range	122-203	122-203

Data Source: Vol. 61, pg. 0143, Section 14.1, Table 2.0.0

The investigator using the histopathology results determined lesion location. There were 13 patients who had more than one lesion diagnosed. The most common locations for the main presenting lesion were the right upper lung lobe (43 patients, 34%) and the left upper lung lobe (31 patients, 24%). See Table 5 below for full representation of location for the main presenting lesion. Seventeen additional lesions were biopsied and reviewed as a secondary endpoint.

Table 5. Location of Main Presenting Lesion

Region of Presenting Lesion	Patients n (%)
RUL	43 (34%)
RML	7 (5%)
RLL	15 (12%)
RH	4 (3%)
RM	5 (4%)
LUL	31 (24%)
LLL	9 (7%)
LH	4 (3%)
LM	1 (1%)
Other	1 (1%)

Data Source: Vol. 61, Section 14.1, Table 3.0.0.

Thirty-two patients had received specific treatment for cancer. Of the 32, 15 patients had some type of treatment within the last year. At the time of the study, none of the patients were being treated with octreotide acetate (Sandostatin[®]). Please see Table 6 for a list of patients having treatment for cancer within the last year. The Sponsor does not give actual treatment dates, therefore, the proximity to Tc99m P892 cannot be assessed.

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**Table 6. Cancer Treatment History For All Patients
Within the past 12 Months.**

Patient Number	Treatment	Time since last treatment
1-9	Surgery	< 1 month
1-24	Surgery	7-11 months
3-6	Surgery Chemotherapy	7-11 months 4-6 months
5-16	Surgery	7-11 months
6-1	Radiation	< 1 month
6-2	Radiation Chemotherapy	4-6 months < 1 month
10-2	Radiation Chemotherapy	1-3 months <1 month
10-10	Surgery	7-11 months
11-18	Surgery	4-6 months
11-20	Surgery	1-3 months
11-28	Surgery Radiation Chemotherapy	7-11 months <1 month 1-3 months
12-1	Radiation	<1 month
12-8	Radiation	1-3 months
12-11	Radiation	<1 month
12-12	Radiation	<1 month

Data Source: Vol. 65, Appendix 16.2.10.5

As part of the demographics, the Sponsor did not report the breakdown of patients presenting by tumor type. This information was generated from histopathology information provided in Appendix 16.2.3. The breakdown by tumor type of those patients that had a biopsy can be found in Table 7.

Table 7. Histopathology Results For All Patients Having Biopsy

Malignant Histopathology	N	Benign Histopathology	N
Adenocarcinoma	36	Granulomatous disease	22
Squamous Cell	32	Hamartoma	3
Non-Small Cell*	5	Inflammatory Process	3
Carcinoid	2	Fibrosis, emphysematous process	3
Large Cell**	5	Neurofibroma	1
Small Cell**	6	Bronchial Cell Hyperplasia	1
Carcinosarcoma	1	No malignant cells found	1
TOTALS	87		34

* Type not specified, ** includes neuroendocrine secreting tumors, No diagnosis was reported in 3 patients that had a biopsy. Data Source: Appendix 16.2.10.3, Vol. 65.

Efficacy Evaluation:

The efficacy evaluable population was comprised of 112 (88%) of the 128 patients enrolled. Of the 16 (13%) patients that were excluded, 13 patients were excluded due to a lack of an evaluable histopathology assessment, 2 patients did not complete Tc99m P829 imaging and one patient did not complete CT imaging.

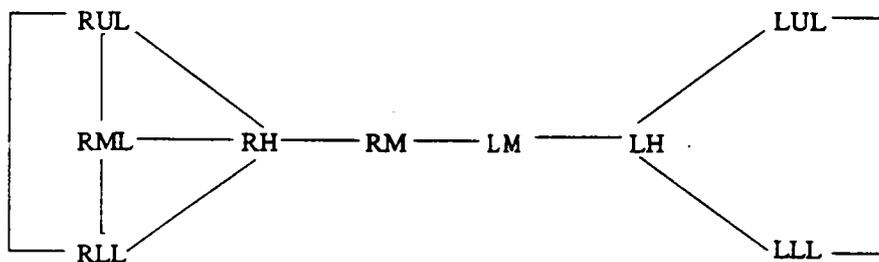
Comment: The Sponsor identified 14 patients in Table 1.3.0 (Vol. 61, pg. 0129) as having been excluded due to lack of an evaluable histopathologic assessment. When the histopathologic information was reviewed, Appendix 16.2.10.3 (part 3 of 6, Vol. 65, page 310), 4 patients that were excluded had histopathologic results listed in this appendix. Three of the 4 were benign results.

Efficacy: The Sponsor added a post hoc statistical analyses plan after the initial site by site analysis data results had been produced. This plan and the Sponsor's explanation for the plan can be found below

After performing the primary efficacy analysis on the ITT population using the One-to-One Region algorithm, an inspection of data indicated that in a small number of cases adjacent anatomical regions were being mismatched by the strict one-to-one matching algorithm. Areas of enhanced uptake in the Technetium Tc 99m P829 scans were identified by investigators and blind readers, and in 10 to 15% of the cases the histopathology results specified an adjacent anatomical region. Imprecise localization of biopsy samples and/or difficulty in exact localization using Technetium Tc 99m P829 images resulted in apparent mismatch of lesions. This introduced artifactual inaccuracy and, therefore, necessitated a re-evaluation of the algorithm for the primary efficacy analysis. The Adjacent Region algorithm and the By-Patient algorithm were proposed to address this issue and were used, in addition to the One-to-One Region algorithm, in the primary efficacy analysis.

Adjacent Region Algorithm

This algorithm compared the histopathology result of the main presenting lesion to the overall Technetium Tc 99m P829 result of the main presenting lesion in that region or in an adjacent region. The following diagram depicts the nine regions of the lung; regions connected by a line are adjacent to one another:



The adjacent regions of the main presenting lesion were defined as any regions adjacent to the region of the main presenting lesion and included the region of the main presenting lesion itself.

For each main presenting lesion, the overall Technetium Tc 99m P829 result from its adjacent regions was defined as follows:

- 1) if at least one Technetium Tc 99m P829 result in the adjacent regions was positive, the overall result was considered positive;
- 2) if all Technetium Tc 99m P829 results in the adjacent regions were negative, the overall result was considered negative;
- 3) if some Technetium Tc 99m P829 results in the adjacent regions were indeterminate or not assessed, the indeterminate or not assessed results were reassigned to a result that was opposite of the histopathology result of the main presenting lesion. Then the rules that are described in Step 1 and 2 of this algorithm were applied.

The Adjacent Region algorithm was considered more appropriate for efficacy analyses and was therefore used for primary inferences and analysis of the additional lung lesions and all other secondary efficacy analyses involving Technetium Tc 99m P829 evaluations.

