

Analysis of the Rate of Missing Data, the Rate of Discordance between Readers, and the Rate of Site versus Central Discordance in Clinical Studies of Recently Approved Breast Cancer Agents that Have Used Blinded Independent Central Review



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Background Information

The United States Food and Drug Administration (USFDA) recommends blinded independent central review (BICR) for oncology registration studies when the primary study endpoint is based on tumor measurements, such as progression-free survival (PFS), time to progression (TTP), or objective response rate (ORR). However, there is no published guidance regarding acceptable metrics during the BICR.

Methods

The publicly available USFDA Summary Basis of Approvals and Oncologic Drugs Advisory Committee (ODAC) transcripts for the following recently approved breast cancer therapies were reviewed:

- > gemcitabine HCL (Gemzar®), approved May 2004
- > paclitaxel (Abraxane®), approved January 2005
- > lapatinib (Tykerb®), approved March 2007
- > ixabepilone (Ixempra®), approved October 2007
- > bevacizumab (Avastin®), approved February 2008

The review was conducted with attention to metrics referable to the BICR. The findings are summarized.

Results

gemcitabine HCl (Gemzar®)

Primary Endpoint: TTP by WHO

Site vs. Central Discordance:

- The BICR determined the ORR was 24.3% in the treatment arm vs. 11.1% in the control arm. The investigator assessments indicated the ORR was 34.8% in the treatment arm vs. 18.7% in the control arm.

Reported Reasons for Discordance:

- The BICR did not evaluate bone scans, while the investigator assessments included the interpretation of bone scans.
- Imaging studies were only repeated at subsequent time points if they were deemed positive at baseline by the site.

paclitaxel (Abraxane®)

Primary Endpoint: Reconciled Target Lesion Response Rate by RECIST

Missing Data: Clinical data was not available during the BICR. The BICR was unable to evaluate 25 patients: 15 patients had lesions only detected clinically and 10 patients had inadequate or missing radiographic images.

Reported Reasons for Discordance: Radiographic images were submitted to the FDA. An FDA consultant radiologist reviewed a subset of images and the following issues were encountered:

- Quality of radiographic images, completeness of studies (ex. CT Abdomen limited to liver evaluation only).
- The absence of lesions meeting the size criteria to be considered target for the BICR, but assessed as target disease by the site, or the complete absence of measurable disease.
- Measurable disease for eligibility was assessed differently by the investigators and the BICR.
- Evolving definition of target lesion response in the protocol compared with more explicit instructions given to the BICR.
- The BICR only reviewed radiographs from the first 6 cycles of therapy. The investigator assessments went past 6 cycles when applicable and included physical exam and sonogram (which were not available to the BICR).

lapatinib (Tykerb®)

Primary Endpoint: TTP by RECIST

Missing Data: The BICR was unable to evaluate 13% (52 of 399) patients due to missing baseline or all follow-up time points. In 10% of patients, there were no scans sent to the BICR and 3% of patients had insufficient data for tumor assessment.

Site vs. Central Discordance:

- The BICR determined the TTP was 27.1 weeks in the treatment arm vs. 18.6 weeks in the control arm. The investigator assessments indicated a TTP of 23.9 weeks in the treatment arm vs. 18.3 weeks in the control arm.
- The rate of discordance between the site and BICR was reportedly 44% (174 of 399) for the date of progression.
- The rate of discordance between the site and BICR was reportedly 29% (117 of 399) for progression status.
- The BICR determined the response rate was 24% in the treatment arm vs. 14% in the control arm. The investigator assessments indicated the response rate was 32% in the treatment arm vs. 17% in the control arm.

Reported Reasons for Discordance:

- Difference in interpretation of data
- Difference in selection and interpretation of organs/lesions
- Missing data (baseline images, photos, clinical data)

Results

ixabepilone (Ixempra®)

Combination Therapy Primary Endpoint: PFS by RECIST
Monotherapy Primary Endpoint: ORR by RECIST

Combination Therapy

Missing Data: The BICR was unable to evaluate response in 10% (78 of 752) patients. Patients were unevaluable primarily because only a screening exam was performed. Other reasons included the inability to assess target lesions and a complete lack of data at the BICR.

