18 October 2018
EMA/780336/2018
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Mylotarg

gemtuzumab ozogamicin

Procedure no: EMEA/H/C/004204/P46/003

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Introduction

On 9th July 2018 the MAH submitted a completed paediatric study B1761026 for Gemtuzumab Ozogamicin (MYLOTARG), in accordance with Article 46 of Regulation (EC) No1901/2006, as amended.

A short critical expert overview has also been provided.

2. Scientific discussion

2.1. Information on the development program

Study B1761026 is entitled, 'Gemtuzumab Ozogamicin (Mylotarg) Expanded Access Protocol for Treatment of Patients in the United States with Relapsed/Refractory Acute Myelogenous Leukemia (AML) Who May Benefit from Treatment and Have No Access to Other Comparable/Alternative Therapy'.

This was a Marketing Authorisation Holder (MAH)-sponsored study of an authorised medicinal product where 105 (31.7%) patients who were enrolled were <18 years of age.

MYLOTARG received marketing approval in the United States on 01 September 2017 and has a US indication for the treatment of newly-diagnosed CD33-positive acute myeloid leukemia in adults, and relapsed or refractory CD33-positive acute myeloid leukemia in adults and in paediatric patients 2 years and older. On 19 April 2018, Mylotarg received marketing authorization in the European Union (EU) for use in combination with daunorubicin (DNR) and cytarabine (AraC) for the treatment of patients aged 15 years and older with previously untreated, de novo CD33-positive AML, except acute promyelocytic leukaemia (APL).

A Paediatric Investigation Plan (PIP) has been agreed for MYLOTARG with the European Medicines Agency (EMA)/Paediatric Committee (PDCO) (PIP EMEA-001733-PIP02-15-M01).

2.2. Information on the pharmaceutical formulation used in the study

MYLOTARG is an antibody-drug conjugate (ADC) composed of the CD33-directed monoclonal antibody (mAb; hP67.6; recombinant humanized immunoglobulin G4, kappa antibody produced by mammalian cell culture in non-secreting null [NS0] cells) that is covalently linked to the cytotoxic agent N-acetyl (NAc) gamma calicheamicin. The antibody portion binds specifically to the CD33 antigen, a sialic acid dependent adhesion protein found on the surface of myeloid leukaemic blasts and immature normal cells of myelomonocytic lineage, but not on normal hematopoietic stem cells. Binding of the anti-CD33 antibody portion of MYLOTARG to the CD33 antigen results in the formation of a complex, which is then internalized. Upon internalization, the calicheamicin derivative is released inside the lysosomes of the myeloid cell. The released calicheamicin derivative binds to deoxyribonucleic acid (DNA) in the minor groove resulting in DNA double-strand breaks and cell death. After administration of Hu-M195, another CD33-directed antibody, continuous renewed expression of CD33 antigens on the cell surface was observed, as measured by the cell mean peak fluorescence. Mylotarg is available in the form of powder for concentrate for solution for infusion (1 mg/mL).

2.3. Clinical aspects

2.3.1. Introduction

- Study B1761026: 'Gemtuzumab Ozogamicin (Mylotarg) Expanded Access Protocol for Treatment of Patients in the United States with Relapsed/Refractory Acute Myelogenous Leukemia (AML) Who May Benefit from Treatment and Have No Access to Other Comparable/Alternative Therapy'.

2.3.2. Clinical study B1761026

Description

Methods

Objective(s)

The primary objective of the study was to provide expanded access in accordance with FDA regulations to allow compassionate access to MYLOTARG for treatment of patients with CD33 positive acute myeloid leukaemia (AML) (including APL and myelodysplastic syndrome with rising or persistent blasts) who were thought to have the potential to derive clinical benefit and who had exhausted other appropriate and reasonable treatment options including investigational studies. No formal objectives were evaluated.

This paper describes the safety results from this US only study.

Study design

This was an open-label (US only) expanded access protocol to treat patients with relapsed or refractory AML including myelodysplastic syndrome (MDS) or relapsed or refractory acute promyelocytic leukaemia (APL). The protocol allowed the investigator to choose for each patient enrolled an optimal treatment plan, choosing from several MYLOTARG-containing regimens. The protocol allowed for treatment regimens tested in clinical trial settings and reported in peer reviewed journals. Data indicated that these treatment regimens could potentially benefit a patient with relapsed/refractory AML, MDS, or APL.

The protocol allowed to use of MYLOTARG as a single agent at ≤9 mg/m^2/dose for AML or in combination with all-trans retinoic acid (ATRA) and/or arsenic trioxide for treatment of APL. Other doses included the use of MYLOTARG up to 3 mg/m^2/dose in combination with anthracycline, nucleoside-antagonist containing treatment regimens, or hypomethylating agents. The protocol was to remain open to provide compassionate access to MYLOTARG for patients within the US until the clinical development of the drug was discontinued, or when MYLOTARG was commercially available within the US, whichever occurred first.

Study population /Sample size

Patients were eligible for enrolment into the study only if they met all the inclusion criteria outlined in the protocol.

Diagnosis and Main Criteria for Inclusion:

Patients aged ≥3 months with confirmed diagnosis of relapsed or refractory AML, including MDS, with persisting or rising blasts, and no other comparable or satisfactory alternative therapy available (including patients not eligible for or with access to investigational therapies through participation in a clinical trial) or confirmed diagnosis of relapsed or refractory APL with persisting or rising leukaemic burden (either by morphology, cytogenetic analysis or by molecular techniques), and no other comparable or satisfactory alternative therapy available (including patient was not eligible for or with access to investigational therapies via a clinical trial) were eligible to be included in this study. Patients with documentation that malignant cells expressed CD33 and patients with adequate non-hematologic organ function were eligible to be included in this study**.**

Patients were allowed to re-enrol into the study and were assigned a different patient identification number at re-enrolment

Treatments

The following treatment regimens were used to treat patients with a diagnosis of relapsed or refractory AML.

Treatment Regimen 1 – Monotherapy

- A dose of ≤9 mg/m^2 of MYLOTARG was administered on Day 1 and Day 15 of a 28-day treatment cycle. In the absence of a complete remission CR[a] [CR[a] was defined as ≤5% marrow blasts with complete recovery of haematopoiesis, defined as absolute neutrophil count (ANC) ≥1000/µL and platelets ≥100,000/µL in the absence of growth factor or transfusion support], a total of 2 treatment cycles of MYLOTARG was administered.
- Alternate treatment regimens tested in clinical trial settings and reported in peer reviewed journals were permitted where published results demonstrated that the regimen was tolerated and effective.

Treatment Regimen 2 – MYLOTARG in combination with recognized anthracycline and/or nucleoside-antagonist containing regimens

- MYLOTARG was administered in combination with tested standard chemotherapy induction and consolidation regimens for AML where published results from a clinical trial demonstrated that the combination was tolerated and effective.

Treatment Regimen 3 – Treatment for APL

- For APL only, MYLOTARG was administered as a monotherapy or in tested combinations with all-trans retinoic acid (ATRA) and/or arsenic trioxide.
- For APL only, if CR[a] was achieved utilizing MYLOTARG as monotherapy or in combination with ATRA, a total of 5 post-remission treatment cycles of single agent MYLOTARG at a dose of ≤9 mg/m^2/dose on Day 1 of each 28 day post-remission treatment cycle may have been administered provided complete hematologic recovery was documented, platelet count ≥100,000/µL and ANC ≥1000/µL prior to initiation of each MYLOTARG post-remission cycle. During such maintenance therapy, safety assessments were completed at least every 2 weeks. MYLOTARG as maintenance therapy was only allowed for patients with APL who achieved a CR[a] following the induction treatment regimen.

Outcomes/endpoints

Safety Evaluations: Safety data were summarized for all patients who received at least 1 dose of MYLOTARG. Only Grade 3-5 AEs were recorded. Actual laboratory results were not collected on the case report form (CRF); however, laboratory results that met Grade 3-5 criteria were captured as AEs.

For serious adverse events (SAEs), the active reporting period to Pfizer began from the time that patient provided informed consent up through and including 60 calendar days after the last administration of MYLOTARG. SAEs occurring after the active reporting period ended were reported to the Sponsor if the investigator became aware of them; at a minimum, all SAEs that the investigator believed had at least a reasonable possibility of being related to MYLOTARG were reported to the Sponsor. Grade 3-5 AEs (serious and non-serious) were recorded on the CRF from the time the patient had taken at least 1 dose of protocol treatment through 60 calendar days after last administration of MYLOTARG.

If a patient began a new anticancer therapy, the AE reporting period for non-serious AEs ended at the time the new treatment was started. Death was reported if it occurred during the SAE reporting period, irrespective of any intervening treatment.

Statistical Methods

Not applicable

Results

Recruitment/ Number analysed

Enrolment /Re-enrolment

- 316 unique patients received study treatment with a total enrolment of 331 patients [15 (4.5%) patients re-enrolled].
- At first enrolment, 132 patients enrolled in monotherapy, 175 patients enrolled in combination, and 9 patients enrolled in treatment for APL.
- 330 (99.7%) enrolled patients were analysed for AEs (138 [99.3%], 183 [100.0%], and 9 [100.0%] patients in the monotherapy, combination, and treatment for APL groups, respectively).

Discontinuation

- 168 (50.8%) patients discontinued from the study (94 [67.6%], 71 [38.8%], and 3 [33.3%] patients in the monotherapy, combination, and treatment for APL groups, respectively).
- Main reasons for discontinuation were patient death: 100 (30.2%) patients overall (60 [43.2%], 38 [20.8%], and 2 [22.2%] patients in the monotherapy, combination, and treatment for APL groups, respectively) and other reasons: 60 (18.1%) patients overall (28 [20.1%], 31 [16.9%], and 1 [11.1%] patients in the monotherapy, combination, and treatment for APL groups, respectively).

