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The Effect of Transplant Status on Exposure-Adjusted AE Rates in Melflufen-Treated RRMM Patients in a Pooled Safety Population From 4 Studies

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CONCLUSIONS

- After adjusting the safety evaluation for melflufen exposure, the overall and Grade 3/4 adverse events (AEs)/patient year, serious and fatal AEs/patient year, and resolution of most types of AEs were lower in the target population (patients with no previous autologous stem cell transplantation [ASCT] or time to progression [TTP] >36 months after ASCT) compared with the non-target population (patients with TTP <36 months after ASCT)
- Grade 3/4 hematologic AEs occurred later in the target population than in the non-target population
- Grade 3/4 infection rates were similar in the target and non-target populations after adjusting for exposure, highlighting the susceptibility of patients with relapsed/refractory multiple myeloma (RRMM) to developing infections
- These results reinforce the positive benefit-risk profile of melflufen and dexamethasone in the target population and underline the importance of taking exposure into account when evaluating safety results in clinical studies

BACKGROUND

- Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate that utilizes increased peptidase and esterase expression to rapidly release potent alkylating agents inside tumor cells (**Supplemental Figure 1**)[1-5]
- Melflufen has been investigated in several clinical trials and has demonstrated clinically meaningful efficacy and a manageable safety profile in patients with RRMM[6-9]
- Melflufen is approved in the EU and the European Economic Area for use in patients with triple-class refractory multiple myeloma with ≥3 lines of therapy and without prior ASCT or with a TTP >36 months after prior ASCT
- Approval was based on:
  - Results from the phase 2 HORIZON study and supported by the phase 3, randomized, controlled OCEAN study[6,7]
  - Analyses of a pooled safety population from 4 clinical studies[6-9]
- Standard AE analyses (comparison of number and percentage of patients with AEs) do not take into account differences in drug exposures
- One way to minimize the effect of exposure differences is to compare the number of events per patient year of exposure instead of number and percentage of patients with AEs

OBJECTIVE

- Here, we assess exposure-adjusted AE rates by using number of events per patient year of exposure in the target and non-target populations of melflufen-treated patients with RRMM in a pooled safety population from 4 studies that included:
  - **Target population:** patients with no previous ASCT or TTP >36 months after ASCT
  - **Non-target population:** patients with TTP <36 months after ASCT

METHODS

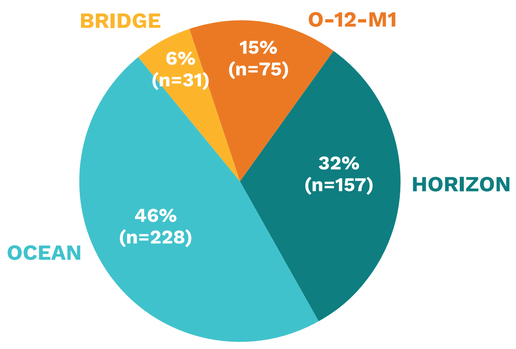
- A retrospective analysis of exposure-adjusted AE rates was performed using pooled safety data from 4 clinical studies:
  - **O-12-M1 study[8]:** Phase 1/2 study of melflufen and dexamethasone in patients with RRMM to determine the maximum tolerated dose and investigate safety and efficacy (data cutoff: November 9, 2017)
  - **HORIZON (OP-106) study[7]:** Phase 2 study that evaluated the efficacy and safety of melflufen plus dexamethasone in patients with RRMM (data cutoff: March 31, 2020)
  - **OCEAN (OP-103) study[6]:** Phase 3, randomized, open-label, head-to-head study of melflufen plus dexamethasone vs pomalidomide plus dexamethasone in patients with RRMM (data cutoff: February 3, 2021)
  - **BRIDGE (OP-107) study[9]:** Phase 2, open-label, single-arm study to evaluate the pharmacokinetics, efficacy, and safety of melflufen plus dexamethasone in patients with RRMM who have reduced renal function (data cutoff: April 5, 2021)
- Melflufen was administered through a central venous infusion for all patients
- Exposure-adjusted rates were calculated by number of events per patient year of exposure

