HORIZON (OP-106): Melflufen Plus Dexamethasone in Patients With Relapsed/Refractory Multiple Myeloma (RRMM)—Analysis of Adverse Events Related to Hospitalizations

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Melphalan Flufenamide (Melflufen) in RRMM

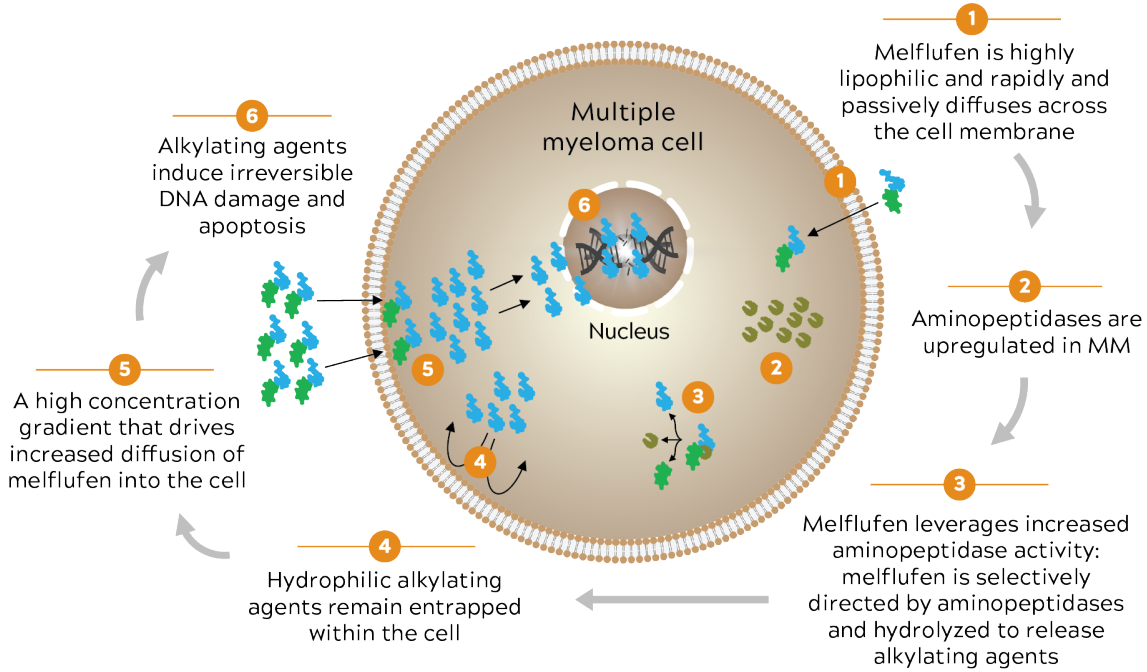
HORIZON

Objective: To further **elucidate the healthcare resource utilization of patients with RRMM treated with melflufen** in a clinical trial by evaluating the impact of AEs on hospitalizations in HORIZON.

Patients with RRMM and Hospitalization:

- Patients with RRMM are a very sick population due to disease symptoms, comorbidities, side effects from treatments, and age-related fragility[1]
- In patients with RRMM, AEs (including hematologic AEs) are common, can impact quality of life, treatment compliance, and are a major cost driver, with hematologic AEs having the highest cost[2]
- Real-world studies suggest that >50% of patients with AEs require readmittance to the hospital after initial treatment[3,4]
  - There are limited published data to date on the impact of AEs on hospitalizations from clinical trials

Melflufen is an investigational first-in-class peptide-drug conjugate (PDC) that **targets aminopeptidases and rapidly releases alkylating agents into tumor cells.**[5-9]



AEs, adverse events; RRMM, relapsed/refractory multiple myeloma.

1. Chim CS, et al. *Leukemia*. 2018;32:252. 2. Felber G, et al. ASH 2019. Abstract 4725. 3. Yeaw J, et al. ISPOR 2020. Abstract PCN78. 4. Yong K, et al. *Br J Haematol*. 2016;175:252. 5. Chauhan D, et al. *Clin Cancer Res*. 2013;19:3019-31. 6. Ray A, et al. *Br J Haematol*. 2016;174:397-409. 7. Wickström M, et al. *Oncotarget*. 2017;8:66641-55. 8. Wickström M, et al. *Invest New Drugs*. 2008;26:195-204. 9. Strese S, et al. *Biochem Pharmacol*. 2013;86:888-95.

Melflufen in Patients With RRMM From HORIZON

In the pivotal, single-arm, multicenter, phase 2 HORIZON study (NCT02963493), **melflufen plus dexamethasone showed clinically meaningful efficacy** and a **safety profile** consisting primarily of clinically **manageable** hematologic AEs in patients with advanced RRMM.[1]

- Eligible patients with advanced RRMM who were refractory to pomalidomide and/or an anti-CD38 mAb received melflufen (40 mg on day 1) plus dexamethasone (40 mg/week) in 28-day cycles until disease progression or unacceptable toxicity
- Primary endpoint: ORR
- Secondary endpoints included PFS, OS, safety, HRQoL

Outcomes in the Intention-To-Treat Population[1]	N=157
ORR, % (95% CI)	29 (22.3-37.1)
Median OS, months (95% CI)	11.6 (9.3-15.4)
Most common grade 3/4 TEAEs, %	
Thrombocytopenia	57
Neutropenia	53
Anemia	43
SAEs, %	49
Pneumonia	9
Febrile neutropenia	5

Methods for examining hospitalizations related to TRAEs[a]:

- Data for specific SAEs potentially related to the study drugs (melflufen and/or dexamethasone; TRAEs) were examined
- TRAEs reported as requiring hospitalizations >24 h were compared with all potential TRAEs and within each preferred term
- TEAEs were classified as TRAEs if reported as related, probably related, or possibly related to either study drug by the treating physician

[a]Because not all hospitalization may have been captured, the safety database for each patient with hospitalizations was analyzed.