By-Patient Algorithm

In order to compare the results of the Technetium Tc 99m P829 scan with the histopathology results for any indication of the presence of cancer in the lung for each patient, the By-Patient Algorithm was proposed and used in the primary efficacy analysis. This algorithm compared the histopathology result of the main presenting lesion to the overall Technetium Tc 99m P829 result for the patient.

The overall Technetium Tc 99m P829 result for each patient was defined as follows:

- 1) if at least one Technetium Tc 99m P829 result in the nine regions was positive, the overall result for the patient was considered positive;
- 2) if all Technetium Tc 99m P829 results in the nine regions were negative, the overall result for the patient was considered negative;
- 3) if some Technetium Tc 99m P829 results in the nine regions were indeterminate or not assessed, the indeterminate or not assessed results were reassigned to a result that was opposite of the histopathology result of the main presenting lesion. Then the rules that are described in Step 1 and 2 of this algorithm were applied.

Comment: The Sponsor admitted that the method for matching histopathology location with the Tc99m P829 image location was not precisely identified. However, as evident by their initial analysis, it appears that the intent was to do a one-to-one region analysis. It was only after obtaining results by this method that the Sponsor decided to change the analysis plan. The Sponsor's rationale for changing the plan was related to discrepancies seen between biopsy location and Tc 99m P829 blinded read location. It is a known fact that Nuclear medicine imaging has never been known for its anatomical localization, however, with SPECT imaging, localization has improved.

If each of the primary lesions had SPECT imaging performed, as was planned for in the protocol, the localization when compared with histopathology should have improved. Given this, it still may be possible that the blinded readers could have misidentified the location of a lesion. In these cases, the region identified by biopsy and that identified by blinded reader should have been close enough to account for the rationale of the poor resolution of the Nuclear Medicine image. The current solution of an adjacent algorithm analysis provides a loose correlation between the location of the lesion biopsied and what was seen on Tc99m P829 images. The diagram of the regions that allows for correspondence of image localization and biopsy localization appears too liberal. The Sponsor should have further subdivided the regions, particularly at the boundary points, to get a better one to one correspondence. It is understandable to have left upper lung near the hilum turn out to be hilum on biopsy, than a lesion in the apex of the left lung turn out to be hilum. Loose correlation is not the goal of a diagnostic test. To support the adjacent region algorithm as the method of choice for the primary efficacy analysis, the Sponsor should provide the completed CRF, Tc99m P829 and CT images on film and histopathology site of biopsy for all those patients that had results that were not in agreement with the one-to-one analysis that changed to agreement using the adjacent region algorithm. Review of this information is expected to result in the ability to determine if the adjacent region algorithm was applied appropriately.

Efficacy Results: The Sponsor presented all efficacy results based on the adjacent region algorithm and majority blinded read despite the Division's request to present the primary efficacy results by individual blinded readers, on a site to site basis. However, the Sponsor did analyze the results per blinded reader and by a one-to-one algorithm, therefore, the following will provide both presentations for the reader's benefit.

The primary efficacy endpoint was to determine the ability of Tc 99m P829 to correctly identify malignant lesions as confirmed by histopathology diagnosis. Below, table 8 shows the sensitivity, specificity and agreement rate for each individual blinded read and the majority read. The majority read was a post hoc addition to the conduct of the study. The Sponsor defined it as a 2/3 majority from the three blinded readers therefore, if 2 out of 3 blinded readers indicated a positive results for a given region, the blinded majority read results would be positive. If the three individual blinded read results were positive, negative and indeterminate: positive, indeterminate and not assessed; or negative, positive and not assessed, then the blinded majority read result was considered indeterminate.

Sensitivity and Specificity: As seen in the Table 8. below, the sensitivities and specificities for the individual blinded readers vary between reader and between algorithm, however, for the adjacent region algorithm, the variability between readers appears less. Between algorithms, it was seen that for all blinded readers, the adjacent region analysis resulted in increased values for true positives, and true negatives while decreased values were seen for false negatives and false positives when compared to the one-to-one region algorithm. Thus, showing greater sensitivity using the adjacent region algorithm and greater specificity using the one-to-one algorithm.

These results were expected because the adjacent region algorithm gives a greater opportunity to find agreement because a larger region is being assessed versus the single region which the one-to-one algorithm uses. The resulting decrease in sensitivity seen with the one-to-one analysis is a result of a drop in the number of true positives identified by Tc-99m P829. Twelve cases were identified where the adjacent region resulted in a success and the one-to-one analysis resulted in a false negative.

Table 8. Primary Efficacy Results using the One to One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology

Reader	Algorithm	Parameter	Sens.	Spec.	Agreement	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	83.3%	64.3%	78.6%	70	18	10	14	112
		Lower CI			71.1%					
	One to One	Rates	73.8%	78.6%	75.0%	62	22	6	22	112
		Lower CI			67.3%					
Reader 2	Adjacent	Rates	82.1%	60.7%	76.8%	69	17	11	15	112
		Lower CI			69.2%					
	One to One	Rates	66.7%	78.6%	69.6%	56	22	6	28	112
		Lower CI			61.6%					
Reader 3	Adjacent	Rates	78.6%	64.3%	75.0%	66	18	10	18	112
		Lower CI			67.3%					
	One to One	Rates	71.4%	92.9%	76.8%	60	26	2	24	112
		Lower CI			69.2%					
Majority Read	Adjacent	Rates	82.1%	60.7%	76.8%	69	17	11	15	112
		Lower CI			69.2%					
	One to One	Rates	70.2%	85.7%	74.1%	59	24	4	25	112
		Lower CI			66.3%					

Data Source: Supplemental Information submitted after filing, pg.005 Table 11-B(Letter Date 7/22/98)

The false negatives occurred with greater frequency with the Blinded read than the investigator read. The Sponsor attributes this occurrence to the fact that the blinded readers did not have access to the other diagnostic information. Thirteen of the 15 false negative cases identified by the blinded readers for the adjacent region algorithm were read as true positives by the investigator. The discordance between the blinded read and investigator read is attributed, by the Sponsor, to the following:

- 1) location of the lesion near a rib or the hilum; 2) size of the lesion (smaller lesions are more difficult to detect); 3) presence of diffuse Technetium Tc 99m P829 uptake in the diseased lung producing decreased target to background ratio; 4) presence of multiple lesions in the thorax that were not the target of the biopsy evaluation but were identified by the blinded readers; and 5) technical issues such as over-smoothing and poor reconstruction techniques by the site for images used in the blinded read. The Sponsor's descriptions of those cases discordant can be found in Vol. 1.61 pg. 070-072. Those cases reported as positive by the investigator (adjacent region algorithm) but negative by the blinded majority read are displayed in table 9. The individual blinded reader and investigator read results for the on-to-one algorithm for these cases are given.

Comment: It is the stance of the Division to review individual blinded reader data in support of an NDA. The use of a consensus read and/or the investigator read are not considered acceptable.