RESULTS

PATIENTS

- The melflufen safety pool comprised 491 patients from the 4 studies (**Figure 1**), including:
  - 287 patients with no previous ASCT or TTP >36 months after ASCT (the target population) and
  - 204 patients with TTP <36 months after ASCT (non-target population)
- 478 patients were treated with melflufen plus weekly dexamethasone and 13 patients with melflufen alone

Figure 1. Number of Patients From the 4 Studies in the Safety Pool



- Patient baseline characteristics are detailed in **Table 1**

Table 1. Patient Baseline Characteristics

Characteristics	Target Population[a] n=287	Non-Target Population[b] n=204	Total N=491
Age, median (range), years	71 (42-91)	63 (35-80)	67 (35-91)
Male sex, n (%)	161 (56)	120 (59)	281 (57)
ECOG PS, n (%)			
0	97 (34)	74 (36)	171 (35)
1	153 (53)	112 (55)	265 (54)
2	37 (13)	18 (9)	55 (11)
ISS score at study entry, %			
I	119 (41)	85 (42)	204 (42)
II	105 (37)	75 (37)	180 (37)
III	56 (20)	40 (20)	96 (20)
Median no. of prior lines of therapy, range	3 (2-13)	4 (2-14)	3 (2-14)
No. of prior lines of therapy			
2	92 (32)	41 (20)	133 (27)
3	63 (22)	54 (26)	117 (24)
4	62 (22)	39 (19)	101 (21)
5	32 (11)	25 (12)	57 (12)
≥6	38 (13)	45 (22)	83 (17)

[a]Target population includes patients with no previous ASCT or TTP >36 months after ASCT.
[b]Non-target population includes patients with TTP <36 months after ASCT.
ASCT, autologous stem cell transplantation; ECOG PS, Eastern Cooperative Oncology Group performance status; ISS, International Staging System; No., number; TTP, time to progression

EXPOSURE TO MELFLUFEN

- Patients in the target population had substantially longer melflufen exposure compared with the non-target population
  - Median treatment duration (range): 24.9 (1.1-164.3) vs 15.4 (3.1-103) weeks, respectively
  - Median number of treatment cycles (range): 6 (1-40) vs 3 (1-20), respectively

SAFETY

- There were no differences in proportion of patients with AEs between the target and non-target populations (**Table 2**)
- Analyses taking exposure into account showed clear differences
  - The rate of Grade 3/4 AEs/patient year were lower in the target population compared with the non-target population (**Table 2**)
  - The rate of serious AEs/patient year were lower in the target population compared with the non-target population, while the rate of fatal events/patient year was similar in the target and non-target populations (**Table 2**)

SAFETY (CONTINUED)

Table 2. Overall Safety Profile

	Target Population[a] n=287		Non-Target Population[b] n=204		Total N=491	
	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year
Overall AEs	286 (99.7)	30.8	203 (99.5)	43.1	489 (99.6)	34.7
Grade 3/4 AEs	259 (90)	12.7	189 (93)	19.1	448 (91)	14.8
Serious AEs	133 (46)	1.4	87 (43)	2.1	220 (45)	1.6
Fatal AEs	30 (10)	0.2	15 (7)	0.2	45 (9)	0.2
COVID-19 pneumonia	3 (1)	0.0	4 (2)	0.0	7 (1)	0.0
Pneumonia	4 (1)	0.0	1 (0.5)	0.0	5 (1)	0.0
AEs leading to dose modification	218 (76)	5.2	166 (81)	7.9	384 (78)	6.1
AEs leading to dose delay	180 (63)	3.7	131 (64)	5.5	311 (63)	4.2
AEs leading to dose reduction	103 (36)	1.0	72 (35)	1.4	175 (36)	1.1
AEs leading to drug discontinuation	66 (23)	0.5	66 (32)	1.1	132 (27)	0.7

[a]Target population includes patients with no previous ASCT or TTP >36 months after ASCT.
[b]Non-target population includes patients with TTP <36 months after ASCT.
AE, adverse event; ASCT, autologous stem cell transplantation; TTP, time to progression.

