Errata to FDA Briefing Document

Meeting of the Oncologic Drugs Advisory Committee (ODAC)

March 15, 2024

This erratum contains corrections to FDA's briefing information for the March 15, 2024, ODAC Meeting. The Committee will discuss the results of the CARTITUDE-4 trial submitted under a supplemental biologics license application (sBLA) 125746.74 for CARVYKTI (ciltacabtagene autoleucel) for the following proposed indication: treatment of adult patients with relapsed or refractory multiple myeloma, who have received at least one prior line of therapy, including a proteasome inhibitor, and an immunomodulatory agent, and are refractory to lenalidomide.

1. On page 6, section 1- Executive Summary, first paragraph currently reads "Serious adverse events (SAEs) occurred in **36%** and **37%** of patients in the cilta-cel and standard therapy arms, respectively."

   This paragraph should read: "Serious adverse events (SAEs) occurred in **37.8%** and **38.9%** of patients in the cilta-cel and standard therapy arms, respectively."

2. On pages 7 and 8, section 2 Background and section 3 Product and Regulatory History currently reads "**Median duration of response was 21.8 months (95% CI: 21.8, NE)"** "USPI 2022."

   This paragraph should read:
   "…**median duration of response has not been reached**."

3. On Page 8, section 3- Product and Regulatory History, titled Regulatory History's table row 6 currently reads "Jun 6, 2023. The Sponsor submitted efficacy supplement based on PFS results from the **second** interim analysis of CARTITUDE-4, with a cutoff date of November 1, 2022."

   This row should read "Jun 6, 2023. The Sponsor submitted efficacy supplement based on PFS results from the **first** interim analysis of CARTITUTDE-4, with a cutoff date of November 1, 2022."

4. On page 8, section 3- Key Regulatory History ‘s table row 9 currently reads: “T-con in which FDA communicated its decision to convene an oncology drug advisory committee to obtain committee’s input regarding the benefit-risk of **ide-cel** for the indicated population given the observed early OS detriment with **the** cilta-cel"

   This row should read: “Tcon in which FDA communicated its decision to convene an oncology drug advisory committee to obtain committee’s input regarding the benefit-risk of **cilta-cel** for the indicated population given the observed early OS detriment with cilta-cel"

5. On Page 9, subsection 4.1- Study Design reads: “Bridging therapy with PVd or DPd **could** be administered to patients in the cilta-cel arm at the investigator’s discretion during the interval between leukapheresis and lymphodepleting chemotherapy.”

   This paragraph should read: “Bridging therapy with PVd or DPd **should** be administered to patients in the cilta-cel arm at the investigator’s discretion during the interval between leukapheresis and lymphodepleting chemotherapy.”

6. On page 9, subsection 4.1- Study Design, reads “Randomization was stratified by investigator’s choice of PVd or DPd **for the control arm**, International Staging System (ISS) staging (I versus II versus III), and number of prior lines of therapy (one versus two or three).”

   This paragraph should read: “Randomization was stratified by investigator’s choice of PVd or DPd, International Staging System (ISS) staging (I versus II versus III), and number of prior lines of therapy (one versus two or three).”

7. On page 11, “Table 1: Demographics Characteristics, ITT Population, CARTITUDE-4,” row 19- the cell in column four for Total n (%) Hispanic/Latino Ethnic Group Not Reported currently reads **80 (19)**

   This cell should read: “Table 1: Demographics Characteristics, ITT Population, CARTITUDE-4” row 19- the cell in column four for Total n (%) Hispanic/Latino Ethnic Group Not Reported **74 (18**)

8. On page 11, “Table 1: Demographics Characteristics, ITT Population, CARTITUDE-4,”and row 23 the cell in column four under Total n (%) for “Asia” currently reads **529 (12).**

This cell should read: “Table 1: Demographics Characteristics, ITT Population, CARTITUDE-4” row 23 the cell in column four under Total n (%) for “Asia” **52 (12).**

9. On page 13, subsection 4.6.2-Subject Disposition, currently reads: “Thirty-two subjects randomized to the cilta-cel arm (15% of the total number randomized to cilta-cel) had discontinued the **study** and 51 subjects randomized to the standard therapy arm (24% of the subjects randomized to SOC) had discontinued in the arm.”

   This paragraph should read: “Thirty-two subjects randomized to the cilta-cel arm (15% of the total number randomized to cilta-cel) had discontinued the **study treatment** and 51 subjects randomized to the standard therapy arm (24% of the subjects randomized to **standard therapy**) had discontinued in the arm.”

10. On page 16, Table 7 footnote currently reads: “Source: FDA analysis, data cutoff **January** 1, 2022. 1. Including MR, SD, PR, and NE. 2. One-sided Cochran-Mantel-Haenszel test controlling for pooled strata...”

    The footnote should read: “Source: FDA analysis, data cutoff **November** 1, 2022. 2. One-sided Cochran-Mantel-Haenszel test controlling for pooled strata...”

11. On page 17, Interpretation of OS Analysis Results, second bullet currently reads: “The average HR for OS at the time of the **second** interim analysis for PFS was reported as 0.78 (95% CI: 0.51, 1.20).”

    This paragraph should read: The average HR for OS at the time of the **first** interim analysis for PFS was reported as 0.78 (95% CI: 0.51, 1.20).”