The majority read proposed by the Sponsor is acceptable, however, individual blinded reader results must be presented. The Sponsor chose to present all supportive data in the form of a majority read even though a recommendation to present individual blinded reader data was made by the Division. For purposes of this reviewer's analysis, the individual reader data will be analyzed in support of the NDA.

As stated by the Sponsor, the clinical trials performed do not meet with what typically occurs in clinical practice, however, the purpose of the clinical trial is to prove a drug efficacious on its own merits. The Sponsor could have easily designed the study incorporating a randomized blinded read and a randomized read with other imaging modalities. The first read would prove the efficacy of the drug and the second would support the notion that the drug adds clinically meaningful information when used in conjunction with other diagnostic modalities. It is not apparent from the trial design that the intention was to establish Depreotide as an adjunct to other diagnostic tests. However, after completion of the study it appears as though this concept would be useful to investigate.

As seen in the table 9, there were more false negatives seen for the blinded read than for the investigator read. In all algorithm groups, the blinded readers had less false positives than compared to the investigator read. This may have been the result of the investigator overreading based on the CT findings. The Sponsor's rationale for these false negative cases is conjecture. Review of these cases showed that several patients (8 out of 15) had lesions 2 cm or larger in size and therefore should have been readily identified if there was good concentration of Tc99m P829 by the tumor.

Table 9. False Negative Cases for the Majority Blinded Read for both the Adjacent and One-to-One Algorithms

Patient Number	Region	Biopsy Result	Lesion Size	Tc99m P829 Read for One-to-One Algorithm				CT Read			
				PI	BR1	BR2	BR3	PI	BR1	BR2	BR3
1-05	LUL	Carcinoid	2.4cm	-	-	-	-	+	+	+	+
1-32	RUL	Squamous	1.5cm	-	-	-	-	-	+	+	-
2-02	LUL	Squamous	2cm	+	-	-	-	+	+	+	+
11-06	LUL	Adeno.	1.3cm	+	-	-	-	+	+	+	+
11-20	LUL	Adeno.	1.1cm	-	-	-	-	+	+	-	+
11-29	RLL	Carcinoid	3cm	+	-	-	-	+	+	+	+
12-09	RUL	Adeno.	4cm	-	-	-	-	+	+	+	+
10-02	RML	Adeno.	2cm	+	ND	-	-	+	+	+	-
11-18	RUL	Adeno.	3cm	-	+	IND	-	-	IND	+	+
2-01	LUL	Large	1.2cm	+	-	-	-	+	+	-	-
1-20	LLL	Adeno.	ND	-	-	-	-	+	+	IND	ND
5-06	LUL	Squamous	3cm	+	-	+	-	+	+	-	-
10-10	RML	Squamous	1cm	-	-	-	-	-*	-*	-*	-*
11-26	RLL	Squamous	ND	+	-	-	-	+	+	+	+
12-15	RUL	NSC	3cm	+	-	-	-	+	+	+	+

PI= site investigator, BR1,2,3=Blinded reader, *identified a lesion in the RUL, ND= not done, IND= Indeterminate, Data Source: Vol. 61, Table 11.0.0, pg.0195

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Of the 15 cases reported to be false negative by majority blinded read for the adjacent algorithm, 7 were also read as negative by the investigator. This finding could be the result of Three problems: 1. Poor anatomic resolution provided by Nuclear Medicine imaging, or 2. The lesion biopsied was not the same lesion imaged or 3. Variability of Somatostatin receptor expression on the surface of the tumor. In most of these cases, the CT reported a lesion in the region of the main presenting lesion, therefore, the biopsy region should have been reported accurately. Of the 7 cases thought to be read negative due to location close to a rib or hilum, most of the lesions were greater than 1 cm, the resolution of SPECT imaging. These lesions should have been large enough to be seen with SPECT if there was adequate concentration of the drug by the tumor. Two of the 7 cases were also read as negative by the investigator leading more to the conclusion that there was poor concentration of the radiotracer by the tumor. This problem is more a factor of the function of the drug rather than the instrument. In these cases, variability in expression of somatostatin receptors on the surface of the tumor may account for the poor localization

The discordance based on diffuse lung uptake should be investigated more carefully in those patients receiving chemotherapy.

Table 10 represents the additional cases that were reported as false negative by the majority read for the one-to-one algorithm analysis. These cases were not discussed individually by the Sponsor like the false negative cases reported by the majority read for the adjacent algorithm as seen in Table 9. Therefore, no explanation for why these cases were read false negative is given. These cases were read as positive when the adjacent region algorithm was applied.

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Table 10 . False Negative Cases for the Majority Blinded Read for One-to-One Algorithm Which Were Found to be Positive by Adjacent Region Algorithm

Patient Number	Region	Biopsy Result	Lesion Size	Tc99m P829 Read for One-to-One Algorithm				CT Read			
				PI	BR1	BR2	BR3	PI	BR1	BR2	BR3
5-01	RUL	Adeno.	4.5 cm	-	+	-	- RML	+	+	+	+
5-02	LH	Squamous	3.2 cm	+ LLL	- LLL	+	- LLL	+	+ LLL	+ LLL	+
5-11	RUL	Small Cell	NA	+ RH	- RH	- RH	-	+	+	+	+
5-17	RML	Squamous	NA	- RH	- RH	- RH	- RH	+	+	+	-
6-01	LLL	Squamous	1.0 cm	+ LUL	+ LUL	- LUL	- LUL	+ LUL	+ LUL	+ LUL	+ LUL
6-02	LH	Large Cell	NA	+ LUL	- LUL, LM	- LUL, LM	+ LUL	+ LM, LUL	+	+	+ LM
11-07	RLL	Squamous	2.0 cm	+ RUL	- RH	+ RUL, RH	- RUL, RH	+	+	+	+
11-16	RML	Squamous	NA	+	- RLL	- RLL	+ RLL	+ RLL	+ RLL	+	-
12-11	RM	Squamous	7.0 cm	+	- RUL	+ RUL	- RUL	+	+	+	+ RUL
12-13	LLL	Adeno.	NA	+ LUL	- LUL	- LUL	+ LUL	+ LUL	- LUL	- LUL	IND LUL

PI= site investigator, BR1,2,3=Blinded reader, , ND= not done, IND= Indeterminate, Data Source: Vol. 61, Table 11.0.0, pg.0195

Comment: Regions identified below positive or negative signs for the blinded P829 readers in Table 10 above, identify the region that made the read positive on adjacent region algorithm. If these regions were positive on the CT read, they were identified for the particular reader that read it as positive.

Two out of the 10 cases that were reported as false negative using the one-to-one algorithm were reported as false negative by the principal investigator. In all other cases, the blinded Tc99m P829 readers invariably had positive results in other regions, some of which were noted to be positive on CT as well. It is these cases that localization may have been a problem.

