Errata to FDA Briefing Document

Meeting of the Oncologic Drugs Advisory Committee (ODAC)

October 5, 2023

This erratum contains corrections to FDA's briefing information for the October 5, 2023, ODAC Meeting. The committee will discuss the results of Study 2019009 (CodeBreaK 200) submitted under supplemental new drug application (sNDA) 214665 s005, for sotorasib, by Amgen, Inc, for the following proposed indication: the treatment of patients with KRAS G12C-mutated non-small cell lung cancer (NSCLC), who had received at least one prior systemic therapy.

1. On page 9, under section "1.1 Sotorasib Development History", the sixth paragraph currently reads:

   Public awareness and enthusiasm for sotorasib was evident before initiation of CodeBreaK 200 and continued throughout the course of the trial. Press releases regarding the therapeutic benefit of sotorasib were issued as early June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200.

   This paragraph should read:

   Public awareness **of** sotorasib was evident before initiation of CodeBreaK 200 and continued throughout the course of the trial. Press releases regarding the **investigation** of sotorasib were issued as early June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200.

2. On page 11, under section "1.2 Concerns for Systemic Bias and Study Conduct Issues", the fourth paragraph currently reads:

   Further issues related to study conduct included a lack of adherence to the imaging charter. Multiple imaging assessments were conducted by the BICR to resolve discrepancies between investigator and BICR assessments, which was considered a protocol violation, triggering additional concern regarding data quality and integrity.

   This paragraph should read:

   Further issues related to study conduct included a **potential** lack of adherence to the imaging charter. Multiple imaging assessments were conducted by the BICR to resolve discrepancies between investigator and BICR assessments. **The Applicant's comparison of COP-based events and BICR-based events, which led to these**

multiple imaging assessments, was considered a **potential** protocol violation, triggering additional concern regarding data quality and integrity.

3. On page 12, under section "1.3 Regulatory Considerations", the fourth paragraph currently reads:

   Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. Investigators, and likely patients as well, were eager to access sotorasib given its early success and differing route of administration and toxicity profile.

   This paragraph should read:

   Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. **In this open-label trial, it is possible that emerging data from other trial results, and a control arm that patients may have considered suboptimal, may have increased patient and investigator awareness of sotorasib and desire to access sotorasib.**

4. On page 12, under section "1.3 Regulatory Considerations", the fifth paragraph currently reads:

   Violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest that there were not well defined and reliable methods to assess response.

   This paragraph should read:

   Potential violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest that there were not well defined and reliable methods to assess response.

5. On page 15, under section "2.2 Regulatory History", between the third and fourth paragraphs, the following sentence was added:

   (The committee will not be asked to opine on the results of this PMR for the dose comparison study.)

6. On page 15, under section "2.2 Regulatory History", the first sentence of the fifth paragraph currently reads:

   Press releases regarding the therapeutic benefit of sotorasib were issued as early as June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200.

This sentence should read:

Press releases regarding the **investigation** of sotorasib were issued as early as June 3, 2019, almost one year before the first patient enrolled onto CodeBreaK 200.

7. On page 16 in "Figure1: Clinical Development Timeline of Sotorasib", the date for "Implementation of crossover in CodeBreaK 200" currently reads:

   03/25/21

   This date should read:

   03/10/21

8. On page 18, in "Table 3: Key Regulatory History for Sotorasib", the date in the ninth row currently reads:

   March 25, 2021

   This date should read:

   March 10, 2021

9. On page 18, in "Table 3: Key Regulatory History for Sotorasib", the third paragraph in the twelfth row currently reads:

   The **[redacted]** BICR radiologists re-read discordant scans which led to updated PFS results which were then deemed to be statistically significant, based on changed readings of 12 scans. See Section 4.6 for additional details.

   This paragraph should read:

   The **[redacted]** **imaging vendor** BICR radiologists re-read discordant scans which led to updated **interim analysis** PFS results which were then deemed to be statistically significant, based on changed readings of 12 scans. See Section 4.6 for additional details.

