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.

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 the body. 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.

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

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.

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.

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% (116 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.

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:

- 8% (9 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.

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.