The Impact of the Inclusion of Clinical Data Review on Overall Radiographic Response and Progression in Oncology Clinical Trials as Assessed by Blinded Independent Central Review

Nicolette Wangler BS [1], Kristin Borradaile MS [1], Robert Ford MD [1]

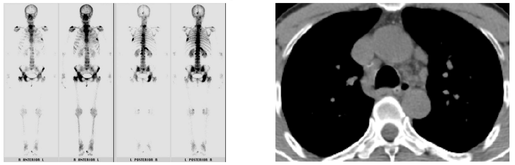
[1] RadPharm Imaging Core Lab (Princeton, NJ)

Background Information

The United States Food and Drug Administration (USFDA) advocates blinded independent central review (BICR) of radiographic exams for oncology registration studies when the primary endpoint is based on tumor measurements, such as progression-free survival, time to progression or objective response rate. However, a proportion of subjects may progress clinically prior to radiographic evidence of disease progression and in certain indications, measurements of cutaneous lesions may be incorporated into response criteria calculations.

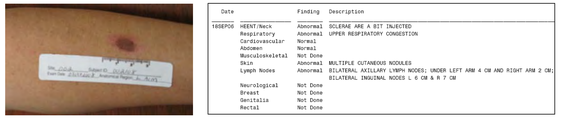
Radiographic vs. Clinical Evidence of Disease

Radiographic evidence of disease refers to any CT, MRI, X-Ray or other radiographic exam performed on a subject which demonstrates the presence or absence of disease which is occurring within that subject.



Examples of radiographic exams. (Left to Right: Nuclear Medicine Bone Scan, CT)

Clinical evidence of disease, for the purpose of BICR, refers to objective findings documented during non-radiographic clinical visits which demonstrate the presence or absence of disease. Data incorporated into a BICR clinical review generally includes photographs of cutaneous abnormalities or clinical data listings generated from a sponsor's clinical trial database. Examples of information which may be included in clinical data listings are medical history, prior radiation therapy, prior surgeries, physical exam findings, procedures performed while on-study, selected adverse events, cytology or pathology reports, and symptomatic deterioration.



Date		Finding	Description
18SEP06	HEENT/Neck	Abnormal	SCLERAE ARE A BIT INJECTED
	Respiratory	Abnormal	UPPER RESPIRATORY CONGESTION
	Cardiovascular	Normal	
	Abdomen	Normal	
	Musculoskeletal	Not Done	
	Skin	Abnormal	MULTIPLE CUTANEOUS NODULES
	Lymph Nodes	Abnormal	BILATERAL AXILLARY LYMPH NODES; UNDER LEFT ARM 4 CM AND RIGHT ARM 2 CM; BILATERAL INGUINAL NODES L 6 CM & R 7 CM
	Neurological	Not Done	
	Breast	Not Done	
	Genitalia	Not Done	
	Rectal	Not Done	

Examples of clinical data. (Left to Right: Photograph showing cutaneous lesion, Physical exam findings from clinical data listing)

Best Response, Best Response Date & Date of Progression

Best Response refers to the best response a subject achieves from the start of therapy until they are off-study. Best Response Date refers to the date that a patient first achieves their best response (CR, PR, SD) while on study. Date of Progression refers to the date when progression was first demonstrated. Current USFDA guidance indicates there are multiple dating conventions deemed acceptable and the dating conventions chosen should be applied consistently for all subjects throughout the study.

Radiological Response vs. Clinical Response vs. Overall Response

Radiological Response is the response determined on the basis of tumor measurements and assessments obtained from radiological exams performed while on-study.

Clinical Response is the response determined on the basis of clinical evidence obtained while on-study. Tumors can only be assessed clinically by BICR if tumor assessments are included within the medical reports received or if there are photographs which allow independent measurement of cutaneous lesion(s) from the images. The clinical review serves as an additional way to identify lesions or clinical characteristics which may indicate metastatic disease that radiographs have been unable to identify.

Overall Response is the response determined on the basis of combined evidence from both the radiological exams and clinical assessments. The inclusion of a clinical review during BICR can result in response being downgraded (from a complete response to a partial response, for example) in a percentage of subjects. This can occur when the presence of clinical characteristics of disease prohibits the call of certain responses. Clinical review can also result in an earlier date of progression than was assessed radiographically. Examples of this occurrence include positive cytology results confirming malignancy of a new pleural effusion identified radiographically, the identification of a new skin lesion assessed by physical exam, or the investigator assessment of symptomatic deterioration. In addition, for some subjects, inclusion of a clinical review can upgrade a response assessed radiographically (from progressive disease to stable disease or from stable disease to a partial response, for example) if the response criteria allows cutaneous lesions to be included in the measurable disease assessment.