10. On page 18, in section "2.3 Public Interest in Sotorasib", the first paragraph currently reads:

    Public awareness and enthusiasm for sotorasib was evident at the time of initiation of CodeBreaK 200 and throughout the course of the trial. At the onset, sotorasib was a novel therapy against a previously "undruggable" target and docetaxel had a historically poor response rate. On October 5, 2020, within three months of initiation of CodeBreaK 200, the Applicant issued a press release indicating "durable anticancer activity" was observed for sotorasib in CodeBreaK 100. On December 7, 2020, FDA granted sotorasib Breakthrough Therapy Designation which is reserved for drugs that have

preliminary clinical evidence demonstrating a potential substantial improvement over available therapy. Topline results for CodeBreaK 100 were announced on January 30, 2021, at the Presidential Symposium for IASCL World Conference. Public awareness and interest in sotorasib was evident throughout enrollment of CodeBreaK 200 which may have made the trial more susceptible to open-label bias.

This paragraph should read:

Public awareness for sotorasib was evident at the time of initiation of CodeBreaK 200 and throughout the course of the trial. On October 5, 2020, within three months of initiation of CodeBreaK 200, the Applicant issued a press release indicating "durable anticancer activity" was observed for sotorasib in CodeBreaK 100. On December 7, 2020, FDA granted sotorasib Breakthrough Therapy Designation which is reserved for drugs that have preliminary clinical evidence demonstrating a potential substantial improvement over available therapy. Topline results for CodeBreaK 100 were announced on January 30, 2021, at the Presidential Symposium for **IASLC** World Conference. Public awareness **of** sotorasib was evident throughout enrollment of CodeBreaK 200 which may have made the trial more susceptible to open-label bias. **In today's information age, we may see evidence of this bias with increased early patient dropout due to increased public awareness of available therapies.**

11. On page 19, in section "2.3 Public Interest in Sotorasib", the first sentence of the second paragraph currently reads:

    Selected Applicant press releases for sotorasib in NSCLC, which may have contributed to study conduct issues for CodeBreaK 200, include the following:

    This sentence should read:

    Selected press releases for sotorasib in NSCLC, which may have contributed to study conduct issues for CodeBreaK 200, include the following:

12. On page 23, in section "3.3 Efficacy Analyses", the fourth sentence of this section currently reads:

    The independent data monitoring committee (iDMC) reviewed both results and recommended continuing the trial without stopping and to perform a global re-reading of scans for the final PFS analysis.

    This sentence should read:

    The independent data monitoring committee (iDMC) reviewed both results and recommended continuing the trial without stopping.

13. On page 29, in section "3.3.3.1 Accounting for PFS Assessment Interval", the third sentence in the second paragraph currently reads:

The estimated median PFS results from this analysis were 4.2 months (95% CI: 3.9, 7.8) for the sotorasib arm and 4.3 months (95% CI: 2.9, 4.8) for the docetaxel arm with an estimated HR of 0.71 (95% CI: 0.54, 0.95).

This sentence should read:

The estimated median PFS results from this analysis were **4.47** months (95% CI: 3.9, 7.8) for the sotorasib arm and 4.3 months (95% CI: 2.9, 4.8) for the docetaxel arm with an estimated HR of 0.71 (95% CI: 0.54, 0.95).

14. On page 31, in section "3.3.3.3 Interpretation of the PFS Results", the fifth bullet point in the first paragraph currently reads:

    There was lack of adherence to the imaging charter and protocol, involving multiple BICR assessments of the PFS primary endpoint. This protocol deviation erodes confidence in the overall trial conduct and data integrity. (Section 4.6)

    This bullet point should read:

    There was a **potential** lack of adherence to the imaging charter and protocol, involving multiple BICR assessments of the PFS primary endpoint. This **potential** protocol deviation erodes confidence in the overall trial conduct and data integrity. (Section 4.6)

15. On page 46, in section "4.6 BICR Assessment of PFS and Imaging Vendor Procedures", the second paragraph currently reads:

    The potential impact of COP on the BICR assessment of progression events is usually minimal if the COP procedure is used as intended. However, there was a lack of adherence to the imaging charter and protocol as the COP assessments were indirectly used to audit the BICR assessments.