Site vs. Central Discordance:

- The BICR identified ≥ 2 sites of disease in 89.6% of patients in the treatment arm and 91% of patients in the control arm. The investigators identified ≥ 2 sites of disease in 83.7% of patients in the treatment arm and 83.8% of patients in the control arm.
- The BICR determined PFS was 5.85 months in the treatment arm vs. 4.17 months in the control arm. The investigator assessments indicated PFS was 5.26 months in the treatment arm vs. 3.81 months in the control arm.
- The rate of discordance between the site and BICR was reportedly 48.8% (367 of 752) for the date of progression. This degree of discordance was reportedly similar to that observed in other trials. In most cases, the discrepancies were due to an earlier date of progression assessed by the BICR.
- The BICR determined the response rate was 34.7% in the treatment arm vs. 14.3% in the control arm. The investigator assessments indicated the response rate was 41.9% in the treatment arm vs. 22.5% in the control arm.

Monotherapy

Missing Data: The BICR was unable to evaluate response in 10% (13 of 126) patients. Patients were reportedly unevaluable because only a screening exam was performed, lack of measurable disease, or because the BICR identified disease in scans that were not performed at subsequent time points.

Site vs. Central Discordance:

- All 126 treated patients had measurable disease at baseline identified by the investigators. The BICR did not identify measurable disease in 9% (11 of 126) patients.
- The BICR identified ≥ 3 sites of disease in 64.3% of patients. The investigators identified ≥ 3 sites of disease in 42.8% of patients.
- The BICR diagnosed ascites, effusions, one CNS metastasis, and peritoneal disease while the investigators did not. The BICR diagnosed more patients with liver, lymph node, and other metastases as compared to the investigator assessments. The BICR diagnosed fewer patients with pleural and skin/soft tissue metastases as compared to the investigator assessments.
- The BICR determined the response rate was 12.4% vs. the investigator response rate of 18.3%. The investigator assessments showed one patient with a complete response (CR) and 22 patients with a partial response (PR). Of the 22 patients assessed as PR by the investigators, 11 patients (50%) had the PR confirmed by the BICR. The CR assessed by the investigator was not confirmed by the BICR.
- The rate of discordance between the site and BICR was reportedly 29% (36 of 126) for best response.

Reported Reasons for Discordance:

- Exclusion of physical exam measurements from BICR assessments
- Unevaluable assessments due to incomplete radiology assessments and BICR selection of baseline lesions from scans not performed at regular intervals
- Variability in measurement of small lesions
- Differences in the choice and classification of lesions (weight given to target and non-target lesions)
- Differences in the timing and identification of new lesions
- Missing baseline scans at the BICR resulting in new disease being diagnosed instead of known disease improving

BICR Inter-reader & Intra-reader Variability Testing: Inter-reader variability testing was assessed by the BICR in 20% of study cases. Intra-reader variability testing was assessed in 10% of study cases.

- One-step response discrepancies (PR vs. SD, SD vs. PD) were identified during inter-reader variability in 8% (2 of 24) patients.
- One-step response discrepancies were identified during intra-reader variability in 31% (4 of 13) patients.
- The frequency of one-step discrepancies was in line with past experience.

bevacizumab (Avastin®)

Primary Endpoint: PFS by RECIST

Missing Data: Due to a retrospective image collection, the BICR was unable to evaluate response in 10% (73 of 722) patients because scans were not received at the BICR.

Site vs. Central Discordance:

- The BICR determined the PFS was 11.3 months in the treatment arm vs. 5.8 months in the control arm. The investigators determined the PFS was 11.4 months in the treatment arm vs. 5.8 months in the control arm.
- The rate of discordance between the site and BICR was reportedly 51% (368 of 722) for the date of progression.
- The rate of discordance between the site and BICR was reportedly 24% (174 of 722) for progression status.

Discordance Between 2 Readers at the BICR:

- The rate of discordance between 2 readers at the BICR in best response and/or date of progression was 50.5% (328 of 649).
- The rate of discordance between 2 readers at the BICR in the date of progression was 34.2% (222 of 649).

Conclusion

Based on FDA approvals, metrics as described above may prove to be valuable benchmarks when using BICR data to determine endpoints in future breast cancer studies.