From the blind read of the Technetium Tc 99m P829 images, false positive results were seen in 11 of 28 patients with non-malignant pathology. Eight of the eleven cases occurred in the presence of inflammatory but non-malignant histopathology and were considered to be positive by both blinded read and investigator read; three were considered negative by the investigator read. There were five other patients that were considered to be false positive by the investigator read but not by the blinded read. A description of the false positive cases can be found in table 11.

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Table 11. Description of False Positive Cases from Blinded Read Efficacy Evaluable Data Set Using Adjacent Match Criteria to Histopathology

Patient	Majority Blinded Read	Investigator Read	Comment/Description
1-6	Positive	Positive	Necrotizing granuloma
1-23	Positive	Positive	Granuloma with hyphae
1-26	Positive	Positive	Granuloma
1-30	Positive	Positive	Necrotizing granuloma
5-5	Positive	Positive	Fibrosis and emphysema
5-12	Positive	Negative	Granulomatous inflammation
8-1	Positive	Negative	Granulomatous caseating lymphadenitis consistent with tuberculosis
8-3	Positive	Negative	Peri-bronchial inflammation
10-7	Positive	Positive	Bronchial hamartoma
11-10	Positive	Positive	Organizing pneumonia
11-15	Positive	Positive	Sarcoid

Sponsor Text Table 11-C

Comment: The overall indication for the drug is to differentiate benign from malignant disease. As seen above, many benign disease states localize Tc99m P829 and were read as positive by both blinded readers and the investigator who had all diagnostic information available. The five cases read as false positive by the investigator were not singled out by the Sponsor. It would be interesting to know what the disease states were that produced a false positive. Again, the overreading that accompanies the knowledge of other diagnostic tests is witnessed here.

Agreement:

Agreement was defined as whether or not the Technetium Tc 99m P829 correctly identified the main presenting lesions in each patient as malignant or benign as confirmed by the histopathology diagnosis. Agreement for the adjacent region algorithm was 76.8% for blinded read and 85.7% for the investigator read. The rate of agreement between Technetium Tc 99m P829 and the histopathology diagnosis for the Adjacent Region algorithm was significant at the 0.01 level for the investigator read. The rate of agreement was not statistically significant for the majority blinded read performed using any of the three algorithms (Table 12). Only one individual blinded reader had a statistically significant agreement rate for the adjacent region algorithm.

Table 12. P-Values for Rates of Agreements per blinded Reader and Algorithm

Read	One to One Algorithm P-value	Adjacent Algorithm P-value
Blinded Reader 1	0.146	0.030*
Blinded Reader 2	0.574	0.072
Blinded Reader 3	0.072	0.146
Majority Blinded Read	0.199	0.072

*Significance at the 0.05 level

Data Source Vol.61, Tables 5.1.0, 5.2.0

Interreader variability was assessed for the blinded readers using a kappa statistic. The results can be found in Table 13. The kappa statistic showed good agreement between readers for this study.

Table 13. Kappa Statistics for Blinded Read

Algorithm	Blinded Readers			Overall
	1 vs. 2	1 vs. 3	2 vs. 3	
One-to-One	0.671	0.781	0.639	0.697
Adjacent	0.825	0.789	0.789	0.801

Data Source: Supplement submitted after filing dated 7/22/98, Table 11-D, pg. 008

Intent-To-Treat Analysis

The data for the ITT population was very similar to that of the efficacy evaluable population which was not unexpected because the two populations only differed by two patients. The same trends and patterns in the data were noted for sensitivity, specificity, and agreement.

Secondary Efficacy Analysis:

Negative and Positive Predictive Value: Using the calculated specificity and sensitivity resulting per blinded read and majority blinded read, negative and positive predictive values were graphically displayed for a wide range of disease prevalence. In cases where high prevalence exists, as was evidence by this trial, negative predictive values were found to be low. In cases where low prevalence existed, the negative predictive value was high, which is expected. For prevalences in between the high and low ends, it appears that this drug does not provide useful predictive information.

Solitary Pulmonary Nodule:

The diagnosis of the main presenting lesion for Tc99m P829 relative to the histopathology results for three solitary pulmonary nodule subgroups was performed. The three SPN subgroups were defined as patients with non-calcified SPN of 1-3 cm in size, non-calcified SPN of ≤ 6 cm and all patients with SPN regardless of size. Of the 112 evaluable patients, 65 (58%) patients presented with a solitary pulmonary nodule. The sensitivity and specificity per blinded reader and per algorithm can be found in Tables 14-16. Sensitivity appears to increase as size of the SPN increased.

Sensitivity is lowest in the 1-3 cm subgroup but steadily increases as the population with larger SPNs are added. Specificity remained relatively the same across all subgroups. The Sponsor does not provide a Kappa statistic to assess interreader variability for this analysis. Both sensitivity and specificity values vary tremendously between readers for the same algorithm. Rates of agreement between the blinded read and histopathology results were not statistically significant for either reader and algorithm

Comment: It is not clear from the study report or protocol, how the Sponsor defined solitary pulmonary nodule. In the strictest sense, it means no other regions are positive, on a diagnostic test. For all those patients who were defined as having a SPN at enrollment, 18 out of 65 SPN patients had other areas read as positive on the site CT read as reported in Table 11.0.0, Vol. 61. If the strict definition of SPN were to be applied, these patients should not have been included in SPN analysis. When comparison of this data is made with the enrolling CT diagnosis as presented in the demographic data, 9 patients had reports of either adenopathy or multiple lesions reported (Appendix 16.2.4.1, Vol. 1.63).

Table 14. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN

Reader	Algorithm	Parameter	Sens.	Spec.	Agreement	P value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	75.0%	76.2%	75.4%	0.208	33	16	5	11	65
		Lower CI			64.9%						
	One to One	Rates	68.2%	85.7%	73.8%	0.294	30	18	3	14	65
		Lower CI			63.2%						
Reader 2	Adjacent	Rates	75.0%	61.9%	70.8%	0.500	33	13	8	11	65
		Lower CI			60.0%						
	One to One	Rates	63.6%	81.0%	69.2%	0.607	28	17	4	16	65
		Lower CI			58.4%						
Reader 3	Adjacent	Rates	70.5%	66.7%	69.2%	0.607	31	14	7	13	65
		Lower CI			58.4%						
	One to One	Rates	59.1%	90.5%	69.2%	0.607	26	19	2	18	65
		Lower CI			58.4%						
Majority Read	Adjacent	Rates	72.7%	66.7%	70.8%	0.500	32	14	7	12	65
		Lower CI			72.1%						
	One to One	Rates	61.4%	85.7%	69.2%	0.607	27	18	3	17	65
		Lower CI			58.4%						

*Indicates significance at the 0.050 level.

Data Source: Supplemental Information submitted after filing, pg.009 Table 11-E1(Letter Date 7/22/98), Vol. 61 Tables 5.1.1, 5.2.1.