Table 1: Patient evaluation groups

	Monotherapy	Combination	Treatment for APL	Total
Number (%) of Patients				
Screened				331
Assigned to Study Treatment	139	183	9	331
Treated	139 (100.0)	183 (100.0)	9 (100.0)	331 (100.0)
Completed[a]	45 (32.4)	112 (61.2)	6 (66.7)	163 (49.2)
Discontinued	94 (67.6)	71 (38.8)	3 (33.3)	168 (50.8)
Analyzed for Safety: AEs[b]	138 (99.3)	183 (100.0)	9 (100.0)	330 (99.7)
Re-enrolled				15 (4.5)

Discontinuations occurring outside the lag period have been attributed to the last study treatment received. Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
AE=adverse event; APL=acute promyelocytic leukemia.
a. A patient was considered to have 'completed' if the treatment regimen was completed and follow-up was completed.
b. Number of patients evaluable for AEs is defined as patients known to have received at least 1 dose of study treatment and have an AE page.

Baseline data

- 331 patients were treated (184 male: 147 female). Majority were white (81.6%) and not Hispanic/Latino (89.4%).
- Ages range 0 to 94 years, with a mean (standard deviation [SD]) age of 42.2 (28.2) years.
- 105 (31.7%) patients were <18 years of age with 21 (15.1%) monotherapy group; 84 (45.9%) combination group. No patients <18 years of age who were enrolled were treated for APL.

Table 2: Demographic characteristics

	Monotherapy			Combination			Treatment for APL			Total		
	Male	Female	Total	Male	Female	Total	Male	Female	Total	Male	Female	Total
Number (%) of Patients	79	60	139	97	86	183	8	1	9	184	147	331
Age												
<18 years	14 (17.7)	7 (11.7)	21 (15.1)	49 (50.5)	35 (40.7)	84 (45.9)	0	0	0	63 (34.2)	42 (28.6)	105 (31.7)
0 - 27 days	0	0	0	0	0	0	0	0	0	0	0	0
28 days - <2 years	1 (1.3)	1 (1.7)	2 (1.4)	6 (6.2)	3 (3.5)	9 (4.9)	0	0	0	7 (3.8)	4 (2.7)	11 (3.3)
2 - <12 years	7 (8.9)	6 (10.0)	13 (9.4)	26 (26.8)	23 (26.7)	49 (26.8)	0	0	0	33 (17.9)	29 (19.7)	62 (18.7)
12 - <18 years	6 (7.6)	0	6 (4.3)	17 (17.5)	9 (10.5)	26 (14.2)	0	0	0	23 (12.5)	9 (6.1)	32 (9.7)
≥18 years	65 (82.3)	53 (88.3)	118 (84.9)	48 (49.5)	51 (59.3)	99 (54.1)	8 (100.0)	1 (100.0)	9 (100.0)	121 (65.8)	105 (71.4)	226 (68.3)
18 - <45 years	9 (11.4)	11 (18.3)	20 (14.4)	10 (10.3)	19 (22.1)	29 (15.8)	4 (50.0)	0	4 (44.4)	23 (12.5)	30 (20.4)	53 (16.0)
45 - <65 years	18 (22.8)	9 (15.0)	27 (19.4)	16 (16.5)	19 (22.1)	35 (19.1)	1 (12.5)	1 (100.0)	2 (22.2)	35 (19.0)	29 (19.7)	64 (19.3)
≥65 years	38 (48.1)	33 (55.0)	71 (51.1)	22 (22.7)	13 (15.1)	35 (19.1)	3 (37.5)	0	3 (33.3)	63 (34.2)	46 (31.3)	109 (32.9)
Mean	53.6	56.0	54.6	32.5	31.6	32.1	55.8	64.0	56.7	42.5	41.8	42.2
SD	25.3	24.9	25.0	28.1	25.3	26.7	20.2	0.0	19.1	28.6	27.7	28.2
Range	1-90	0-94	0-94	0-84	1-80	0-84	33-85	64-64	33-85	0-90	0-94	0-94
Race												
White	67 (84.8)	54 (90.0)	121 (87.1)	74 (76.3)	68 (79.1)	142 (77.6)	6 (75.0)	1 (100.0)	7 (77.8)	147 (79.9)	123 (83.7)	270 (81.6)
Black	8 (10.1)	2 (3.3)	10 (7.2)	6 (6.2)	8 (9.3)	14 (7.7)	1 (12.5)	0	1 (11.1)	15 (8.2)	10 (6.8)	25 (7.6)
Asian	1 (1.3)	1 (1.7)	2 (1.4)	5 (5.2)	3 (3.5)	8 (4.4)	0	0	0	6 (3.3)	4 (2.7)	10 (3.0)
Other	3 (3.8)	3 (5.0)	6 (4.3)	12 (12.4)	7 (8.1)	19 (10.4)	1 (12.5)	0	1 (11.1)	16 (8.7)	10 (6.8)	26 (7.9)
Ethnicity												
Hispanic/Latino	3 (3.8)	2 (3.3)	5 (3.6)	15 (15.5)	13 (15.1)	28 (15.3)	1 (12.5)	0	1 (11.1)	19 (10.3)	15 (10.2)	34 (10.3)
Not Hispanic/Latino	76 (96.2)	58 (96.7)	134 (96.4)	82 (84.5)	72 (83.7)	154 (84.2)	7 (87.5)	1 (100.0)	8 (88.9)	165 (89.7)	131 (89.1)	296 (89.4)
Unspecified	0	0	0	0	1 (1.2)	1 (0.5)	0	0	0	0	1 (0.7)	1 (0.3)

Source: Study B1761026 aCSR In-text Table 3
Age is calculated as (Date of Informed Consent - Date of Birth)/365.25.
Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
APL=acute promyelocytic leukemia; SD=standard deviation.

Efficacy results: No efficacy evaluations were performed in this study.

Safety results

Extent of exposure Details showing the variability of extent of exposure are detailed in tables below:

Table 3: Extent of MYLOTARG exposure in patient population

	Monotherapy	Combination	Treatment for APL	Total
	n (%)			
Number of patients treated	**139**	**183**	**9**	**331**
Received only 1 dose:				
3 mg/m^2	10 (7.2)	96 (52.5)	0	106 (32.0)
6 mg/m^2	14 (10.1)	1 (0.5)	3 (33.3)	18 (5.4)
7.5 mg/m^2	1 (0.7)	0	0	1 (0.3)
9 mg/m^2	21 (15.1)	1 (0.5)	1 (11.1)	23 (6.9)
Other[a]	2 (1.4)	4 (2.2)	0	6 (1.8)
Received doses on 2 or more days:				
3 mg/m^2	33 (23.7)	76 (41.5)	0	109 (32.9)
6 mg/m^2	11 (7.9)	0	4 (44.4)	15 (4.5)
7.5 mg/m^2	4 (2.9)	0	0	4 (1.2)
9 mg/m^2	29 (20.9)	0	1 (11.1)	30 (9.1)
Other[a]	14 (10.1)	5 (2.7)	0	19 (5.7)

Table 4: Extent of MYLOTARG exposure in <18 years

	Monotherapy	Combination	Total
		n (%)	
Number of patients treated	**21**	**84**	**105**
Received only 1 dose:			
3 mg/m^2	2 (9.5)	47 (56.0)	49 (46.7)
6 mg/m^2	2 (9.5)	1 (1.2)	3 (2.9)
7.5 mg/m^2	1 (4.8)	0	1 (1.0)
9 mg/m^2	2 (9.5)	0	2 (1.9)
Other[a]	2 (9.5)	4 (4.8)	6 (5.7)
Received doses on 2 or more days:			
3 mg/m^2	5 (23.8)	30 (35.7)	35 (33.3)
6 mg/m^2	0	0	0
7.5 mg/m^2	3 (14.3)	0	3 (2.9)
9 mg/m^2	2 (9.5)	0	2 (1.9)
Other[a]	2 (9.5)	2 (2.4)	4 (3.8)

Source: Study B1761026 aCSR 14.4.1.1.1.
Patients that received more than 1 dose of Mylotarg, regardless of dosage, were only reported under 'Received doses on 2 or more days'.
Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
n=number of patients receiving dose.
a. Patients in the 'Other' category were either treated with a different dose than listed or for the 'Received doses on 2 or more days' were not treated with the same prescribed dose for all treatment days.

Adverse events (Grade 3-5 only)

Overall 315 (95.2%) AE were reported: 134 (96.4%), 172 (94.0%), and 9 (100.0%) patients in the monotherapy, combination, and treatment for APL groups, respectively.

- 38 (11.5%) patients (25 [18.0%], 11 [6.0%], and 2 [22.2%] in the monotherapy, combination, and treatment for APL groups, respectively) discontinued from study treatment and/or the study during the study period (first dose of investigational product to 60 days after the last dose of investigational product) due to AEs.
- SAEs were reported for 193 (58.3%) patients overall. No dose reductions occurred due to AEs.

All Causality Treatment Emergent AE (TEAE)

MAH states no unexpected TEAEs findings were observed based on the known AE profile of MYLOTARG and the complications of underlying disease.

In the monotherapy group, the most common TEAEs were Anaemia (54 [38.8%]), White blood cell (WBC) count decreased (52 [37.4%]), Platelet count decreased (50 [36.0%]), and Febrile neutropenia (44 [31.7%]).

In the combination therapy group, the most common AEs by PT were Anaemia (86 [47.0%]), Febrile neutropenia (69 [37.7%]), WBC count decreased (66 [36.1%]), Platelet count decreased (65 [35.5%]), and Neutrophil count decreased (57 [31.1%]).

