Errata and Technical Corrections

Sponsor Briefing Document for Oncologic Drugs Advisory Committee on Eflornithine (DFMO) Tablets (Meeting Date: October 4, 2023)

Date: September 19, 2023

1. Error in Description of the SIOPEN Cohort of Patients

In Section 6.4.1.2 of the sponsor Briefing Document, there is an erroneous statement in the description of the SIOPEN cohort of patients.

- **Incorrect statement:** The majority of the DFMO Per SIOPEN cohort received Bu/Mel transplant. However, consolidation was considered comparable if the patient received any single transplant or tandem transplant with C&T/CEM.
- **Explanation:** Patients with tandem transplants were not included in the DFMO Per SIOPEN cohort. The correct description of the consolidation therapy considered comparable for patient inclusion in the cohort is revised below.
- **Revision:** The majority of the DFMO Per SIOPEN cohort received Busulfan/Melphalan (Bu/Mel) transplant. However, consolidation was considered comparable for 3 patients receiving single transplant with conditioning agents other than Bu/Mel. Those patients include two who received treosulphan/melphalan with or without thiotepa, considered pharmacologically similar to Bu/Mel, and one who received carboplatin/etoposide/melphalan (CEM), shown to be inferior to Bu/Mel in a recent study (Ladenstein 2017). The inclusion of these three patients, therefore, was considered appropriate because these consolidation regimens would not be expected to advantage outcomes for the DFMO cohort.
    - **Reference:** Ladenstein R, Pötschger U, Pearson ADJ, et al. Busulfan and melphalan versus carboplatin, etoposide, and melphalan as high-dose chemotherapy for high-risk neuroblastoma (HR-NBL1/SIOPEN): an international, randomised, multi-arm, open-label, phase 3 trial. Lancet Oncol. 2017;18(4):500-514. doi:10.1016/S1470-2045(17)30070-0.

2. Error in Overall Summary of Adverse Events Table

In the "Overall Summary of Adverse Events in the Pooled Safety Population" table (Table 22 on page 97 of the sponsor Briefing Document), a row was incorrectly labeled "SAE (Grade 3 or 4)" when it should have read "Severe AEs (Grade 3 or 4)." In addition, the number of SAEs reported for Both Studies Pooled has been updated to include the single Grade 2 SAE reported in Study 3b.

A corrected version of the table with the update redlined is provided below.

Table 22: Overall Summary of Adverse Events in the Pooled Safety Population

Patients with, n (%):	Study 3b (N=52)	Study 3b Grade ≥ 3 (N=52)	Study 14 (N=259)	Both Studies Pooled* (N=311)
Patients with any AE	42 (80.8)	21 (40.4)	120 (46.3)	141 (45.3)

Patients with, n (%):	Study 3b (N=52)	Study 3b Grade ≥ 3 (N=52)	Study 14 (N=259)	Both Studies Pooled* (N=311)
Grade 2 events	42 (80.8)	-	8 (3.1)	8 (2.6)
Severe AEs ~~SAE~~ (Grade 3 or 4)	21 (40.4)	21 (40.4)	115 (44.4)	136 (43.7)
Highest AE of Grade 3	20 (38.5)	20 (38.5)	93 (35.9)	113 (36.3)
Highest AE of Grade 4	1 (1.9)	1 (1.9)	22 (8.5)	23 (7.4)
SAEs	6 (11.5)	5 (9.6)	46 (17.8)	52 (16.7) ~~51 (16.4)~~*
AEs leading to death	0	0	0	0

AE=adverse event; SAE=serious adverse event.
*Both Studies Pooled column is calculated based on the sum of Study 3b Grade ≥ 3 and the Study 14 columns for all rows except SAEs, which is calculated based on the sum of the Study 3b and the Study 14 columns in order to include the single Grade 2 SAE reported in Study 3.

3. *Error in Summary of Hearing Loss Table*

In the "Summary of Hearing Loss Reported in Primary Safety Population" table (Table 26 on page 102 of the sponsor Briefing Document), a formatting error in the superscripting of numbers altered the meaning of the text in two rows in a manner that may cause confusion.

The original table from the Briefing Document (with the erroneous items highlighted) appeared as follows:

Table 26: Summary of Hearing Loss Reported in Primary Safety Population

Toxicity Assessment Based on Patient-Level Audiogram Data and Adverse Event reporting, n (%):	Study 3b (N=52)	Study 14 (N=259)	Both Studies Pooled (N=311)
Audiogram abnormal at baseline[1]	45 (86.5)	209 (80.7)	254 (82.7)
Patients with hearing loss worsened by at least[1] Grade 2 from baseline	7 (13.5)	33 (12.7)	40 (12.9)
Patients with hearing loss that worsened by at least 1 Grade 2 from baseline and worsened to Grade 3[3]	7 (13.5)	31 (12.0)	38 (12.2)

A corrected version of the table (with the corrected text highlighted) is as follows:

Table 26: Summary of Hearing Loss Reported in Primary Safety Population

Toxicity Assessment Based on Patient-Level Audiogram Data and Adverse Event reporting, n (%):	Study 3b (N=52)	Study 14 (N=259)	Both Studies Pooled (N=311)
Audiogram abnormal at baseline[1]	45 (86.5)	209 (80.7)	254 (82.7)
Patients with hearing loss worsened by at least 1 grade[2] from baseline	7 (13.5)	33 (12.7)	40 (12.9)
Patients with hearing loss that worsened by at least 1 grade[2] from baseline and worsened to Grade 3[3]	7 (13.5)	31 (12.0)	38 (12.2)
Patients with hearing loss requiring dose modification or discontinuation	4 (7.7)	12 (4.6)	16 (5.1)