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Table 15. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN 1-3 cm.

Reader	Algorithm	Parameter	Sens.	Spec.	Agreement	P Value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	63.0%	78.9%	69.6%	0.589	17	15	4	10	46
		Lower CI			56.5%						
	One to One	Rates	59.3%	84.2%	69.6%	0.589	16	16	3	11	46
		Lower CI			56.5%						
Reader 2	Adjacent	Rates	63.0%	63.2%	63.0%	0.883	17	12	7	10	46
		Lower CI			49.8%						
	One to One	Rates	51.9%	78.9%	63.0%	0.883	14	15	4	13	46
		Lower CI			49.8%						
Reader 3	Adjacent	Rates	59.3%	73.7%	65.2%	0.807	16	14	5	11	46
		Lower CI			52.0%						
	One to One	Rates	51.9%	89.5%	67.4%	0.708	14	17	2	13	46
		Lower CI			54.2%						
Majority Read	Adjacent	Rates	59.3%	68.4%	63.0%	0.883	16	13	6	11	46
		Lower CI			49.8%						
	One to One	Rates	51.9%	84.2%	65.2%	0.807	14	16	3	13	46
		Lower CI			52.0%						

Data Source: Supplemental Information submitted after filing, pg.023 Table 11-E2(Letter Date 7/22/98), Vol. 61 Tables 5.1.2, 5.2.2.

Table 16. Primary Efficacy Results using the One-to-One and Adjacent Region Algorithms of the Diagnosis of the Main Presenting Lesion Relative to Histopathology for all Patients with SPN ≤ 6 cm.

Reader	Algorithm	Parameter	Sens.	Spec.	Agreement	P Value	TP	TN	FP	FN	Total
Reader 1	Adjacent	Rates	71.8%	80.0%	74.6%	0.266	28	16	4	11	59
		Lower CI			63.4%						
	One to One	Rates	66.7%	85.0%	72.9%	0.367	26	17	3	13	59
		Lower CI			61.6%						
Reader 2	Adjacent	Rates	71.8%	65.0%	69.5%	0.590	28	13	7	11	59
		Lower CI			58.1%						
	One to One	Rates	59.0%	80.0%	66.0%	0.787	23	16	4	16	59
		Lower CI			54.6%						
Reader 3	Adjacent	Rates	69.2%	70.0%	69.5%	0.590	27	14	6	12	59
		Lower CI			58.1%						
	One to One	Rates	56.4%	90.0%	67.8%	0.695	22	18	2	17	59
		Lower CI			56.3%						
Majority Read	Adjacent	Rates	69.2%	70.0%	69.5%	0.590	27	14	6	12	59
		Lower CI			58.1%						
	One to One	Rates	59.0%	85.0%	67.8%	0.695	23	17	3	16	59
		Lower CI			56.3%						

*Indicates significance at the 0.050 level.

Data Source: Supplemental Information submitted after filing, pg.024 Table 11-E3(Letter Date 7/22/98), Vol. 61 Tables 5.1.3, 5.2.3.

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Comment: Subgroup 1 encompasses all the patients who presented with a SPN, Subgroup 2 encompasses those with a SPN of 1-3cm and subgroup 3 appears to encompass all SPN of 6cm or less which includes subgroup 2. A total of 6 patients had SPN larger than 6cm. Of the efficacy evaluable population, 58% of the patients presented with a solitary pulmonary nodule. When compared to all efficacy evaluable patients, the SPN subgroup sensitivity is slightly lower and the specificity is slightly higher for the majority blinded read (Adjacent Region Algorithm). It is not clear why the Sponsor did not do an analysis on the subgroup of patients with SPNs between 3 and 6 cm in size.

Diagnosis of Main Presenting Lesion Relative to Histopathology Results using Computed Tomography

Computed Tomography efficacy results were presented by majority blinded read for the adjacent region algorithm only. The Sponsor presented the majority blinded CT read data for the three algorithms compared to histopathology. The sensitivities and specificities for this analysis can be found in Table 17.

Table 17. Sensitivity and Specificity of Computed Tomography Compared to Histopathology for the Majority blinded read.

Algorithm	Population	Sens.	Spec.	TP	TN	FP	FN	Total
Adjacent	Efficacy	95.2%	3.6%	69	17	11	15	112
	Evaluable							
	All SPN	100%	4.8%	44	1	20	0	65
	SPN 1-3cm	100%	5.3%	27	1	18	0	46
One to One	SPN≤6cm	100%	5.0%	39	1	19	0	59
	Efficacy	83.3%	7.1%	70	2	26	14	112
	Evaluable							
	All SPN	90.9%	4.8%	40	1	20	4	65
One to One	SPN 1-3cm	92.6%	5.3%	25	1	18	2	46
	SPN≤6cm	92.3%	5.0%	36	1	19	3	59

Data Source: Information submitted after filing, Letter Date 7/22/98, Table 11-F, pg. 012.

The Kappa statistics for the measurement of agreement between the blinded CT readers for the main presenting lesion using the adjacent region algorithm for the evaluable patient population are as follows:

	Kappa Statistic
Reader 1 vs. Reader 2	.648
Reader 1 vs. Reader 3	.543
Reader 2 vs. Reader 3	.696
Overall	.629

This agreement between CT blinded readers was good. The kappa statistic for the blinded read for the one-to-one region algorithm would be useful information to compare to the Tc99m P829 data.

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As per the Sponsor, the blinded read results for all patients (adjacent region algorithm) showed that sensitivity of CT scans ranged from 92.9% to 94.0% among the three blind readers, with 95.2% sensitivity for the majority blind read. Specificity for CT scans was low and variable, with results of 3.6%, 3.6% and 7.1% for blind CT readers one, two and three, respectively, and with 3.6% specificity for the majority read. Agreement was 71.4% for each of the three blind readers, with a majority agreement rate of 72.3%.
 The investigator read results for computed tomography showed sensitivity of 98.8%, specificity of 0.0%, and agreement of 74.1.0%.

Comparison of Sensitivity and Specificity of Technetium Tc 99m P829 and Computed Tomography for Main Presenting Lesion

Sensitivity for the CT scan majority blind read was 95.2% for all lesions, and 100% for all SPN subgroups; the corresponding sensitivities for Technetium Tc 99m P829 were 82.1% for all lesions, and 72.7%, 59.3% and 69.2% for all SPN, SPN between 1 and 3 cm, and SPN ≤6 cm. These differences in sensitivity were all statistically significant at p<0.05. The differences between Technetium Tc 99m P829 and CT scan for specificity were more pronounced, with specificity for CT scan of 3.6% for all lesions, and ≤ 5.3% for any SPN subgroup, compared to Technetium Tc 99m P829 values of 60.7% for all lesions, and ≥66.7% for all SPN subgroups. These differences in specificity were all statistically significant at p<0.05.