In the treatment for APL group, the most common TEAEs by were Febrile neutropenia (7 [77.8%]) and Platelet count decreased (3 [33.3%]).

Table 5: Summary of TEAE (all causalities)

	Monotherapy n (%)	Combination n (%)	Treatment for APL n (%)	Total n (%)
Number (%) of Patients				
Patients evaluable for AEs	139	183	9	331
Number of AEs	704	1027	31	1762
Patients with AEs	134 (96.4)	172 (94.0)	9 (100.0)	315 (95.2)
Patients with SAEs	101 (72.7)	86 (47.0)	6 (66.7)	193 (58.3)
Patients with Grade 3 or 4 AEs	122 (87.8)	168 (91.8)	8 (88.9)	298 (90.0)
Patients with Grade 5 AEs	72 (51.8)	40 (21.9)	2 (22.2)	114 (34.4)
Patients discontinued due to AEs	25 (18.0)	11 (6.0)	2 (22.2)	38 (11.5)
Patients with dose reduced due to AEs	0	0	0	0
Patients with temporary discontinuation due to AEs	5 (3.6)	3 (1.6)	0	8 (2.4)

Includes all data after last dose of study drug.
Except for the 'Number of AEs' patients were counted only once per treatment in each row.
SAEs - according to the investigator's assessment.
Patients discontinued due to AEs based on the action taken or withdrawal from the study on the AE CRF.
Grading was according to CTCAE v4.03. Only AEs of Grade ≥3 were collected.
Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
MedDRA (v20.1) coding dictionary was applied.
AE=adverse event; APL=acute promyelocytic leukemia; CRF=case report form; CTCAE=common terminology criteria for adverse events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with AE; SAE=serious adverse event; v=version.

Paediatric Population

Table 6: Summary of All Causality TEAE in <18 years

System Organ Class	Preferred Term	Grade 3	Grade 4	Grade 5	Total
		n (%)			
Monotherapy (N=21)					
Any TEAE		**3 (14.3)**	**11 (52.4)**	**7 (33.3)**	**21 (100.0)**
Blood and lymphatic system disorders		**14 (66.7)**	**3 (14.3)**	**0 (0.0)**	**17 (81.0)**
	Anaemia	10 (47.6)	0 (0.0)	0 (0.0)	10 (47.6)
	Febrile neutropenia	9 (42.9)	1 (4.8)	0 (0.0)	10 (47.6)
General disorders and administration site conditions		**1 (4.8)**	**0 (0.0)**	**6 (28.6)**	**7 (33.3)**
	Disease progression	0 (0.0)	0 (0.0)	5 (23.8)	5 (23.8)
	Pyrexia	3 (14.3)	0 (0.0)	0 (0.0)	3 (14.3)
Infections and infestations		**9 (42.9)**	**0 (0.0)**	**0 (0.0)**	**9 (42.9)**
	Device related infection	4 (19.0)	0 (0.0)	0 (0.0)	4 (19.0)
Investigations		**1 (4.8)**	**13 (61.9)**	**0 (0.0)**	**14 (66.7)**
	Lymphocyte count decreased	2 (9.5)	1 (4.8)	0 (0.0)	3 (14.3)
	Neutrophil count decreased	1 (4.8)	4 (19.0)	0 (0.0)	5 (23.8)
	Platelet count decreased	2 (9.5)	9 (42.9)	0 (0.0)	11 (52.4)
	White blood cell count decreased	1 (4.8)	6 (28.6)	0 (0.0)	7 (33.3)
Metabolism and nutrition disorders		**5 (23.8)**	**3 (14.3)**	**0 (0.0)**	**8 (38.1)**
	Hypokalaemia	4 (19.0)	3 (14.3)	0 (0.0)	7 (33.3)
	Hypophosphataemia	3 (14.3)	0 (0.0)	0 (0.0)	3 (14.3)
Combination Therapy (N=84)					
Any TEAE		**14 (16.7)**	**50 (59.5)**	**14 (16.7)**	**78 (92.9)**
Blood and lymphatic system disorders		**46 (54.8)**	**11 (13.1)**	**0 (0.0)**	**57 (67.9)**
	Anaemia	37 (44.0)	4 (4.8)	0 (0.0)	41 (48.8)
	Febrile neutropenia	30 (35.7)	3 (3.6)	0 (0.0)	33 (39.3)
General disorders and administration site conditions		**14 (16.7)**	**5 (6.0)**	**2 (2.4)**	**21 (25.0)**
	Pyrexia	8 (9.5)	1 (1.2)	0 (0.0)	9 (10.7)
Infections and infestations		**25 (29.8)**	**6 (7.1)**	**3 (3.6)**	**34 (40.5)**
	Sepsis	4 (4.8)	3 (3.6)	2 (2.4)	9 (10.7)
Investigations		**11 (13.1)**	**51 (60.7)**	**0 (0.0)**	**62 (73.8)**
	Alanine aminotransferase increased	8 (9.5)	2 (2.4)	0 (0.0)	10 (11.9)
	Aspartate aminotransferase increased	7 (8.3)	2 (2.4)	0 (0.0)	9 (10.7)
	Lymphocyte count decreased	5 (6.0)	21 (25.0)	0 (0.0)	26 (31.0)

System Organ Class	Preferred Term	Grade 3	Grade 4	Grade 5	Total
		n (%)			
	Neutrophil count decreased	3 (3.6)	38 (45.2)	0 (0.0)	41 (48.8)
	Platelet count decreased	5 (6.0)	42 (50.0)	0 (0.0)	47 (56.0)
	White blood cell count decreased	4 (4.8)	39 (46.4)	0 (0.0)	43 (51.2)
Metabolism and nutrition disorders		**23 (27.4)**	**13 (15.5)**	**0 (0.0)**	**36 (42.9)**
	Decreased appetite	10 (11.9)	0 (0.0)	0 (0.0)	10 (11.9)
	Hyperglycaemia	10 (11.9)	2 (2.4)	0 (0.0)	12 (14.3)
	Hypokalaemia	13 (15.5)	12 (14.3)	0 (0.0)	25 (29.8)
Respiratory, thoracic and mediastinal disorders		**10 (11.9)**	**5 (6.0)**	**7 (8.3)**	**22 (26.2)**
	Hypoxia	9 (10.7)	3 (3.6)	0 (0.0)	12 (14.3)

Source: Study B1761026 aCSR Table 14.3.1.2.9.2.
Includes all data after last dose of study drug.
Patients are counted only once in each row at the maximum CTCAE grade.
Grading was assessed according to CTCAE v4.03. Only TEAEs of Grade ≥3 severity were collected.
Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
MedDRA (v20.1) coding dictionary was applied.
TEAE=treatment-emergent adverse event; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; N=number of patients; n=number of patients with TEAE; v=version

In the paediatric population subgroup of <18 years of age, it is reported by MAH that no unexpected TEAE findings were noted based on the known AE profile of MYLOTARG plus the complications of underlying disease and consistent with safety data from adults in this study.

Monotherapy group: Most commonly reported were Platelet count decreased (11 [52.4%]), Anaemia (10 [47.6%]), Febrile neutropenia (10 [47.6%]), WBC decreased (7 [33.3%]), and Hypokalaemia (7 [33.3%]).

Combination group: Most commonly reported were Platelet count decreased (47 [56.0%]), WBC count decreased (43 [51.2%]), Anaemia (41 [48.8%]), Neutrophil count (41 [48.8%]), Febrile neutropenia (33 [39.3%]), Lymphocyte count decreased (26 [31.0%]), Hypokalaemia (25 [29.8%]), Hypoxia (12 [14.3%]), Hyperglycaemia (12 [14.3%]) and Aspartate aminotransferase (AST) increased (10 [11.9%]).

There were no paediatric patients in treatment for APL and it is reported by MAH that rates of most common AEs were generally similar to adult population in the monotherapy and combination therapy

groups. Therefore, the remainder of data is presented by MAH as the total population (adults and children):

Treatment-Related Adverse Events (TRAE)

Table 7: Summary of TRAE

	Monotherapy	Combination	Treatment for APL	Total
	n (%)			
Number (%) of patients				
Patients evaluable for AEs	139	183	9	331
Number of AEs	288	369	15	672
Patients with AEs	84 (60.4)	102 (55.7)	7 (77.8)	193 (58.3)
Patients with SAEs	29 (20.9)	39 (21.3)	4 (44.4)	72 (21.8)
Patients with Grade 3 or 4 AEs	83 (59.7)	101 (55.2)	7 (77.8)	191 (57.7)
Patients with Grade 5 AEs	6 (4.3)	9 (4.9)	0	15 (4.5)
Patients discontinued due to AEs	8 (5.8)	6 (3.3)	0	14 (4.2)
Patients with dose reduced due to AEs	0	0	0	0
Patients with temporary discontinuation due to AEs	2 (1.4)	2 (1.1)	0	4 (1.2)

Source: Study B1761026 aCSR In-text Table 9.
Includes all data after last dose of study drug.
Except for the 'Number of adverse events' patients are counted only once per treatment in each row.
SAEs - according to the investigator's assessment.
Patients discontinued due to AEs based on the action taken or withdrawal from the study on the AE CRF.
Grading was assessed according to CTCAE v4.03. Only AEs of Grade ≥3 severity were collected.
Patients were allowed to re-enroll in the study. Such patients are summarized according to each enrollment treatment.
MedDRA (v20.1) coding dictionary was applied.
AE=adverse event; APL=acute promyelocytic leukemia; CRF=case report form; CTCAE=Common Terminology Criteria for Adverse Events; MedDRA=Medical Dictionary for Regulatory Activities; n=number of patients with AE; SAE=serious adverse event; v=version.

