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.

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.

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 lesions 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 and medical exams and clinical assessments. The inclusion of a clinical review during BICR can result in response being downgraded (from a complete response to partial response, for example) if the response criteria allows.

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) in a percentage of subjects.

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

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

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

Methods

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

Results

Conclusion

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

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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.

Inclusion of clinical data impacted response in 3% (32 of 958) of subjects with breast 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

3% of Colorectal Cancer Subjects Impacted

3% of Lymphoma Subjects Impacted

10% of Breast Cancer Subjects Impacted

12% of Melanoma Subjects Impacted

These findings may have implications for future studies.