It is expected that certain indications will have a greater number of subjects with overall responses affected by clinical information.

Methods

BICR data from 4,183 subjects in the following indications was blinded, pooled, and reviewed to determine the impact of clinical review on best response, best response date and date of progression following BICR of radiographic images (Figure 1):

- Lymphoma
- Colorectal Cancer
- Breast Cancer
- Melanoma

Radiographic response was compared to the overall response for each subject reviewed and differences were noted. The findings are summarized.

Results

Lymphoma

27% of Lymphoma Subjects Impacted

Inclusion of clinical data and/ or clinical photography impacted response in 27% (47 of 171) of subjects with lymphoma. Differences were observed in the following response parameters:

- 13% (22 of 171) subjects had differences in Best Response
- 16% (28 of 171) subjects had differences in Best Response Date
- 19% (33 of 171) subjects had differences in Date of Progression

Clinical data was received in the form of clinical data listings and photography.

Colorectal Cancer

3% of Colorectal Cancer Subjects Impacted

Inclusion of clinical data impacted response in 3% (32 of 958) of subjects with colorectal cancer. Differences were observed in the following response parameters:

- 2% (20 of 958) subjects had differences in Best Response
- 2% (20 of 958) subjects had differences in Best Response Date
- 2% (17 of 958) subjects had differences in Date of Progression

Clinical data was received in the form of clinical data listings only.

Breast Cancer

10% of Breast Cancer Subjects Impacted

Inclusion of clinical data and/ or clinical photography impacted response in 10% (308 of 2,947) of subjects with breast cancer. Differences were observed in the following response parameters:

- 4% (112 of 2,947) had differences in Best Response
- 4% (106 of 2,947) had differences in Best Response Date
- 9% (277 of 2,947) had differences in Date of Progression

Clinical data was received in the form of clinical data listings and photography.

Melanoma

12% of Melanoma Subjects Impacted

Inclusion of clinical data and/ or clinical photography impacted response in 12% (13 of 107) of subjects with melanoma. Differences were observed in the following response parameters:

- 6% (6 of 107) subjects had differences in Best Response
- 5% (5 of 107) subjects had differences in Best Response Date
- 8% (9 of 107) subjects had differences in Date of Progression

Clinical data was received in the form of clinical data listing and photography.

Figure 1. Total Subjects Reviewed (n = 4,183)

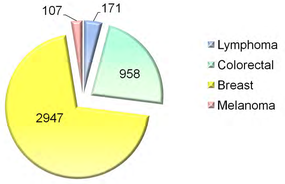
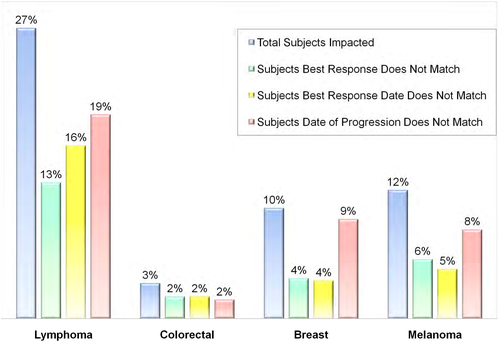


Table 1. Table Illustrating Subjects Impacted by Inclusion of Clinical Data

Indication	Total Subjects Reviewed	Format of Data	Subjects BR, BRD, and/or DOP Do Not Match		Subjects BR Does Not Match		Subjects BRD Does Not Match		Subjects DOP Does Not Match	
			#	%	#	%	#	%	#	%
Lymphoma	171	Photos and Clinical Data	47	27%	22	13%	28	16%	33	19%
Colorectal	958	Clinical Data Only	32	3%	20	2%	20	2%	17	2%
Breast	2,947	Photos and Clinical Data	308	10%	112	4%	106	4%	277	9%
Melanoma	107	Photos and Clinical Data	13	12%	6	6%	5	5%	9	8%

Figure 2. % Subjects Impacted by Inclusion of Clinical Data



Conclusion

When using BICR to determine endpoints in oncology clinical trials, inclusion of a clinical review was relevant in 27% of subjects with lymphoma, 3% of subjects with colorectal cancer, 10% of subjects with breast cancer and 12% of subjects with melanoma in our review of 4,183 subjects enrolled in clinical trials employing BICR. These findings may have implications for future studies.