TRAEs were reported for 193 (58.3%) patients overall: 84 (60.4%), 102 (55.7%), and 7 (77.8%) patients in the monotherapy, combination, and treatment for APL groups, respectively. Treatment-related SAEs were reported for 72 (21.8%) patients. In the monotherapy group, the most common TRAEs were WBC count decreased (44 [31.7%]), Platelet count decreased (35 [25.2%]), and Anaemia (34 [24.5%]). In the combination therapy group, the most common TRAEs were Anaemia (42 [23.0%]) and Febrile neutropenia (35 [19.1%]). In the treatment for APL group, the most common TRAEs were Febrile neutropenia (6 [66.7%]) and Platelet count decreased (3 [33.3%]).

Deaths

114 (34.4%) patients died within the reporting period, with 72 (51.8%) in the monotherapy group, 40 (21.9%) combination therapy group, and 2 (22.2%) patients in the treatment for APL group. In the monotherapy group, the most common Grade 5 AEs were Disease progression (31 [22.3%] patients), AML (16 [11.5%] patients), and Sepsis (7 [5.0%] patients). In the combination group, the most common Grade 5 AEs were Disease progression (14 [7.7%] patients) and Respiratory failure (5 [2.7%] patients). In the treatment for APL group, the Grade 5 AEs were Disease progression and Haemorrhage intracranial, 1 (11.1%) patient each.

Within the paediatric subpopulation, 21 (20.0%) patients died: 7 (33.3%) patients in the monotherapy group and 14 (16.7%) patients in the combination therapy group. In the monotherapy group, the most common Grade 5 AEs were Disease progression (5 [23.8%] patients). In the combination group, the most common Grade 5 AEs were Respiratory failure (3 [3.6%] patients), Disease progression, Sepsis, and Pulmonary haemorrhage (2 [2.4%] patients each).

Grade 5 AEs assessed by the investigator as treatment-related occurred in 15 (4.5%) patients: 6 (4.3%) and 9 (4.9%) patients in the monotherapy and combination groups, respectively. In the monotherapy group, treatment-related Grade 5 AEs were Sepsis (4 [2.9%] patients), Febrile neutropenia (2 [1.4%] patients), and Disease progression (1 [0.7%] patient). In the combination group, all treatment-related Grade 5 AEs were reported in 1 patient each. No treatment-related Grade 5 AEs were reported in the treatment for APL group.

Serious Adverse Events

- All-causality SAEs were reported for a total of 193 (58.3%) patients: 101 (72.7%), 86 (47.0%), and 6 (66.7%) patients in the monotherapy, combination, and treatment for APL groups, respectively.
- Treatment-related SAEs were reported for a total of 72 (21.8%) patients: 29 (20.9%), 39 (21.3%), and 4 (44.4%) patients in the monotherapy, combination, and treatment for APL groups, respectively.
- In the monotherapy group, the most common treatment-related SAEs were Febrile neutropenia (14 [10.1%] patients), Sepsis (5 [3.6%] patients), and Platelet count decreased (3 [2.2%] patients).
- In the combination group, the most common treatment-related SAEs were Febrile neutropenia (11 [6.0%] patients), Septic shock and Sinusitis (3 [1.6%] patients each).
- In the treatment for APL group, the SAEs were all Grade 3 Febrile neutropenia (4 [44.4%] patients).

Permanent Discontinuations Due to Adverse Events

38 (11.5%) patients, with 25 (18.0%) monotherapy group; 11 (6.0%) combination therapy group and 2 [22.2%] APL groups discontinued from study treatment and/or the study during the study period due to AEs. Disease progression, myelosuppression-related PTs such as Febrile neutropenia, Haemoglobin decreased, and Platelet count decreased; hepatotoxicity-related PTs such as Alanine aminotransferase increased, Aspartate aminotransferase increased, and Blood bilirubin increased; and infection-related PTs such as Sepsis were amongst most frequent. MAH states this is consistent with the known safety profile of MYLOTARG as well as the complications from the underlying disease.

Adverse Events of Special Interest

Hepatotoxicity (hepatic venoocclusive disease [VOD]/sinusoidal obstruction syndrome [SOS])

In the monotherapy group, 1 (0.7%) patient each had VOD and Drug-induced liver injury (both Grade 3 in severity). In the combination therapy group, 2 (1.1%) patients had Venoocclusive liver disease (1 Grade 3 and 1 Grade 5), and 1 (0.5%) patient had VOD (Grade 4). All of these patients were paediatric patients. One (1 [1.2%]) paediatric patient in the combination group had a Grade 5 event of Venoocclusive liver disease, and 1 (1.2%]) patient had a Grade 3 event of Venoocclusive liver disease. No patients in the treatment for APL group had hepatotoxicity.

Myelosuppression

Monotherapy group Most frequent were WBC count decreased (45 [38.1%] adult patients; 7 [33.3%] paediatric patients), Platelet count decreased (39 [33.1%] adult patients; 11 [52.4%] paediatric patients), Febrile neutropenia (34 [28.8%] adult patients; 10 [47.6%] paediatric patients), and Lymphocyte count decreased (26 [22.0%] adult patients; 3 [14.3%] paediatric patients). A total of 3 (2.5%) Grade 5 AEs, all Febrile neutropenia and all in adult patients, were reported.

Combination therapy group Most frequent were Febrile neutropenia (36 [36.4%] adult patients; 33 [39.3%] paediatric patients), WBC count decreased (23 [23.2%] adult patients; 43 [51.2%] paediatric patients), Platelet count decreased (18 [18.2%] adult patients; 47 [56.0%] paediatric patients), Neutrophil count decreased (16 [16.2%] adult patients; 41 [48.8%] paediatric patients), and Lymphocyte count decreased (26 [26.3%] adult patients; 26 [31.0%] paediatric patients).

There were no paediatric patients in treatment for APL group.

Severe (Grade ≥3) AE and/or Serious Infections

Monotherapy group

- 33 (28.0%) adult patients had Grade ≥3 AEs of SOC Infections and infestations (Grade 3: 16 [13.6%] patients, Grade 4: 7 [5.9%] patients, and Grade 5: 10 [8.5%] patients).
- In the paediatric population (<18 years), all AEs were Grade 3 in severity
- Most frequent were Infections and infestations AEs were Sepsis (16 [13.6%] adult patients), Pneumonia (10 [8.5%] adult patients), Bacteraemia (4 [3.4%] adult patients), and Device-related infection (4 [2.9%] patients).
- SAEs reported were Sepsis (5 [3.6%]), Device-related infection (1 [0.7%]), and Eye infection (1 [0.7%]).
- In the paediatric subgroup, the most commonly reported AE was Device-related infection in 4 (19%) patients. Other AEs reported in 1 (4.8%) paediatric patient each were Appendicitis, Bacteraemia, Eye infection, Neutropenic sepsis, Respiratory tract infection viral, Sinusitis, Stoma site infection, Systemic candida, and Viraemia.

Combination therapy group:

- 42 (42.4%) adult patients had Grade ≥3 AEs of Infections and infestations (Grade 3: 27 [27.3%] patients, Grade 4: 13 [13.1%] patients, and Grade 5: 2 [2.0%] patients. The most frequently reported Infections and infestations AEs were Sepsis (5 [5.1%] adult patients), Bacteraemia (8 [8.1%] adult patients), Lung infection (7 [7.1%] adult patients, and Device-related infection (3 [3.0%] adult patients).
- SAEs reported in more than 1 patient were Septic shock (3 [1.6%]) and Sinusitis (3 [1.6%]). Additional SAEs reported in 1 (0.5%) patient each were Cellulitis, Device related infection, Lung infection, Meningitis, Pneumonia fungal, and Sepsis.
- Paediatric subgroup, a total of 34 (40.5%) patients had Grade ≥3 AEs (Grade 3: 25 [29.8%]; Grade 4: 6 [7.1%]; Grade 5: 3 [3.6%]). The most frequently reported Infections and infestations AEs were Sepsis in 9 (10.7%) patients, Sinusitis in 5 (6.0%) patients, and Device-related infections in 5 (6.0%) patients.

There were no paediatric patients in APL group.

Haemorrhage

In the monotherapy group, 2 (1.4%) patients each had Gastrointestinal and Mouth haemorrhage, and 1 (0.7%) patient each had Haemorrhage intracranial and Haemorrhage. In the combination therapy group, 3 (1.6%) had Pulmonary haemorrhage, 2 (1.1%) had Mouth haemorrhage, Upper gastrointestinal haemorrhage, and Haemorrhage intracranial; and 1 (0.5%) patient each had Urogenital haemorrhage and Pharyngeal haemorrhage.

In the paediatric subgroup, 2 (2.4%) patients had Upper gastrointestinal haemorrhage, 1 (1.2%) patient each had Mouth haemorrhage, and Pharyngeal haemorrhage. 3 [3.6%]) patients had Pulmonary haemorrhage (1 [1.2%] Grade 3 and 2 [2.4%] Grade 5). One (1 [1.2%]) patient had Grade 5 Haemorrhage intracranial. All the paediatric patients were from the combination therapy group.

For APL group, 1 (11.1%) patient had Haemorrhage intracranial.

Tumour Lysis Syndrome Tumour lysis syndrome (TLS) was reported in 3 (2.2%) patients in the monotherapy group (Grade 3: 1 [0.7%] patient and Grade 4: 2 [1.4%] patients). In the paediatric subgroup, 1 (4.8%) patient had Grade 3 TLS. In the combination therapy, 3 (1.6%) patients had TLS (all events of TLS in the combination group were Grade 3 severity). In the paediatric subgroup, 2 (2.4%) patients had Grade 3 TLS. No patients in the treatment for APL group had TLS.