    This paragraph should read:

    The potential impact of COP on the BICR assessment of progression events is usually minimal if the COP procedure is used as intended. However, there was a **potential** lack of adherence to the imaging charter and protocol as the COP assessments were indirectly used to audit the BICR assessments. **FDA considers the Applicant's use of the COP procedure, including comparing COP assessments with BICR assessments, to be beyond the scope of the purpose of the COP procedure and a potential violation of the protocol and imaging charter.**

16. On page 46, in section "4.6 BICR Assessment of PFS and Imaging Vendor Procedures", the fourth sentence of the third paragraph currently reads:

    The Applicant informed **[redacted]** of a higher-than-expected discordance between the COP-based and BICR-based events of progression.

This sentence should read:

The Applicant informed **[redacted]** **the imaging vendor** of a higher-than-expected discordance between the COP-based and BICR-based events of progression.

17. On page 46, in section "4.6 BICR Assessment of PFS and Imaging Vendor Procedures", the fourth paragraph currently reads:

    Of these 23 patients, **[redacted]** identified unexpected reader variability between COP and BICR assessments for 13 patients. The unexpected reader variability was related to cases of borderline imaging and instances in which the BICR reader may not have fully followed the read rules for imaging assessments. A BICR re-read was selectively performed for these 13 patients.

    This paragraph should read:

    Of these 23 patients, **[redacted]** **the imaging vendor** identified unexpected reader variability between COP and BICR assessments for 13 patients. The unexpected reader variability was related to cases of borderline imaging and instances in which the BICR reader may not have fully followed the read rules for imaging assessments. A BICR re-read was selectively performed **by the imaging vendor** for these 13 patients.

18. On page 46, in section "4.6 BICR Assessment of PFS and Imaging Vendor Procedures", the first sentence of the seventh paragraph currently reads:

    A global re-read for the analysis of the primary PFS endpoint was undertaken under the advisement of the iDMC and FDA, given concerns of data quality and in an effort to achieve consistency in BICR reads from a single data reading entity.

    This sentence should read:

    A global re-read for the analysis of the primary PFS endpoint was undertaken under the advisement of FDA, given concerns of data quality and in an effort to achieve consistency in BICR reads from a single data reading entity.

19. On page 48, in section "5. Summary and Conclusions", the second bullet point in the third paragraph currently reads:

    Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. Investigators, and likely patients as well, were eager to access sotorasib given its early success and differing route of administration and toxicity profile.

    This bullet point should read:

Adequate measures were either not put in place, or not adequately followed to minimize bias on the part of investigators, given the rates of discrepancy between investigator and BICR calls for progression. **In this open-label trial, it is possible that emerging data from other trial results, and a control arm that patients may have considered suboptimal, may have increased patient and investigator awareness of sotorasib and desire to access sotorasib.**

20. On page 48, in section "5. Summary and Conclusions", the third bullet point in the third paragraph currently reads:

    Violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest there were not well defined and reliable methods to assess response.

    This bullet point should read:

    Potential violations of the imaging charter, with confirmation of progression (COP) indirectly used to audit certain BICR assessments resulting in multiple sets of BICR reads, suggest there were not well defined and reliable methods to assess response.

21. On page 49, in section "5. Summary and Conclusions", the fourth sentence in the fifth paragraph currently reads:

    Furthermore, the imaging charter and protocol were violated, with the COP assessments indirectly used to audit the BICR assessments.

    This should read:

    Furthermore, the imaging charter and protocol were **potentially** violated, with the COP assessments indirectly used to audit the BICR assessments.