- The rates of non-hematologic AEs/patient year (12.3 vs 16.3 events/patient year) were lower in the target population compared with the non-target population (**Table 3**)

Table 3. Most Common Non-Hematologic AEs (Any Grade in ≥10% of Patients in the Safety Pool)

	Target Population[a] n=287		Non-Target Population[b] n=204		Total N=491	
	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year
Overall	275 (96)	12.3	186 (91)	16.3	461 (94)	13.5
Fatigue	65 (23)	0.5	41 (20)	0.7	106 (22)	0.6
Nausea	67 (23)	0.5	38 (19)	0.6	105 (21)	0.5
Diarrhea	57 (20)	0.4	38 (19)	0.6	95 (19)	0.5
Asthenia	60 (21)	0.5	33 (16)	0.9	93 (19)	0.6
Pyrexia	55 (19)	0.4	37 (18)	0.6	92 (19)	0.5
Upper respiratory tract infection	42 (15)	0.3	21 (10)	0.4	63 (13)	0.3
Pneumonia	32 (11)	0.2	23 (11)	0.3	55 (11)	0.2
Cough	26 (9)	0.2	28 (14)	0.4	54 (11)	0.3
Dyspnea	34 (12)	0.2	18 (9)	0.2	52 (11)	0.2
Constipation	33 (11)	0.2	19 (9)	0.2	52 (11)	0.2
Back pain	35 (12)	0.2	16 (8)	0.2	51 (10)	0.2

[a]Target population includes patients with no previous ASCT or TTP >36 months after ASCT.
[b]Non-target population includes patients with TTP <36 months after ASCT.
AE, adverse event; ASCT, autologous stem cell transplantation; TTP, time to progression.

- The rates of Grade 3/4 hematologic events/patient year were lower in the target population compared with the non-target population (**Table 4**)
  - Grade 3/4 thrombocytopenia: 4.5 vs 6.9 events/patient year
  - Grade 3/4 neutropenia 4.3 vs 5.8 events/patient year
  - Grade 3/4 anemia: 1.2 vs 2.5 events/patient year
- However, the rates of Grade 3/4 infections/patient year were similar in the target population compared with the non-target population (0.5 vs 0.4; **Table 4**)

Table 4. Grade 3/4 AEs of Special Interest Across All Cycles[a]