Table 18. Comparison of Sensitivity and Specificity of Technetium Tc 99m P829 and Computed Tomography Majority Blind Read - Adjacent Region Algorithm Efficacy Evaluable Population

Population Image Type	TP	FN	Sensitivity	p-value	TN	FP	Specificity	p-value
Main Presenting Lesion (All Patients)								
Technetium Tc 99m P829	69	15	82.1%		17	11	60.7%	
Computed Tomography	80	4	95.2%	0.022	1	27	3.6%	0.000
SPN Subgroup (All SPN Patients)								
Technetium Tc 99m P829	32	12	72.7%		14	7	66.7%	
Computed Tomography	44	0	100%	0.001	1	20	4.8%	0.002
SPN Subgroup (1 to 3 cm Subgroup)								
Technetium Tc 99m P829	16	11	59.3%		13	6	68.4%	
Computed Tomography	27	0	100%	0.003	1	18	5.3%	0.003
SPN Subgroup (≤6 cm Subgroup)								
Technetium Tc 99m P829	27	12	69.2%		14	6	70.0%	
Computed Tomography	39	0	100%	0.001	1	19	5.0%	0.002
Data Source: Section 14.2, Tables 7.0.0, 7.0.1, 7.0.2, 7.0.3								

Data Source: Sponsor Table 11-F Vol. 61 page 082.

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Diagnosis (Benign/Malignant) of Additional Lung Lesions Relative to Histopathology Results

There were 13 patients who had a total of 17 additional lesions biopsied. Of the 17 additional lesions, 14 were found to be positive for malignancy and 3 were found to be benign processes. The Sponsor provided sensitivity and specificity calculations for the additional lesions by Tc99m P829 and CT blinded readers, however, the total number of lesions (n=15) as seen below in Tables 17-18, could not be verified using Sponsor's histopathology data listings (Vol. 65, Appendix 16.2.10.3, page 0300). The Sponsor does not identify this data by algorithm. Again, the sample sizes for this group were extremely small and any inferences drawn from these tables should be done so with caution.

Table 19. Diagnosis of Additional Lesions Relative to Histopathologic Results For Tc 99m P829 (Adjacent Algorithm).

Reader	Sens.	Spec.	Agree- ment	P Value	TP	TN	FP	FN	Total
Reader 1	12/14 (86%)	0/1 (0%)	12/15 (80%)	0.287	12	0	1	2	15
Reader 2	13/14 (93%)	0/1 (0%)	13/15 (87%)	0.130	13	0	1	1	15
Reader 3	10/14 (71%)	0/1 (0%)	10/15 (67%)	0.713	10	0	1	4	15
Majority Read	12/14 (86%)	0/1 (0%)	12/15 (80%)	0.287	12	0	1	2	15

Data Source: Modification of Sponsor Table 9.1.0, Vol. 61, pg 0190.

Table 20. Diagnosis of Additional Lesions relative to Histopathologic Results For Computed Tomography.

Reader	Sens.	Spec.	Agree- ment	P Value	TP	TN	FP	FN	Total
Reader 1	7/14 (50%)	0/1 (0%)	7/15 (47%)	0.988	7	0	1	7	15
Reader 2	6/14 (43%)	0/1 (0%)	6/15 (40%)	0.998	6	0	1	8	15
Reader 3	6/14 (43%)	0/1 (0%)	6/15 (40%)	0.998	6	0	1	8	15
Majority Read	6/14 (43%)	0/1 (0%)	6/15 (40%)	0.998	6	0	1	8	15

Data Source: Modification of Sponsor Table 9.1.0, Vol. 61, pg 0191.

Comment: It is not clear if the data reported in Tables 19 and 20 are for the one-to-one algorithm or adjacent algorithm.

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Technetium Tc 99m P829 Blinded Read Derived Staging Results Compared to AJCC Staging Results for the Main Presenting Lesion for Patients with Primary Lung Cancer

There were 62 patients with a diagnosis of primary lung cancer based on the histopathologic information. The T, N, and M AJCC staging classifications and overall stage were based on the investigator determination, and the computer-generated stage for each blinded Technetium Tc 99m P829 reader. Over half of the patients (n=32) in which the number of involved lymph nodes or presence/absence of distant metastases were recorded as NX or MX, respectively, did not have one or both of these parameters assessed. Given the incompleteness of the staging, these cases were excluded from the staging analysis. Of the remaining 30 evaluable cases, 7 patients had a match between the investigator staging process and the majority blinded reader computer-generated staging. For those cases staged by the computer generated staging process, a majority of the cases were found to be over-staged when compared to the investigator staging.

The Sponsor did an analysis which found agreement rates of 59.7%, 69.4% and 60.7% for blinded readers 1, 2 and 3, respectively, when the computer generated staging process was compared to the investigator's staging. However, agreement for a given patient was considered to be a staging determination by the blind reader that was within one stage level of the AJCC classification.

Comment: This analysis was a post hoc addition to the protocol. The Sponsor's details regarding how this was to be performed can be found in Appendix B. The Sponsor's definition of agreement for the staging process is not adequate given the implications stage has on prognosis and treatment alternatives.

Examination of Demographic Subgroups

When reviewed for age, gender and race, the sensitivities for the majority blinded read per adjacent region algorithm were rather consistent. Specificity values were more variable due to small sample sizes within each subgroup. No meaningful trends were identified from these subgroup analyses.

Examination of Disease History Subgroups

Efficacy analyses on the main presenting lesion were conducted on two disease history subgroups of the efficacy evaluable population based on pre-injection renal and liver function, using the Adjacent Region algorithm. These two subgroups were defined as follows: for renal function subgroups, patients with BUN *or* creatinine > upper limit of the normal range at pre-injection (abnormal) versus patients with BUN *and* creatinine ≤ upper limit of the normal range at pre-injection (normal); for liver function subgroups, patients with AST, ALT, alkaline phosphatase, *or* LDH > upper limit of the normal range at pre-injection (abnormal) versus patients with AST, ALT, alkaline phosphatase, and LDH ≤ upper limit of the normal range at pre-injection (normal).

There was a total of 12 patients with abnormal baseline renal function, therefore, any inferences from the data should be made with caution.

There were 36 patients with abnormal liver function on the baseline assessment. Sensitivity and agreement values for the abnormal versus the normal population for liver function were comparable. Specificity was greater in the abnormal liver function group.

Binding Specificity of Technetium Tc99m P829 to Human Tumor Membranes

The Sponsor harvested tumor membranes for binding assays to determine the specific binding of ^{125}I -somatostatin-14 in the absence and presence of 500nM somatostatin-14, somatostatin-28 and the oxorhenium complex of P829 (P875). Estimated B_{max} and K_d values and specific inhibition study results are provided in Appendix C.