Infusion-Related Reactions

Infusion-related reactions were reported in 5 (3.6%) patients in the monotherapy group with 1 (4.8%) patient in the paediatric subgroup. In the combination therapy group, 3 (1.6%) patients had Infusion-related reactions, none of whom were in the paediatric subgroup. All infusion-related reactions were Grade 3 in severity. No patients in the treatment for APL group had an Infusion-related reaction. Anaphylactic reaction (Grade 4) was reported in 1 (0.7%) patient in the monotherapy group.

Renal Toxicity In the monotherapy group, 1 (0.7%) patient reported Grade 5 event of Renal failure and in the combination group, 1 (0.5%) patient reported Grade 3 Renal failure. Acute kidney injury was reported by 2 (1.4%) patients in the monotherapy group (1 [0.7%] patient each reported Grade 3 and Grade 4 Acute kidney injury) and 3 (1.6%) patients in the combination group (1 [0.5%] patient reported Grade 3 and 2 [1.1%] patients reported Grade 4 Acute kidney injury.

Neurotoxicity One (1) (0.5%) patient in the combination group reported Grade 3 Neuropathy peripheral.

Second Primary Malignancy In the monotherapy group, 2 (1.4%) patients reported Chloroma (1 [0.7%] each Grade 3 and Grade 5 [Patient 10461004]), 2 (1.4%) patients reported Neoplasm progression (both Grade 5), and 1 (0.7%) patient reported Neoplasm malignant (Grade 5). In the combination group, Infected neoplasm and Tumour pain were each reported by 1 (0.5%) patient (both Grade 3). No reports within the APL group. It is reported by MAH that PTs do not appear to reflect secondary malignancies.

2.3.3. Discussion on clinical aspects

With regards to the safety conclusions the MAH states:

Patients with Relapsed/Refractory AML, APL, and MDS have a significant unmet medical need. MYLOTARG given in this setting appeared to be generally tolerable with a manageable safety profile. The observed AEs were consistent with the known safety profile of MYLOTARG and complications of underlying disease, and there were no unexpected major safety findings in this study population. All-causality AEs in >30% of patients (by treatment group) were Anaemia, WBC count decreased, Platelet count decreased, Neutrophil count decreased, and Febrile neutropenia. The frequency and types of other significant AEs such as VOD, myelosuppression, infection, haemorrhage, including Grade 5 AEs within these categories, were consistent with the known safety profile of MYLOTARG. In the paediatric population subgroup <18 years of age, no unexpected AE findings were observed based on the known safety profile of MYLOTARG and complications of underlying disease. In the monotherapy group, the most common all-causality Grade 3-5 AEs were ALT increased, Platelet count decreased, Anaemia, Febrile neutropenia, and WBC count decreased. In the combination therapy group, the most common

Grade 3-5 AEs by PT were Platelet count decreased, WBC count increased, Anaemia, Neutrophil count, Febrile neutropenia, Lymphocyte count decreased, Hypokalaemia, and AST increased.

The MAH states that study B1761026 met its primary objective of providing access to MYLOTARG for the treatment of paediatric and adult patients with relapsed or refractory CD33-positive AML (including APL) or MDS who were good candidates to potentially derive clinical benefit from a CD33-directed therapy, and who had exhausted other appropriate and reasonable treatment options. An assessment of benefit could not be made, as efficacy and post-MYLOTARG hematopoietic stem cell transplantation outcomes were not collected as a part of this expanded access study. The safety risks of MYLOTARG treatment, used in a broad range of doses and combination regimens were acceptable for this patient population with serious, life-threatening disease. Safety risks were generally consistent between the paediatric population and the entire safety population (adult and paediatric patients). No new safety signals were observed, and the AEs of MYLOTARG were consistent with its known safety profile.

The SmPC states with respect to the paediatric population specifically:

4. 2 Posology Paediatric population

The safety and efficacy of MYLOTARG in patients less than 15 years of age has not been established. Currently available data are described in sections 4.8, 5.1, and 5.2 but no recommendation on a posology can be made.

4. 8 Undesirable effects: Paediatric population

The safety and efficacy of MYLOTARG in children and adolescents below the age of 15 years has not been established (see section 4.2).

In the completed randomised paediatric Phase 3 Study AAML0531 (see section 5.1) of gemtuzumab ozogamicin combined with intensive first-line therapy in newly diagnosed children, and young adults with de novo AML aged 0 to 29 years, the safety profile was similar with that observed in the other studies of gemtuzumab ozogamicin combined with intensive chemotherapy in adult patients with de novo AML. However, the optimal dose of gemtuzumab ozogamicin for paediatric patients was not established, since in Study AAML0531 during the second intensification period, a larger proportion of patients in the gemtuzumab ozogamicin arm experienced prolonged neutrophil recovery time (> 59 days) as compared with the comparator arm (12.0% versus 6.3%), and more patients died during remission (4.2% versus 2.4%).

5.1 Pharmodynamic properties

In a randomised study (COG AAML0531) that evaluated standard chemotherapy alone or combined with MYLOTARG in 1,022 newly diagnosed children (94.3% of patients < 18 years of age), and young adults (5.7% of patients); median age was 9.7 years (range: 0.003-29.8 years), patients with de novo AML were randomly assigned to either standard 5-course chemotherapy alone or to the same chemotherapy with 2 doses of MYLOTARG (3 mg/m^2/dose) administered once in induction Course 1 and once in intensification Course 2. The study demonstrated that addition of MYLOTARG to intensive chemotherapy improved EFS (3 years: 53.1% versus 46.9%; HR 0.83; 95% CI: 0.70, 0.99; p=0.04) in de novo AML owing to a reduced relapse risk, with a trend towards longer OS in the MYLOTARG arm which was not statistically significant (3 years: 69.4% versus 65.4%; HR 0.91; 95% CI: 0.74, 1.13; p=0.39). However, it was also found that increased toxicity (post-remission toxic mortality) was observed in patients with low-risk AML which was attributed to the prolonged neutropenia that occurred after receiving gemtuzumab ozogamicin during intensification Course 2 (see sections 4.2 and 4.8). Thus, the optimal dose of gemtuzumab ozogamicin for paediatric patients was not established (see section 4.2).

5.2 PK properties

The results of the population modelling showed that the PK behaviour of gemtuzumab ozogamicin (hP67.6 antibody and unconjugated calicheamicin) is similar between adult and paediatric AML patients following the 9 mg/m^2 dosing regimen.

Rapporteurs Comments

This study fulfils its primary aim of providing access to MYLOTARG to patients with life threatening disease who have exhausted all clinical treatments and therefore have a significant unmet need. This is an expanded access study on compassionate grounds and therefore cannot be expected to fulfil the criteria of benefit: risk clinical trials and the data can only be contextualised within those boundaries in a descriptive manner. This study is not mentioned within the SmPC for Mylotarg. The majority of information detailed in SmPC is from an adult study (ALFA-0701) and post marketing measures. One Phase 3 study (Study AAML0531) including paediatric subjects is detailed in SmPC (as above). This product is licenced only in patients older than 15 years. Within the SmPC it is stated regarding the paediatric population that 'the *safety profile was similar with that observed in the other studies of gemtuzumab ozogamicin combined with intensive chemotherapy in adult patients with de novo AML'.* Overall the following comments are made:

Study design: The enrolment and re-enrolment is not clear in terms of how these patients were treated with respect to treatment assignation. Both treatments and study population are very heterogenous with 3 broad treatment arms, with variable dosing of MYLOTARG, different drugs regimes used in populations with differing pathologies. There were deviations from protocol detailed within abbreviated Case Study Report (aCSR).

Safety evaluations are limited as only grade 3-5 events were captured for all patients receiving at least 1 dose of MYLOTARG. Laboratory parameters themselves were not recorded and only captured as part of a Grade 3-5 AE.

Safety data Although the MAH states that some of the treatment related effects were thought by investigator to be attributable to MYLOTARG, this would have been challenging to determine in the context of confounding factors such chemotherapy and underlying disease for some of the AEs.

MAH stated that there is no overall difference between adult and paediatric data for 'deaths, serious adverse events and temporary discontinuation due to AE' therefore these data were not presented by age sub groups. As these data were not presented by age subgroups it is difficult to draw conclusions exclusively with respect to the licensed paediatric population.

Exposure to MYLOTARG was very variable with patients receiving 1 or more doses and dose levels up to 9 mg/m^2.

Within the SmPC, AEs are described in tabular form (Table 5 [combination study] and 6 [monotherapy study], Section 4.8) as all grades of AEs or grade 3-4 therefore making a direct comparison between this study and those adult studies described in SmPC somewhat challenging.

Overall 95.2 % AEs were reported and commonly included anaemia, reduction in WBC, platelets, neutrophils and febrile neutropenia. These AEs are included within the Mylotarg SmPC. The MAH states that no unexpected safety AEs and no unexpected TAEs were noted.

Within the paediatric population, commonly reported Grade 3-5 TEAEs were decreased Platelet Count, Anaemia, Febrile neutropenia, WBC reduction, and Hypokalaemia (*monotherapy group*); platelet and WBC reduction, Anaemia, Neutrophil count reduction, Febrile neutropenia, Lymphocyte count decreased, Hypokalaemia, Hypoxia, Hyperglycaemia and Aspartate aminotransferase (AST) increased (*combination group*). It is reported by MAH that no unexpected TEAEs were noted based upon safety profile of disease and complication of disease and that safety data were consistent with adult studies. Hypoxia and hypokalaemia are not mentioned in SmPC for Mylotarg but, however, are mentioned in FDA label. The way in which laboratory parameters were collected in this study do not allow a robust conclusion on these observed AEs to warrant a change to SmPC. However, it is recommended that hypoxia and hypokalaemia should be further assessed and reported in following PV activities for this drug.