12. On Page 18-19, “Table 10: Treatment Emergent Adverse Events Occurring in ≥10% of Subjects, GT Safety Population, CARTITUDE-4” rows 6 and 7 currently read Encephalopathy (GT) **27 (14), 3 (1.6),** 9 (4), **0**. Parkinsonism (GT) **27 (14), 3 (1.6), 0, 0.**

    These rows should read: “Table 10: Treatment Emergent Adverse Events Occurring in ≥10% of Subjects, GT Safety Population, CARTITUDE-4” Encephalopathy (GT) **10 (10.6), 2 (1.1)**, 9 (4), **2 (1).** Parkinsonism (GT) **2 (1), 0, 0, 0.**

13. On Page 19, “Table 11: Laboratory Abnormalities Occurring in ≥10% of the Safety Population, CARTITUDE-4” rows 9 and 10 currently read ALK increased **86(45.7), 11 (5.9), 30 (14.4),4 (1.9).** AST increased **25(28), 0, 30(14.4), 4 (1.9**)

    These rows should read “Table 11: Laboratory Abnormalities Occurring in ≥10% of the Safety Population, CARTITUDE-4” ALK increased **76 (40.7), 8 (4.3), 53 (25.5), 0.** AST increased **86 (45.7),11 (5.9), 30 (14.4), 4 (1.9)**

14. On page 20, “Table 12: Nonfatal Serious Treatment Emergent Adverse Events Occurring in ≥2% of the Safety Population, CARTITUDE-4 row 11 currently reads Febrile neutropenia 0,**3 (1.6), 0**, and row 19 currently reads Cytokine release syndrome 12(6.4), 4(2.1), **0**, 0.

    These rows should read: **“**Table 12**:** Nonfatal Serious Treatment Emergent Adverse Events Occurring in ≥2% of the Safety Population, CARTITUDE-4 row 11 Febrile neutropenia **0, 0, 5 (2.4), 5 (2.4),** and row 19 should read Cytokine release syndrome 12 (6.4), 4 (2.1), **1 (0.5),** 0.

15. On page 20, “Table 13: Adverse Events of Special Interest (AESI), CARTITUDE-4” in row 5 (HLH/MAS) the cell in column 4 [Any Grade (n/%), under “Standard Therapy N=208”], reads 1 (2).

    This cell should read **0 (0).**

    In the same table, in row 8 (Hematologic neoplasm) in the third column [Grade ≥3 (n/%), under Cilta-cell N=188], the cell reads **1 (0.5).**

    This cell should read **3 (1.6)**.

16. On page 21, “Table 14: Prolonged and Recurrent Cytopenia, Safety Population, CARTITUDE-4, row 2 (lymphopenia) the cell in the third column (titled Grade 3-4 Not Recovered by Day 30 (n/%)] reads **6 (3.2)**

    This cell should read: **55 (29.3%).**

17. On page 22 Section 5.1-Increased Rate of Early Deaths in the Cilta-Cel Arm, the second paragraph currently reads “As presented in Section 4, the OS results from the CARTITUDE-4 study demonstrated an observed early detriment in OS in subjects randomized to the cilta-cel arm compared to those randomized to

standard therapy ... The pattern of increased early deaths in the cilta-cel arm is also observed in an analysis of PFS events which indicates that a higher proportion of subjects died before disease progression in the cilta-cel arm (8%) compared to the standard therapy arm (2%) (Table 6)."

This paragraph should read: "Furthermore 13% and 22% of subjects died in the cilta-cel and standard therapy arms, respectively (Table 16). However, more deaths due to AEs occurred in the cilta-cel arm (11%) compared to the standard therapy arm (8%) in the safety population. A similar trend of deaths due to AEs was observed when analyzing deaths in the ITT population (cilta-cel arm: 11%; standard therapy arm: 7%; **Table 17**). The pattern of increased early deaths in the cilta-cel arm is also observed in an analysis of PFS events which indicates that a higher proportion of subjects died before disease progression in the cilta-cel arm (8%) compared to the standard therapy arm (2%) (Table 6)."

18. On page 24 Table 18 Piecewise Hazard Ratio Assessment, ITT Population row 11 currently reads: "Time interval of **11 months**" and row 12 currently reads: "**0-≤11**…"

    These rows should read: row 11 "Time interval of **10.6 months**" and row 12 "**0-≤10.6**…"

19. On page 27 Appendix 8.1, the first paragraph currently reads: "The Applicant listed five subpopulations that may have caused the crossing hazards pattern for OS with an early OS detriment … Figure 9 shows the Kaplan-Meier curves for OS if subjects in both arms who have progressive disease within 3 months after randomization are excluded."

    This paragraph should read "The Applicant listed five subpopulations that may have caused the crossing hazards pattern for OS with an early OS detriment … Figure 9 shows the Kaplan-Meier curves for OS if subjects in both arms who have progressive disease within 3 months after randomization are excluded. These five high-risk subpopulations were retrospectively identified as:

    A. **Subjects in the cilta-cel arm with high-risk, rapidly progressive disease defined as those in the cilta-cel arm who received subsequent therapy after disease progression.**
    B. **Subjects with extramedullary plasmacytomas.**
    C. **Subjects with baseline beta-2 microglobulin level >2.5 mg/L.**
    D. **Subjects with baseline ECOG value >=1.**
    E. **Subjects in the cilta-cel arm who had progressive disease within 3 months after randomization**."