The clinical findings of the human tumor samples for 15 patients are as follows:

Table 21. Clinical and Binding Assay Results

Patient	Tumor Type	Histopathology Results	Tc99m P829 Imaging Results	P829 binding to tumor expressed SSTR
A1-16	Adenocarcinoma	RLL Adenocarcinoma	positive	not detectable
A1-15	Adenocarcinoma	LUL Adenocarcinoma	positive	positive
A5-01	Adenocarcinoma	RUL Adenocarcinoma	positive	not detectable
A5-08	Adenocarcinoma	LLL Adenocarcinoma	positive	positive
A5-13	Adenocarcinoma	RUL Adenocarcinoma	positive	positive
A1-25	Squamous Cell	RUL Squamous Cell	positive	positive
A12-02	Squamous Cell	RUL Squamous Cell	positive	positive
A5-06	Squamous Cell	LUL Squamous Cell	positive	positive
A5-02	Squamous Cell	LUL Squamous Cell	positive	positive
A5-11	Squamous Cell	RUL & RML Squamous Cell	positive	not done
A1-32	Squamous Cell Tumor Lymph node Surrounding Lung	RUL Squamous Lymph node:metastatic Squamous Surrounding Lung :Normal	positive negative negative	not done not done positive
A5-15	Squamous Cell	RUL Squamous Cell	positive	positive
A-12-15	Large Cell	RUL Large Cell	positive	positive
2-91	Breast	No biopsy	positive	not detectable
A8-01	Granuloma	R inguinal node granulomatous caseating lymphadenitis consistent with TB	positive	positive

Data Source Appendix 16.1.13, Tables 1, 2 and 3.

Of the 15 patients who had biopsies tested, 11 tumors tested positive for specific P829 binding to SSTR expressed on the tumor (4 adenocarcinoma, 5 squamous cell carcinoma, 1 large cell lung carcinoma and 1 granuloma). Two lung tumors did not exhibit detectable specific binding: 2 adenocarcinomas. One breast cancer tumor was found to exhibit somatostatin receptors but specific binding of P829 to the receptor was not detectable. One lymph node with metastatic squamous cell carcinoma tested positive for the receptor, however, specific binding of P829 was not done. Specific binding was not done for a total of 4 biopsy samples.

Comment: The amount of tumor biopsies tested was tremendously low (15). Tc99m P829 was found to bind to both benign and malignant tumors demonstrating that this drug cannot distinguish benign from malignant tumor. Two lung tumors had positive receptor assays but non-detectable specific binding by P829. This finding may be a result of the technical issues surrounding the assay, however, the implication that Tc99m P829 may not always bind to somatostatin receptors cannot be ruled out by this study. The Sponsor should do further analysis to clarify this issue.

Change in Safety Analyses

Due to the small percentage of patients with significant changes in vital sign measurements from pre-injection, the analysis on the proportion of such patients were not performed.

The safety analyses were not performed by the subgroups defined by demographic characteristics, renal function, and liver function, as described in Section 9.7.1.7, due to the small magnitude of incidence of each safety parameter. A by-patient listing was produced for patients with significant changes in vital sign measurements, including information on demographic characteristics and patient's renal function and liver function status.

Safety:

Deaths: 0

Withdrawals due to an Adverse Event: 0

Serious Adverse Events: 0

Severe Adverse Events: 0

Extent of Exposure: All patients received a single intravenous injection of Technetium Tc 99m P829 at a dose of 50 µg P829 peptide radiolabeled with 15 to 20 mCi of Technetium Tc 99m over 15 to 20 seconds. Investigators prepared the radiolabeled peptide using a kit containing 50 µg of P829 peptide and sufficient Technetium Tc 99m to administer 15 to 20 mCi of activity, using the entire contents of the vial. Contents of the kit were heated during the course of dose preparation. In the efficacy evaluable population, the mean injected dose of P829 peptide was 44.3 µg and a mean injected radioactivity dose was 19.9mCi. There were 21 (19%) efficacy evaluable patients who received a mCi dose of greater than 22mCi.

The highest mCi dose administered to any patient was 29.8 mCi. Volumes of injected dose ranged from 0.45 - 2.0ml. The Lot numbers used for the study were 9509B01D, 9609B02E, and 9609B02F.

Adverse Events:

Patients were observed for adverse events throughout the first hour following injection of Technetium Tc 99m P829 and were evaluated again at 18 to 30 hours post-injection. Eleven adverse events occurred in eight (6%) of 128 patients. No serious adverse events were reported and none of the patients discontinued the study due to an adverse event. The most frequently reported adverse event was headache (2%). All but two of the adverse events were considered "mild" in severity; two reports of headache were assessed as moderate. The majority of events were judged "probably not related" or "unrelated" to study drug; and three events in two patients (two reports of headache and one of nausea) were judged possibly related to treatment.

Table 22. Adverse Events

Patient	Adverse event	Preferred Term	Onset time post injection	Severity	Treatment Required	Relationship to study drug
1-19	malaise	malaise	24 hrs.	mild	no	unrelated
2-1	pain, lower back	back pain	3.5 hrs.	mild	yes	unrelated
6-2	headache	headache	12 hrs.	mild	yes	probably not related
10-1	left ant. Chest pain	chest pain	30 min.	mild	no	probably not related
	diarrhea	diarrhea	NR	mild	no	probably not related
11-1	headache	headache	1.5 hrs.	moderate	yes	possibly related
11-21	weight loss	weight decrease	NR	mild	no	unrelated
12-1	nausea	nausea	25 min.	mild	no	possibly related
	headache	headache	24 hrs.	moderate	yes	possibly related
12-9	left leg cramp	leg cramp	1.5 hrs.	mild	no	unrelated
	left leg numbness	hypoesthesia	1.5 hrs.	mild	no	unrelated

Data source: Appendix 16.2.7, NR= not reported.

Comment: Vital signs were noted to be stable for patients 6-2, 10-1 and 11-1 around the time of onset of their respective adverse events. Patient 12-1 was not to have elevated systolic and diastolic blood pressures accompanying the adverse event, headache.

Hematology Data:

Mean changes from the baseline value per post-injection timepoint can be found in Table 23. At 2 to 4 hours post-injection, small but statistically significant mean decreases from pre-injection values were noted in hematocrit (-0.71%); hemoglobin (-0.16 g/dL); RBC count ($-0.05 \times 10^6/\text{mm}^3$); and neutrophil count (-1.91%). There was a statistically significant mean increase in lymphocyte count (1.93%). None of these mean changes were clinically significant. At 18-30 hours, there were no statistically significant or clinically notable changes in any hematology parameter.