In this study, overall, most common TEAEs included anaemia, reduced WBC, Platelet reduction, febrile neutropenia (*monotherapy group*); anaemia, febrile neutropenia, WBC reduction, platelet and neutrophil count reduction (*combination group*) and febrile neutropenia and platelet reduction (*APL treatment group*). SmPC (Section 4.8) states that selected data considered most important in understanding the drug's safety profile, including TEAEs of haemorrhages, VOD, and severe infections and all determined to be ADRs. Although AEs of special interest do occur including VOD and haemorrhage, in this study haemorrhage is much less common with the exception of the APL group, than described in the SmPC. All the paediatric patients with haemorrhage were from the combination therapy group.

Febrile neutropenia, although mentioned in the monotherapy table 6 of section 4.8 of SmPC, is not described within the combination group of the SmPC and is also a common feature of the combination arm of this study.

Treatment-related AEs, overall in the study population, (AEs that the investigator believed had at least a reasonable possibility of being related to MYLOTARG) were reported for 58.3% patients overall:60.4%, 55.7%, and 77.8% patients in the monotherapy, combination, and treatment for APL groups, respectively. Treatment-related SAEs were reported for 21.8% patients. Common TRAEs were similar to TEAEs (anaemia, thrombocytopenia, febrile neutropenia, leukopenia). Most common TRAE were decreased WBC, platelet count and Anaemia (*monotherapy group*); Anaemia and Febrile neutropenia (*combination group*); Febrile neutropenia and Platelet count decreases (*APL treatment group,*). There are no paediatric patients in APL treatment group. It is difficult to determine how these AEs could be solely attributed to MYLOTARG due to confounding factors of underlying disease and treatment.

Overall in the study population, common treatment related SAEs were febrile neutropenia, sepsis and reduced platelet (*monotherapy group*) ; febrile neutropenia, septic shock and sinusitis (*combination group*) and febrile neutropenia (APL treatment group) Clinically relevant SAEs described in the SmPC for the adult studies are infusion related reactions (2.5%), thrombocytopenia (21.7%), and neutropenia (34.3%) for the monotherapy group and hepatotoxicity, including VOD/SOS (3.8%), haemorrhage (9.9%), severe infection (41.2%), and tumour lysis syndrome (1.5%) for the combination group. In the SmPC in monotherapy adult studies the most common adverse reactions (> 30%) included pyrexia, nausea, infection, chills, haemorrhage, vomiting, thrombocytopenia, fatigue, headache, stomatitis, diarrhoea, abdominal pain, and neutropenia; the most common adverse reactions (> 30%) in the combination therapy adult study were haemorrhage and infection. Keeping in mind that AEs tables within the SmPC (Section 4.8) describe either all grades of AEs or grade 3-4 and this study does not capture the totality of AEs, a direct comparison between safety findings of this study and those already described in SmPC cannot be conducted.

Deaths Overall 34.4 % of patients died within the reporting period and 20% in paediatric population. Although a large number it is not surprising given the nature of population in the study. Within the paediatric subpopulation, 21 (20.0%) patients died: 7 (33.3%) patients in the monotherapy group and 14 (16.7%) patients in the combination therapy group. In the monotherapy group, the most common Grade 5 AEs were Disease progression (5 [23.8%] patients). In the combination group, the most common Grade 5 AEs were Respiratory failure (3 [3.6%] patients), Disease progression, Sepsis, and Pulmonary haemorrhage (2 [2.4%] patients each. Respiratory failure is not mentioned specifically within the SmPC, and although the MAH does not recognise it as a TRAE, respiratory failure is defined as a TEAE within the abbreviated clinical summary report. Clarity is sought from the MAH as to whether the respiratory failure seen in the paediatric population was thought to be treatment related. Multiorgan failure is mentioned in the SmPC.

Discontinuations due to AE Overall 11.5% patients discontinued and MAH states that the reasons were consistent within known safety profile of MYLOTARG and underlying disease. Frequently observed PTs included Disease progression, myelosuppression-related PTs such as Febrile neutropenia, Haemoglobin decreased, and Platelet count decreased; hepatotoxicity-related PTs such as Alanine aminotransferase increased, Aspartate aminotransferase increased, and Blood bilirubin increased; and infection-related PTs such as Sepsis.

In the SmPC it states that the most frequent (≥ 1%) adverse reactions that led to permanent discontinuation in monotherapy studies were infection, haemorrhage, multi-organ failure, and VOD. In the SmPC the most frequent (≥ 1%) adverse reactions that led to permanent discontinuation in the combination therapy study were thrombocytopenia, VOD, haemorrhage and infection and in the monotherapy, studies were infection, haemorrhage, multi-organ failure, and VOD. These are differences noted in discontinuation, however, it is difficult to make direct comparisons with SmPC-included data and this more complex treatment population and therefore no changes to the SmPC wording is currently proposed.

Significant adverse events included hepatotoxicity (VOD, SOS). All hepatotoxic (VOD) patients were from the paediatric subgroup and frequency ranged for 0.7-1.2 % which appears overall to be less than stated in the SmPC, however it is difficult to make a direct numerical comparison. Similarly, this is the case for haemorrhages with the exception of the APL group where there were no paediatric patients. As a trend, paediatric patients were more affected by myelosuppression compared to adult patients. In the paediatric subgroup, 1 (4.8%) patient had Grade 3 TLS in monotherapy and combination therapy, 3 (1.6%) patients had TLS (Grade 3 severity). In the paediatric subgroup, the most commonly reported AE of serious infection was Device-related infection (monotherapy) and sepsis, sinusitis and device related infection (combination therapy). Overall these significant SAEs as well as infusion related events are detailed within the current SmPC adult studies.

Renal toxicity, neurotoxicity, second primary malignancy as rare adverse events were found in this study but are not described within the clinical overview report as TRAEs or TEAEs; equally they are not described within the SmPC. It is not clear if these are adult or paediatric patients.

3. Rapporteur's overall conclusion and recommendation

Overall the data presented in this expanded access study are generally consistent with the known safety profile of Mylotarg as well as those of the underlying disease. Febrile neutropenia, although mentioned in the monotherapy adult study only (Section 4.8, table 6) of SmPC, is described here in the combination arm of this study. As discussed this maybe reflective of the fact that only selected AEs were included within Table 5 (*combination therapy*) of SmPC and this is a study in a very complex and heterogenous treatment population compared to the licensed indication. Hypoxia and hyperkalaemia are seen in paediatric population; and rare events of second primary malignancy, neurotoxicity, renal failure do occur, however it is unclear if these were treatment related and whether they occurred in adult or paediatric patients. Respiratory failure is mentioned as a cause of death but the MAH is asked to clarify whether this was related to treatment or not.

Overall, the rapporteur considers that due to the study limitations, changes to the SmPC paediatric related safety information based on this study for MYLOTARG are not proposed at this time.

☐ **Fulfilled:**

☒ **Not fulfilled:**

Based on the data submitted, the MAH should provide additional clarifications requested below as part of this procedure. (see section "Additional clarification requested")

☒ **Not fulfilled:**

4. Additional clarification requested

Based on the data submitted, the MAH should address the following questions as part of this procedure:

The MAH should provide clarification on whether the deaths relating to respiratory failure in children were related to treatment with MYLOTARG?

Renal toxicity, neurotoxicity and second primary malignancy as rare adverse events were found in this study. The MAH should clarify if these are treatment related events and if they occur in adults or paediatric patients?

The timetable is a 30 day response timetable without clock stop.

MAH responses to Request for supplementary information

MAH RESPONSE

For this expanded access study, only Grade 3-5 adverse events (AEs) and Grade 3-5 laboratory results that met Grade 3-5 criteria were captured as AEs and reported on the AE Case Report Form (CRF). AEs were reported for 315 (95.2%) patients overall: 134 (96.4%), 172 (94.0%), and 9 (100.0%) patients in the monotherapy, combination, and treatment for acute promyelocytic leukaemia (APL) groups, respectively (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2).

Deaths of patients in the study were not collected on a separate CRF; however, Grade 5 AEs were collected on the AE CRF. All deaths were reported if they occurred during the SAE reporting period (from the time the patient had taken at least 1 dose of protocol treatment through 60 calendar days after the last administration of Mylotarg) (Module 5.3.5.4 B1761026 CSR).

All-causality Grade 5 AEs were reported for 7 (33.3%) and 14 (16.7%) paediatric patients in the monotherapy and combination groups, respectively. No paediatric patients were included in the acute promyelocytic leukaemia (APL) group. More than 1 Grade 5 AE could have been reported per patient. In the monotherapy group, the most common Grade 5 AEs for paediatric patients were Disease progression (5 [23.8%] patients), Cardiac arrest, Multiple organ dysfunction syndrome, Chloroma, and Respiratory failure (each 1 [4.8%] patients). In the combination group, the most common Grade 5 AEs for paediatric patients were Respiratory failure (3 [3.6%) patients), Pulmonary haemorrhage, Sepsis, and Disease progression (each 2 [2.4%] patients) (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2). Narratives were written for all AEs leading to death (Module 5.3.5.4 B1761026 CSR Section 14.3.3).

Respiratory Failure

Paediatric patients (in the monotherapy group), (in the combination treatment group) experienced Grade 5 respiratory failure. (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7). Of the four reported cases, patient had an event of respiratory failure in the course of disease progression that was considered to be possibly related to Mylotarg by the investigator, however considered not related by the sponsor. Summaries of each of the events are listed below:

Patient is an 11 year old male patient with relapsed AML who received Mylotarg as a single agent on 07Aug2016. The patient was transferred from an outside institution with the inability to extubate him. At the time of transfer on 06Aug2016 the patient was stable on the ventilator, awake and alert with blood counts showing White blood cell count (WBC) of 7580 and 86% circulating blasts.