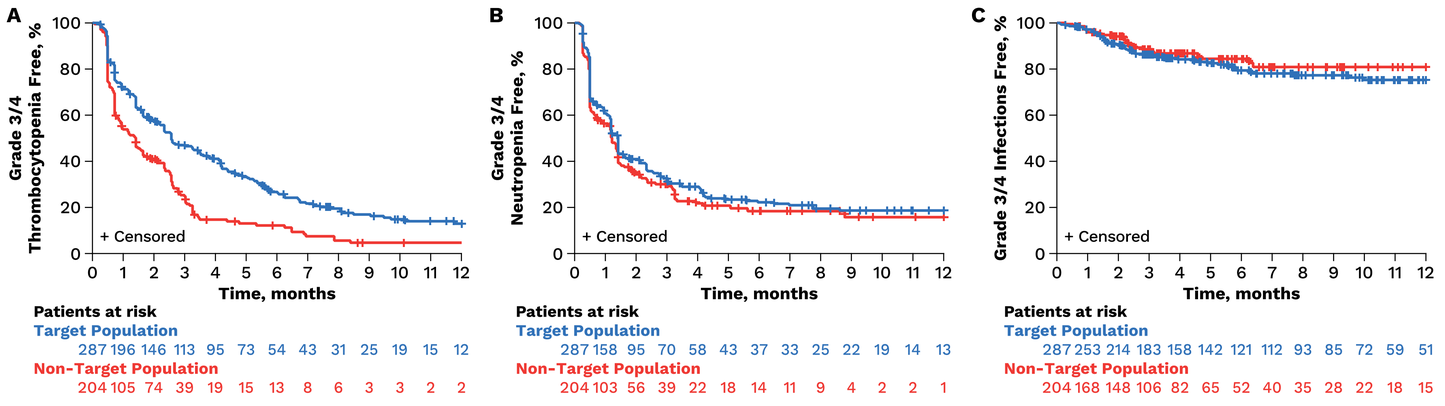
	Target Population[b] n=287				Non-Target Population[c] n=204				Total N=491			
	Any Grade		Grade 3/4		Any Grade		Grade 3/4		Any Grade		Grade 3/4	
	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year	n (%)	Events/patient year
Thrombocytopenia	226 (79)	6.9	196 (68)	4.5	182 (89)	10.0	167 (82)	6.9	408 (83)	7.9	363 (74)	5.3
Bleeding events	54 (19)	0.5	7 (2)	<0.1	47 (23)	0.8	5 (2)	0.1	101 (21)	0.6	12 (2)	0.1
Anemia	183 (64)	3.3	112 (39)	1.2	140 (69)	5.4	90 (44)	2.5	323 (66)	3.9	202 (41)	1.6
Neutropenia	206 (72)	6.4	191 (67)	4.3	148 (73)	8.4	134 (66)	5.8	354 (72)	7.0	325 (66)	4.8
Febrile neutropenia	10 (3)	0.1	10 (3)	0.1	9 (4)	0.1	9 (4)	0.1	19 (4)	0.1	19 (4)	0.1
Infections	159 (55)	1.9	58 (20)	0.5	95 (47)	2.2	25 (12)	0.4	254 (52)	2.0	83 (17)	0.4
Pneumonia	35 (12)	0.2	27 (9)	0.2	23 (11)	0.3	12 (6)	0.2	58 (12)	0.2	39 (8)	0.2

[a]AEs of special interest represent events per the following MedDRA terms: thrombocytopenia includes hematopoietic thrombocytopenia (SMQ); bleeding events includes broad terms (hemorrhage terms [excluding laboratory terms]) and narrow terms from SMQ (hemorrhage laboratory terms); anemia includes hematopoietic erythropenia (SMQ); neutropenia includes sponsor CMQ (preferred terms: neutropenia, febrile neutropenia, neutrophil count decreased, neutropenic sepsis, neutropenic infection, cyclic neutropenia, band neutrophil count decreased, band neutrophil percentage decreased, neutrophil percentage decreased, agranulocytosis, granulocyte count decreased, granulocytopenia); febrile neutropenia includes febrile neutropenia (preferred term), infections includes infections and infestations (system organ class); and pneumonia includes infective pneumonia (narrow; mSMQ).
[b]Target population includes patients with no previous ASCT or TTP >36 months after ASCT.
[c]Non-target population includes patients with TTP <36 months after ASCT.
AE, adverse event; ASCT, autologous stem cell transplantation; CMQ, customized MedDRA queries; MedDRA, Medical Dictionary for Regulatory Activities; mSMQ, modified Standardised MedDRA Queries; TTP, time to progression.

- Grade 3/4 thrombocytopenia and neutropenia occurred later in the target population than in the non-target population, while infections occurred around the same time in both populations (**Figure 2**)
  - Median time to onset for thrombocytopenia: 50 vs 27.5 days[a]
  - Median time to onset for neutropenia: 27 vs 15 days[a]
  - Median time to onset of infections: 68 vs 67 days[a]
- The thrombocytopenia and neutropenia resolved quickly
  - Median time to resolution: 15 days and 8 days, respectively[a]

[a]Conditional to event being reached, and thus, may be different to the ones in Fig 2.

Figure 2. Time to First Grade 3/4 AE



[a]Target population includes patients with no previous ASCT or TTP >36 months after ASCT.
[b]Non-target population includes patients with TTP <36 months after ASCT.
AE, adverse event; ASCT, autologous stem cell transplantation; TTP, time to progression.

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