Toxicity Assessment Based on Patient-Level Audiogram Data and Adverse Event reporting, n (%):	Study 3b (N=52)	Study 14 (N=259)	Both Studies Pooled (N=311)
Temporary interruption[4]	3 (5.8)	9 (3.5)	12 (3.9)
Dose reduction[4]	2 (3.8)	6 (2.3)	8 (2.6)
Drug discontinuation[4]	1 (1.9)	4 (1.5)	5 (1.6)
Among patients with dose modification or discontinuation			
Improved but did not return to baseline[5]	2 (50.0)	4 (33.3)	6 (37.5)
Resolved to baseline[5]	0	4 (33.3)	4 (25.0)

1. Percents calculated using the number of patients with a non-missing baseline audiogram.
2. Assessed per CTCAE.
3. No patient experienced a worsening to Grade 4.
4. Patients with more than one action taken with study drug are counted in each applicable row.
5. Percents calculated using the number of patients requiring a dose modification or discontinuation as the denominator.

4. Error in Stratum 2 Demographics and Disease Characteristics Table

In table for "Demographics and Disease Characteristics for Study 3b Stratum 2, Patients in Remission Following R/R Therapy (ITT)" (Table 19 on page 86 of the sponsor Briefing Document), two numbers were transposed for the relapsed cohort in the TTFR rows.

The original table from the Briefing Document (with the erroneous items highlighted) appeared as follows:

Table 19: Demographics and Disease Characteristics for Study 3b Stratum 2, Patients in Remission Following R/R Therapy (ITT)

Parameter, n (%):	Refractory (N=7)	Relapsed (N=28)	All R/R (Stratum 2) (N=35)
Age at HRNB Diagnosis			
< 18 months	1 (14.3)	2 (7.1)	3 (8.6)
≥ 18 months and < 6 years	4 (57.1)	25 (89.3)	29 (82.9)
≥ 6 years	2 (28.6)	1 (3.6)	3 (8.6)
Stage at HRNB Diagnosis			
3	0	1 (3.6)	1 (2.9)
4	6 (85.7)	26 (92.9)	32 (91.4)
4s	1 (14.3)	1 (3.6)	2 (5.7)
Histology			
Favorable	2 (28.6)	3 (10.7)	5 (14.3)
Unfavorable	2 (28.6)	20 (71.4)	22 (62.9)
Not available	3 (42.8)	5 (17.9)	8 (22.9)
MYCN Amplification			
Amplified	1 (14.3)	9 (32.1)	10 (28.6)
Non-amplified	4 (57.1)	18 (64.3)	22 (62.9)
Unknown	2 (28.6)	1 (3.6)	3 (8.6)
Time to First Relapse (months)			
> 6 to ≤ 18	-	22 (78.6)	-
> 18	-	6 (21.4)	-
Number of Prior Relapses			
1 Prior Relapse	-	23 (82.1)	-
≥ 2 Prior Relapses	-	5 (17.9)	-
Received Chemoimmunotherapy (yes)	0	1 (3.6)	1 (2.9)

HRNB=high-risk neuroblastoma, ITT=intent-to-treat
Note: Chemoimmunotherapy defined as a combination regimen of irinotecan, temozolomide, and dinutuximab.
Patients in remission after relapse/refractory therapy = Stratum 2

A corrected version of the table (with the corrected text highlighted) is as follows:

Table 19: Demographics and Disease Characteristics for Study 3b Stratum 2 Patients in Remission Following R/R Therapy (ITT)

Parameter, n (%):	Refractory (N=7)	Relapsed (N=28)	All R/R (Stratum 2) (N=35)
Age at HRNB Diagnosis			
< 18 months	1 (14.3)	2 (7.1)	3 (8.6)
≥ 18 months and < 6 years	4 (57.1)	25 (89.3)	29 (82.9)
≥ 6 years	2 (28.6)	1 (3.6)	3 (8.6)
Stage at HRNB Diagnosis			
3	0	1 (3.6)	1 (2.9)

Parameter, n (%):	Refractory (N=7)	Relapsed (N=28)	All R/R (Stratum 2) (N=35)
4	6 (85.7)	26 (92.9)	32 (91.4)
4s	1 (14.3)	1 (3.6)	2 (5.7)
Histology			
Favorable	2 (28.6)	3 (10.7)	5 (14.3)
Unfavorable	2 (28.6)	20 (71.4)	22 (62.9)
Not available	3 (42.8)	5 (17.9)	8 (22.9)
MYCN Amplification			
Amplified	1 (14.3)	9 (32.1)	10 (28.6)
Non-amplified	4 (57.1)	18 (64.3)	22 (62.9)
Unknown	2 (28.6)	1 (3.6)	3 (8.6)
Time to First Relapse (months)			
> 6 to ≤ 18	-	6 (21.4)	-
> 18	-	22 (78.6)	-
Number of Prior Relapses			
1 Prior Relapse	-	23 (82.1)	-
≥ 2 Prior Relapses	-	5 (17.9)	-
Received Chemoimmunotherapy (yes)	0	1 (3.6)	1 (2.9)

HRNB=high-risk neuroblastoma; MIBG=metaiodobenzylguanidine.
Note: Chemoimmunotherapy included irinotecan, temozolomide, and dinutuximab as studied in ANBL1221.