Physical exam was remarkable for decreased breath sounds on the left and massive hepatosplenomegaly. His WBC decreased as did his percentage of circulating blasts but his lung disease persisted on the left side. WBC dropped from 6350 with 87% blasts to 0.800 with 68% blasts on 10Aug2016. A CT of the head/chest/abdomen on 10Aug2016 showed a large chloroma in the left frontal brain and in the brain stem, several in the abdomen (liver and kidneys) and a very large one in

the left chest with pleural effusion. After reviewing the CT findings, Mylotarg was stopped and the patient died on 10Aug2016. The investigator and company assessed that the events of respiratory failure, asystole, left lung pleural effusion, left frontal lobe chloroma, brainstem chloroma and left chest chloroma as unrelated to Mylotarg (Module 5.3.5.4 B1761026 CSR Section 14.3.3.1).

Patient is a 12 year old female with relapsed/refractory AML who was treated with fludarabine and cytarabine from 16Jun2017 to 20Jun2017 with Mylotarg on 17Jun2017 (Day2). On 17Jun2017, prior to receiving Mylotarg, the patient had new respiratory symptoms with a possible pneumonia and small pleural effusion on X-ray. Subsequent imaging showed worsening pleural effusions, requiring a right thoracentesis. The etiology was suspected to be due to prolonged neutropenia prior to the most recent therapy. On 26Jul2017, the patient died with a cause of death of disease progression, with pleural effusion and respiratory failure as fatal events. The investigator assessed pleural effusion and respiratory failure as possibly related to Mylotarg. The company assessed these events as unrelated to Mylotarg (Module 5.3.5.4 B1761026 CSR Section 14.3.3.1).

Patient is a 10-year-old male with relapsed/refractory AML who was treated with Mylotarg from 03Apr2017 to 09Apr2017. The patient experienced respiratory failure and sepsis on 01Jun2017. On 01Jun2017, patient started having altered mental status, difficulty walking and then vomited and likely aspirated based on his respiratory decompensation. In the emergency department, he was saturating in 80s on room air and was not responsive even to painful stimuli. He was intubated with great difficulty and multiple attempts due to copious secretions which had particulates suggestive of aspiration. He required high vent settings. Despite transfusions, he continued to have hypotension requiring several epinephrine boluses. After much work to stabilize him, he was transported to PICU. In the PICU patient continued to be hypotensive despite increasing doses of inotropes and boluses of calcium. As his blood pressures continued to decrease, parents elected to remove life support. The patient died on 01Jun2017, cause of death was disease progression, respiratory failure and sepsis. Autopsy was not done. The investigator and company assessed that the events of respiratory failure and sepsis as unrelated to Mylotarg (Module 5.3.5.4 B1761026 CSR Section 14.3.3.1).

Patient is a 12 year old male patient with refractory AML who received Mylotarg on 23Nov2016 as part of a combination regimen. The patient also received busulfan, IV intermittent, as transplant prophylactic at 30 mg every 6 hours (38 mg Q6H from 04Jan2017 to 07Jan2017). The patient was found to be in minimal residual disease (MRD) negative remission on 18Jan2017 and was referred for a bone marrow transplant. He started conditioning on 03Jan2017 for his procedure with prophylaxis for infection as well as veno-occlusive disease (VOD). Three days post transplant, the patient developed right upper quadrant pain and was diagnosed with venoocclusive disease. He was intermittently admitted to PICU for continuous venovenous hemofiltration (CVVH) for renal failure, hypervolemia and respiratory failure.

He was readmitted to PICU on 21Feb2017 for respiratory failure secondary to a combination of idiopathic pulmonary syndrome, cytomegalovirus (CMV) pneumonitis and pulmonary edema requiring CVVH. He was started on broad spectrum antibiotics, ruxolitinib, entancercept in addition to mycophenolate mofetil (CELLCEPT) after developing air leak syndrome and on 10Mar2017 he was place on extracorporeal membrane oxygenation (VV-ECMO) to aid in lung healing from air leak syndrome. He had improved subcutaneous emphysema but persistent bilateral pulmonary infiltrates on chest X-ray (CXR) while on VV-ECMO. On day 15 of VVECMO with multiple days of no clinical or radiographic evidence of subcutaneous emphysema, the decision was to increase his ventilator settings to challenge his respiratory effort. He then developed radiographic evidence of air leak syndrome again with subcutaneous emphysema and pneumomediastinum. Day 21 on VVECMO on 30Mar2017, family and multidisciplinary team decided to discontinue ECMO support. The patient died on 30Mar2017 with

withdrawal of support. The cause of death was respiratory failure, autopsy was performed. The investigator and company considered there was not a reasonable possibility that the event respiratory failure was related to Mylotarg (Module 5.3.5.4 B1761026 CSR 14.3.3.1).

Summary

In all four cases reporting respiratory failure with a fatal outcome the patients suffered severe complications associated with the progressive nature of the underlying acute leukaemia or subsequent treatment. There were no new safety information or unusual trends identified that would have altered the established benefit-risk profile of the product.

Renal Toxicity

The following preferred terms are summarized as possibly associated with acute renal failure:

Acute renal failure, Renal failure, and Acute kidney injury.

No patients in any group experienced Acute renal failure.

In the monotherapy group, there were no paediatric patients that experienced renal toxicity. There was 1 adult patient that experienced renal failure, and 2 adult patients that experienced acute kidney injury:

Patient was an adult patient that experienced a grade 5 event of Renal failure in the setting of refractory AML, pancytopenia, septic arthritis, bacteremia, pneumonia, and ultimately multi-organ dysfunction. The Renal failure was not considered to be related to study drug but was attributed to disease under study (Module 5.3.5.4 B1761026 CSR 14.3.3.1 and Table 16.2.7).

Patient was an adult patient that experienced grade 4 acute kidney injury, following emergency room admission for diarrhea, chills, shortness of breath, cough, agitation and symptoms of septic shock. Blood culture was positive for Gram positive cocci. The investigator concluded that the event of acute kidney injury was not related to study drug. Concurrent grade 4 events of platelet count decreased, and tumour lysis syndrome and grade 5 events of febrile neutropenia and sepsis were assessed as possibly related to Mylotarg by the investigator (Module 5.3.5.4 B1761026 CSR 14.3.3.1 and Table 16.2.7). Patient was an adult patient that experienced grade 3 acute kidney injury in the setting of relapsed AML, acute respiratory distress syndrome, hypotension, left ventricular dysfunction (LVEF <15%) and decreased platelets and white blood cells. The acute kidney injury was attributed to disease under study and was not considered related to study drug (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

In the combination group, 1 adult patient experienced renal failure, and 1 adult patient and 2 paediatric patients experienced acute kidney injury:

Patient is an adult patient who experienced grade 3 Renal failure concurrent with an event of fungaemia and grade 4 neutropenia. The events of fungaemia and renal failure were not considered to be related to study drug and were attributed to disease under study (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

Patient is an adult patient who experienced acute kidney injury. This 20-year-old female patient was admitted for treatment with Mylotarg plus fludarabine, cytarabine, G-CSF (FLAG) chemotherapy. Treatment began on 10May2016 with most recent dose on 04Jun2016. On 05Jun2016, the patient developed sepsis (neutropenic with Gram-positive cocci in blood cultures), pulmonary edema and respiratory failure / acute respiratory distress syndrome (ARDS). The patient’s status worsened with

intubation required on 10Jun2016. Acute kidney injury started on 11Jun2016 with grade 4 creatinine elevation starting from 16Jun2016. Serious adverse event was reported as acute kidney injury (grade 4 creatinine elevation) with onset date 11Jun2016 and serious as life-threatening and resulted in death. The patient started dialysis for acute kidney injury with continuous renal replacement therapy (CRRT) on 16Jun2016. The events, multi-organ failure and acute kidney injury overlapped, as acute kidney injury never resolved: only worsened and ended at death. The patient started to have multi-organ failure, and this resulted in death on 19Jun2016. The investigator did not believe that the death was related to fatal disease progression. The investigator considered there was a reasonable possibility that the event acute kidney injury (grade 4 creatinine elevation) was related to study drug Mylotarg and concomitant drug FLAG chemotherapy, but unrelated to clinical trial procedures. Acute kidney injury with fatal outcome was considered unrelated by the sponsor (Module 5.3.5.4 B1761026 CSR 14.3.3.1, Table 16.2.7).

Patient is a 17 year old patient who experienced grade 4 acute kidney injury following events of neutropenia, decreased platelet count, and hypoxia. Acute kidney injury was attributed to 'other' cause that was not disease or study drug. (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

Patient is an 8 year old patient who was enrolled in the combination group and experienced an event of acute kidney injury that was considered by the investigator to be related to study drug. This patient received Mylotarg on 15Sept2017 and on 24Sept2017 was brought to the emergency department with febrile neutropenia. The patient developed nausea that was complicated by emesis and subsequent fall. While in the emergency department, the patient started complaining of generalized abdominal pain, as a result, the patient was transferred to the PICU 24Sep2017 for acute respiratory failure and septic shock. Lab results showed that the patient was pancytopenic, acidotic and had hypokalaemia and was now in acute renal failure. On early morning 25Sep2017 exam, the patient's breath sounds were more diminished and the patient's liver edge became palpable 5-7 cm below the costal margin concerning for induced cardiogenic shock in addition to septic shock. Blood culture was positive for gram positive cocci and the patient was started on broad spectrum antibiotics. Therapeutic measures were taken as a result of sepsis. The patient also experienced pulmonary haemorrhage with onset date 29Sep2017. He died on 29Sep2017, preliminary cause of death was noted to be pulmonary haemorrhage due to acute respiratory failure and coagulopathy in setting of pancytopenia. Cause of death was confirmed as pulmonary haemorrhage; no autopsy was performed. The event of renal failure was considered to be related to study drug. The investigator and sponsor considered there was a reasonable possibility that the events sepsis and pulmonary haemorrhage was related to study drug Mylotarg and to concomitant drug azacitidine, but unrelated to clinical trial procedure (Module 5.3.5.4 B1761026 CSR 14.3.3.1, and Table 16.2.7).