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Table 23. Hematology Tests: Mean Changes from Pre-Injection Values

Laboratory Test	Statistic ¹	Pre-Injection Value	Change from Pre-Injection Value	
			2-4 Hours	18-30 Hours
Hematocrit (%)	n	121	117	102
	Mean	40.60	-0.71	0.47
	p-value		<0.001**	0.169
Hemoglobin (g/dL)	n	121	117	102
	Mean	13.23	-0.16	0.05
	p-value		0.002**	0.397
RBC Count (10 ⁶ /mm ³)	n	121	117	102
	Mean	4.36	-0.05	0.01
	p-value		0.001**	0.788
WBC Count (10 ³ /mm ³)	n	121	117	102
	Mean	8.472	0.007	0.053
	p-value		0.454	0.748
Neutrophils (%)	n	121	117	101
	Mean	66.27	-1.91	-0.88
	p-value		<0.001**	0.133
Basophils (%)	n	121	117	101
	Mean	0.70	-0.01	0.05
	p-value		0.538	0.129
Eosinophils (%)	n	121	117	101
	Mean	1.99	-0.03	-0.09
	p-value		0.978	0.103
Lymphocytes (%)	n	121	117	101
	Mean	24.36	1.93	1.08
	p-value		<0.001**	0.055
Monocytes (%)	n	121	117	101
	Mean	6.68	0.05	-0.15
	p-value		0.549	0.286
Platelet Count (10 ³ /mm ³)	n	115	110	96
	Mean	267.5	-3.2	4.4
	p-value		0.118	0.369

Data source: Section 14.3.5, Table 14.1.0
¹ P-values assess the difference between pre-and post-injection values and were determined using the Wilcoxon Signed Rank test
* indicates significance at the 0.050 level; ** indicates significance at the 0.010 level.

Data Source: Sponsor Text Table 12-C

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Shift table analysis results for the hematology parameters can be found in table 24 .

Table 24. Hematology Shift Table results relative to normal ranges

Parameter	2-4 hr.		18-30 hr.	
	Increase	Decrease	Increase	Decrease
Hematocrit	4	9	5	4
Hemoglobin	3	7	4	3
RBC Count	1	7	6	8
WBC Count	5	6	5	8
Platelets	1	3	2	5
Neutrophils	13	2	3	8

2-4 hr: N=117, 18-30 hr: N=102, Data Source Table 14.2.1

Review of the scatter plot data revealed that of the above statistically significant mean changes, only lymphocytes had outliers reported. Of the 5 patients reporting outliers, 4 had an increased in lymphocyte count which was still within the normal range. One patient had an elevation just above the upper limit of normal at the 2-6 hour timepoint that remained above normal at the 18-30 hour timepoint. Further review of the scatter plots revealed all the changes seen in basophil and eosinophil counts resulted in post-injection values that remained within the normal range for each parameter. Of the outliers identified for monocyte and lymphocyte counts, all were increases from baseline and all but three, remained within the normal reference range. The actual numbers of outliers per parameter can be found in table 25.

Table 25. Number of Patients identified as Outliers for Hematology Parameters

Parameter	2-4hr.	18-30 hr.
Basophil Count	9	14
Eosinophil Count	10	16
Monocyte Count	4	4
Lymphocyte Count	3	3
WBC	1	3

Data Source: Additional Information submitted, Letter date 7/24/98. (timepoints are not mutually exclusive.)

The following table presents those changes that represented shifts in laboratory values that met the criteria of a 25% change toward abnormal and that shifted or remained outside of the normal range.

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Table 26. Incidence of Treatment-Emergent Clinically Significant Hematology Values

Laboratory Test	Statistic	Post-Injection Evaluation Time	
		2-4 Hours	18-30 Hours
Hematocrit	CS/N (%) [Patient ID]	0/117	0/102
Hemoglobin	CS/N (%) [Patient ID]	0/117	0/102
RBC Count	CS/N (%) [Patient ID]	2/117 (2%) [1-03, 12-09]	2/102 (2%) [11-19, 12-09]
WBC Count	CS/N (%) [Patient ID]	3/117 (3%) [1-01, 5-02, 12-10]	5/102 (5%) [1-01, 1-28, 5-02, 10-07, 12-10]
Platelet Count	CS/N (%) [Patient ID]	2/110 (2%) [11-01, 12-09]	2/96 (2%) [11/01, 12-09]

Data Source: Section 14.3.4, Table 13.1.0
 Note: CS=number of patients with a clinically significant change from pre-injection value; N=total number of patients with a pre-injection value and a post-injection value at the specified time point.
 Note: Patient ID = patient identification number.

Sponsor Text Table 12-E

None of the patients with changes in RBC counts had pre-injection values, making evaluation of low post-injection values difficult. None of the changes were cited by the investigators as attributable to Technetium Tc 99m P829. A total of five patients had increases in total WBC count of 25% or more and was outside of the normal range. All of these patients had pre-injection WBC counts within the normal range and slightly elevated counts at one or both post-injection assessments. Among these patients, Patient 1-28 had the largest relative increase in WBC count (pre-injection, $6.54 \times 10^3/\text{cm}^3$ and 18 to 30 hours post-injection, $14.41 \times 10^3/\text{cm}^3$). Only one patient's increase in WBC count was considered by the investigator to be possibly attributable to Technetium Tc 99m P829 (Patient 5-02; pre-injection, $10.0 \times 10^3/\text{cm}^3$ and 18 to 30 hours post-injection, $12.7 \times 10^3/\text{cm}^3$). Two patients had a change in platelet count that met the criteria for clinical significance. Patient 12-09 had low platelet count at both post-injection assessments, with no pre-injection assessment available for comparison; the investigator commented that the values were not clinically significant. Patient 11-01 had an increase in platelet count, compared to the pre-injection value ($315,000 \text{ cells}/\text{mm}^3$), at 2 to 4 hours ($469,000 \text{ cells}/\text{mm}^3$) and 18 to 30 hours ($509,000 \text{ cells}/\text{mm}^3$) post-injection. The Investigator considered the changes unevaluable and no follow-up measurements were obtained.

Comment: Of the 13 reported decreases in the 2-4 hr. evaluation, 12 of those values changed from high to normal with only one value changing from normal to low. All of the 8 decreases in Neutrophil counts for the 18-30 were changes from high to normal values. Of the Decreases seen in hematocrit, hemoglobin and RBC count, 8, 7, and 7 values dropped from normal to low for each parameter respectively. There were no clinically significant changes seen for decreases in hematocrit

Of those patients with clinically significant changes in WBC count, 5 out of the 6 had increases in WBC count above the normal range. All patients with clinically significant changes noted for RBC count had missing baseline values. The one patient with a clinically significant decrease in platelet count (12-9) was missing the baseline value for comparison.

No statement to suggest any clinically significant trends can be made from the data.

Clinical Chemistry: Mean changes from the baseline value per post-injection timepoint can be found in table 27. Of the parameters studied, statistically significant differences were reported for Alkaline phosphatase (2-4 hr.) total protein (2-4 hr.), total bilirubin (2-4 and 18-30hr.), BUN (2-4 hr.) and LDH (18-30 hr.). Of the parameters with statistically significant changes from baseline, all but the change seen in total bilirubin were mean decreases from baseline and not considered clinically significant.

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