AE, adverse event; HRQoL, health-related quality of life; mAb, monoclonal antibody; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; RRMM, relapsed/refractory multiple myeloma; SAE, serious adverse event; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Richardson PG, et al. EHA 2020. Poster EP945.

Results and Baseline Characteristics in Patients Hospitalized for TRAEs

HORIZON

Characteristic	Patients Hospitalized for TRAEs (N=35)
Age, median (range), years	63 (43-84)
Sex (male/female), %	57 / 43
Time since diagnosis at study entry, median (range), years	7.1 (1.8-14.3)
No. prior lines of therapy at study entry, median (range), n	5 (3-12)
ISS stage at study entry (I/II/III/unknown or missing), %[a]	37 / 26 / 31 / 6
Albumin level at study entry, n (%)	
≥35 g/dL	23 (66)
<35 g/dL	12 (34)
High-risk cytogenetics, n (%)[a]	17 (49)
High LDH (1.5 x ULN) at study entry, n (%)[b]	5 (15)
Triple-class refractory, n (%)[c]	27 (77)
Refractory to prior alkylator, n (%)	25 (71)

- Of 157 patients enrolled and treated, 35 (22%) were hospitalized due to a TRAE
- Baseline characteristics for patients hospitalized due to TRAEs were generally consistent with those of the overall population and representative of a population with advanced RRMM and poor-risk features[1]

[a]ISS stage and fluorescence in situ hybridization (FISH) risk group at study entry were assessed as described.[2] [b]Information is missing for 1 patient. [c]Triple-class–refractory is defined as refractory to or intolerant of at least one immunomodulatory drug, at least one proteasome inhibitor, and at least one anti-CD38 monoclonal antibody.

ISS, International Staging System; LDH, lactate dehydrogenase; TRAE, treatment-related adverse event; RRMM, relapsed/refractory multiple myeloma; ULN, upper limit of normal.

1. Richardson PG, et al. EHA 2020. Poster EP945. 2. Palumbo A, et al. *J Clin Oncol*. 2015;33:2863-2969.

Most Common TRAEs (>1 Event) Requiring Hospitalization for >24 h

HORIZON

TRAEs Leading to Hospitalization (>1 Event)	TRAEs Resulting in Hospitalization (n=58), n (%)	Proportion of Hospitalizations in Relation to Specific TRAE, n/N (%)	Proportion of Hospitalizations in Relation to Total TRAEs Reported (n=2688)[a], %
Pneumonia	11 (19)	11/14 (78.6)	0.41
Febrile neutropenia	10 (17)	10/12 (83.3)	0.37
Thrombocytopenia[b]	9[c] (16)	9/653 (1.4)	0.33
Neutropenia[d]	2[e] (3)	2/662 (0.3)	0.07
Bronchitis	2 (3)	2/4 (50.0)	0.07
Pyrexia	2 (3)	2/12 (16.7)	0.07
Urosepsis	2 (3)	2/2 (100)	0.07

- Of 118 TEAEs that resulted in a hospitalization, 58 were TRAEs
- TRAEs resulting in the most hospitalizations were
  - Pneumonia (11 hospitalizations; 78.6% of pneumonia TRAEs; 0.41% of all TRAEs)
  - Febrile neutropenia (10 hospitalizations; 83.3% of febrile neutropenia TRAEs; 0.37% of all TRAEs)
- Treatment-related thrombocytopenia and neutropenia resulted in 9 hospitalizations (1.4% of thrombocytopenia TRAEs; 0.33% of all TRAEs) and 2 hospitalizations (0.3% of neutropenia TRAEs; 0.07% of all TRAEs), respectively
- All TRAEs that resulted in hospitalization were grade 3/4 except for 2 events (1 pyrexia [grade 1]; 1 pneumonia [grade 2])

[a]A total of 2688 TRAEs were reported in HORIZON, of these, 58 resulted in hospitalizations. [b]Thrombocytopenia includes platelet count decreased. [c]For 3 events it is unclear whether the hospitalization was for >24 h. [d]Neutropenia includes neutrophil count decreased. [e]For 1 event, it is unclear if the hospitalization was for >24 h.
TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

Conclusions

- Inpatient services are a major driver of economic burden in RRMM and have been shown to be highly utilized in less heavily pretreated populations than HORIZON[1,2]
- In HORIZON, hematologic TEAEs were common but led to few hospitalizations overall: thrombocytopenia (9 hospitalizations; 1.4% of thrombocytopenia TRAEs; 0.33% of all TRAEs) and neutropenia (2 hospitalizations; 0.3% of neutropenia TRAEs; 0.07% of all TRAEs)
- Although 11 of 14 (78.6%) TRAEs of pneumonia required hospitalization, these events represent a small fraction of all TRAEs reported (0.41%), and infections are normally expected in advanced RRMM[3]
- The results of this analysis suggest there is limited use of inpatient services for TRAEs with melflufen plus dexamethasone. Further analyses of real-world data on melflufen are warranted to confirm the results presented from this analysis

RRMM, relapsed/refractory multiple myeloma; TEAE, treatment-emergent adverse event; TRAE, treatment-related adverse event.

1. Felber G, et al. ASH 2019. Abstract 4725 2. Yeaw J, et al. ISPOR 2020. Abstract PCN78. 3. Blimark C, et al. *Haematologica*. 2015;100:107-113.

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- Melflufen is being discussed in other presentations at this meeting:
  - Melflufen plus dexamethasone and daratumumab or bortezomib; abstract: 417 (oral)
  - Melflufen plus dexamethasone; abstracts: 2293, 2321, 3214, 3237, 3477 (posters)