There were no patients in the APL group who experienced renal toxicity.

Summary

In all seven cases reporting renal toxicity, the patients suffered complications associated with myelosuppression, infection, and the progressive nature of the underlying AML. There were no new safety information or unusual trends identified that would have altered the established benefit-risk profile of the product.

Neurotoxicity

The following preferred terms are summarized as possibly associated with neurotoxicity:

Demyelination, Neuropathy peripheral, and Cranial nerve disorder. There were no patients in the monotherapy group or the APL group who reported a Neurotoxicity preferred term.

Patient was an adult patient in the combination group who experienced Grade 3 Neuropathy peripheral concurrent with events of paraplegia (verbatim term: paralysis from low chest down), low lymphocytes, low granulocytes, lymphopaenia, asthenia and *clostridium difficile* infection. The investigator attributed this event of neuropathy peripheral to the disease under study and not to study drug. The event of paraplegia (grade 3) resolved and was also attributed to the disease under study (Module 5.3.5.4 B1761026 CSR, Table14.3.1.2.9.2 and Table 16.2.7).

Secondary Malignancy

Preferred terms from the system organ class (SOC) of Neoplasms benign, malignant and unspecified are summarized as possibly associated with second primary malignancy. Acute myeloid leukaemia is the disease under study, so was not considered to be a second primary malignancy and is not summarized.

In the monotherapy group, 2 paediatric patients experienced Chloroma:

Patient is an 18 month old male who experienced grade 3 chloroma in the setting of refractory AML, multi-system organ failure due to progressive disease. This event of chloroma was considered to be unrelated to study drug and was attributed to AML disease progression (Module 5.3.5.4 B1761026 CSR 14.3.3.1, Table 16.2.7).

Patient is an 11 year old male who experienced grade 5 chloroma in the setting of advanced AML. Events are summarized in this document, under the heading of Respiratory Failure. The event of grade 5 chloroma was not considered to be related to study drug but was attributed to disease progression (Module 5.3.5.4 B1761026 CSR 14.3.3.1, Table 16.2.7).

Also in the monotherapy group, 2 adult patients (patients 10131004 and 10661002) experienced Neoplasm progression, both of which were grade 5, unrelated to study drug and were attributed to disease under study. Both events were summarized in narrative reports as progression of their AML (Module 5.3.5.4 B1761026 CSR 14.3.3.1, Table 16.2.7).

One adult patient (patient) in the monotherapy group experienced grade 5 unrelated Neoplasm malignant (attributed to disease under study). This event is summarized in the narrative as being progression of the patient’s AML (Module 5.3.5.4 B1761026 CSR 14.3.3.1).

In the combination group, 1 adult patient (patient) experienced grade 3 Infected neoplasm (infectious cervical mass), concurrent with anemia, febrile neutropenia and fungal pneumonia. This event was considered to be unrelated to study drug and was attributed to disease under study (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

Also, in the combination group, paediatric patient experienced grade 3 Tumour pain, which was concurrent with neutrophil and lymphocyte count decreased and paraesthesia. The event of tumour pain was considered to be unrelated to study drug and attributed to disease under study (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

No patients in the treatment for APL group reported preferred terms in the SOC of Neoplasms benign, malignant, and unspecified (Module 5.3.5.4 B1761026 CSR, Table 14.3.1.2.9.2 and Table 16.2.7).

Summary

The search for “second primary malignancy” included a broad preferred terms search and thus it identified AEs other than second primary malignancies (e.g., non-malignant AEs, primary

malignancies). In the study none of the identified AEs were considered to be secondary primary malignancies.

Conclusion

The observed AEs were consistent with the known safety profile of Mylotarg and there were no unexpected major safety findings in this study population. In this study, both adult and paediatric patients experienced events of renal toxicity and events that fall under the SOC of Neoplasm benign, malignant and unspecified while one adult patient experienced an event associated with neurotoxicity. The majority of the events summarized were due to the underlying disease and/or effects of prior chemotherapy and in the setting of myelosuppression. There were no new safety information or unusual trends identified that would alter the established benefit-risk profile of the product.

Assessment of MAH response

Respiratory failure

Of the 4 patients described within the paediatric population with respiratory failure, the MAH explains that 3 out the 4 were not related to MYLOTARG treatment. One case of respiratory failure was possibly related to MYLOTARG by the investigator, but the company assessed these events as unrelated to MYLOTARG. The explanation provided that this was unrelated to MYLOTARG is acceptable as respiratory events occurred prior to commencing MYLOTARG.

Renal toxicity

Monotherapy group:

The MAH provided the following information:

- There were no paediatric cases of renal toxicity. (1 adult with acute renal failure not attributed to MYLOTARG but to disease; and 2 adults with Acute Kidney Injury (AKI), not related to study drug but to disease).

Combination group there were:

- 1 adult patient with renal failure not attributable to MYLOTARG but the disease.
- 1 adult patient with AKI. The investigator considered that there was reasonable possibility that AKI was due to MYLOTARG and concomitant drug chemotherapy. The AKI with fatal outcome was considered unrelated by the sponsor. It is recognised that events surrounding this case would be difficult to attribute solely to MYLOTARG, however, this potential serious ADRs should be continued to be monitored.
- Paediatric patients were a 17 year old with AKI which the MAH reports were unrelated to MYLOTARG. An 8 year old with AKI and subsequent renal failure was considered to be related to the study drug. The patient died with cause of death noted to be pulmonary haemorrhage due to acute respiratory failure and coagulopathy in setting of pancytopenia. The investigator and sponsor considered that a reasonable possibility that events of sepsis and pulmonary haemorrhage where related to the study drug and to concomitant drug use but unrelated to clinical trial procedure.

The events surrounding renal toxicity should be continued to be monitored, especially as they are not detailed in Section 4.8 of the SmPC.

Neurotoxicity

There were no paediatric patients within this group and the adult patient in the combination group who experience neurotoxicity, not related to MYLOTARG.

Secondary Primary malignancies

Monotherapy group there were

- 2 paediatric patients experienced chloroma, both attributed to disease progression and not MYLOTARG.
- 3 adult patients experience neoplasm related to disease under study and not MYLOTARG.

Combination group there were

- 1 paediatric patient experienced tumour pain not related to MYLOTARG and related to disease.
- 1 adult patient infected neoplasm not related to MYLOTARG but to the disease under study.

None of the AEs were considered to be secondary primary malignancies.

Conclusion

In view of the MAH's clarification, it is agreed that the majority of events were related to confounding factors such as underlying disease, myelosuppression or chemotherapy related effects. A change to the SmPC with regards to this safety information is not recommended at this stage.

However, this study does provide additional evidence regarding treatment for relapsed or refractory AML in the paediatric population; although the MAH does not plan to seek this indication, it is strongly recommended, that the totality of available paediatric data from relapsed and refractory AML studies are reviewed and submitted to seek a paediatric indication for this patient group. The MAH is encouraged to enter a meaningful discussion with regulatory authorities on the details of such a submission, overcoming any limitations of bibliography data and taking into account also the current clinical experience on the field.

Finally, the MAH should continue safety monitoring of ADRs including those for renal toxicity, hypoxia, hypokalaemia; and febrile neutropenia in the combination therapy.

This Article 46 procedure is concluded.

☒ **Fulfilled**

☐ Not fulfilled

Annex. Line listing of all the studies included in the development program

The studies should be listed by chronological date of completion:

Clinical studies

Product Name: Mylotarg Active substance: Gemtuzumab Ozogamicin

Study title	Study number	Date of completion	Date of submission of final study report
A Phase III Randomized Trial of Gemtuzumab Ozogamicin (Mylotarg) Combined with Conventional Chemotherapy for De Novo Acute Myeloid Leukemia (AML) in Children, Adolescents, and Young Adults	AAML0531	Last Subject Last Visit (LS/LV) 31 March 2013	Available study information has been submitted with the initial Mylotarg MAA dossier on 01 December 2016. An abbreviated study report is submitted on 09 July 2018.
Population Pharmacokinetic Modeling of Gemtuzumab Ozogamicin in Pediatric Patients with Acute Myeloid Leukemia (AML)	PMAREQDDB176asNDA-492	19 May 2016	Submitted with Mylotarg MAA dossier on 01 December 2016.
Population Modeling of Exposure-Response for Efficacy and Safety Endpoints in Acute Myeloid Leukemia (AML) Patients Receiving Gemtuzumab Ozogamicin (PF-05208747)	PMAREQDDB176asNDA-491	18 July 2016	Submitted with Mylotarg MAA dossier on 01 December 2016.
Systematic review of studies evaluating safety, activity and / or efficacy with relapse of, or progressive acute myeloid leukaemia	N/A	Report signed 26 June 2018	Planned in August 2018
Randomised open label multi-centre dose-escalating trial to evaluate pharmacokinetics, toxicity, safety and activity of gemtuzumab ozogamicin in combination with intensified	MyeChild 01	LS/LV June 2022	Estimated December 2022

induction regimens in paediatric patients from 1 month to less 18 years of age with newly-diagnosed, *de novo* or secondary acute myeloid leukaemia.			
A single arm, open label, Phase 4 study evaluating QT interval, pharmacokinetics, and safety of gemtuzumab ozogamicin (Mylotarg) as a single-agent regimen in patients with relapsed or refractory CD33-positive acute myeloid leukemia.	B1761031	Study to be initiated	Within 6 months from LS/LV