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Maintained renal function with melflufen therapy in RRMM: results from analysis of pooled clinical data

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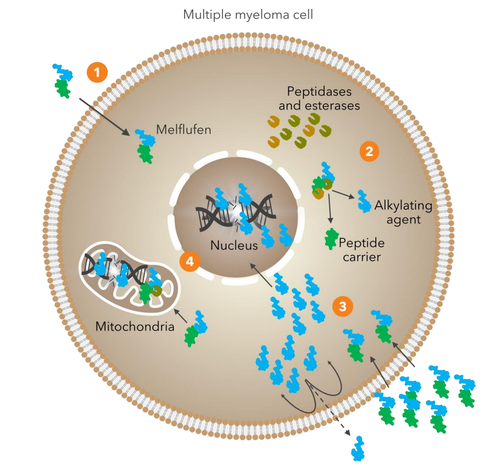
CONCLUSIONS

- Pooled data from three clinical studies showed that renal function remained stable during treatment with melflufen and renal AEs were uncommon.
- Patients with moderate renal impairment (eGFR <60) had stable eGFR throughout melflufen treatment.
- These results indicate that melflufen can be administered in patients with RRMM without negatively affecting renal function or safety outcomes.

BACKGROUND

- Melphalan flufenamide (also known as melflufen) is a lipophilic peptide–drug conjugate that improves intracellular delivery of alkylating agents and selectivity toward malignant cells (**Figure 1**).[1-6]
- Melflufen is approved by EMA, in combination with dexamethasone, for the treatment of adult patients with multiple myeloma who have received at least three prior lines of therapies and whose disease is triple-class refractory. For patients with a prior autologous stem cell transplantation, the time to progression should be at least 3 years from transplantation.[7]
- Reduced kidney function related to disease burden and prior therapies represents a clinical challenge in RRMM.[8] Although no renal safety signal was observed with melflufen in the Phase 1/2 O-12-M1 study [9], further evaluation of renal function outcomes of melflufen is relevant.

Figure 1. Melflufen: A peptide-drug conjugate (PDC)



1. Lipophilic entry
Melflufen is highly lipophilic and diffuses quickly and passively through the cell membrane, without the need of transporter proteins.[1,2]

2. Rapid hydrolyzation
Melflufen utilizes the overexpression of peptidases and esterases inside tumor cells and is rapidly hydrolyzed to release cytotoxic hydrophilic alkylating agents.[3,4]

3. Gradient-driven influx & accumulation
The rapid hydrolysis of melflufen creates a concentration gradient that drives further influx of melflufen into the cell, resulting in an intracellular peak of alkylating agents.[4,5]

4. Nuclear damage and apoptosis
Alkylating metabolites of melflufen cause irreversible nuclear and mitochondrial damage by breaking DNA strands which induces apoptosis.[5,6]

DNA, deoxyribonucleic acid; Melflufen, melphalan flufenamide.

OBJECTIVE

- The purpose was to investigate changes in renal function during treatment with melflufen in a pooled patient population from three clinical studies and to compare renal function over time in patients treated with melflufen vs pomalidomide.

METHODS

- Patients with relapsed/refractory multiple myeloma (RRMM) from the single-arm studies O-12-M1 and OP-106 HORIZON, and the randomized Phase 3 study OP-103 OCEAN were included.[9-11]
  - Patients received either intravenous melflufen 40 mg on day 1 or oral pomalidomide 4 mg daily on days 1-21 of each 28-day cycle. In O-12-M1, 28 patients received melflufen in 21-day cycles.
  - Patients also received 40 mg dexamethasone weekly, or 20 mg if ≥75 years of age. Dose reduction due to age, was only made in OP-106 and OP-103.
  - All studies required an estimated creatinine clearance ≥ 45 ml/min at screening.
- Renal function was assessed from baseline to day 1 in cycle 7 (C7) and from baseline to end of treatment (EOT).
- The analysis comprised a pooled cohort of melflufen-treated patients and a separate comparison between melflufen and pomalidomide in patients from the OCEAN study.
- In addition, outcomes were assessed in a subgroup of melflufen treated patients with baseline eGFR <60 mL/min/1.73 m².
- Safety assessment focused on renal function.

RESULTS

PATIENTS

- The pooled analysis included 430 patients treated with melflufen. The median eGFR at baseline was 81.2 mL/min/1.73m², 74 patients (17%) had eGFR <60. (**Table 1**).
  - Reason for EOT was predominantly due to progressive disease (54.0%) or adverse events (20.7%).
- The comparative analysis between melflufen and pomalidomide included 228 patients receiving melflufen and 246 patients receiving pomalidomide from the OCEAN trial (**Table 1**).
  - Baseline characteristics were similar between the groups including eGFR (median 81.4 mL/min/1.73m² for melflufen vs. 79.6 for pomalidomide).
  - Patients with eGFR <60 showed similar baseline characteristics (**Table 1**).

Table 1. Baseline demographics

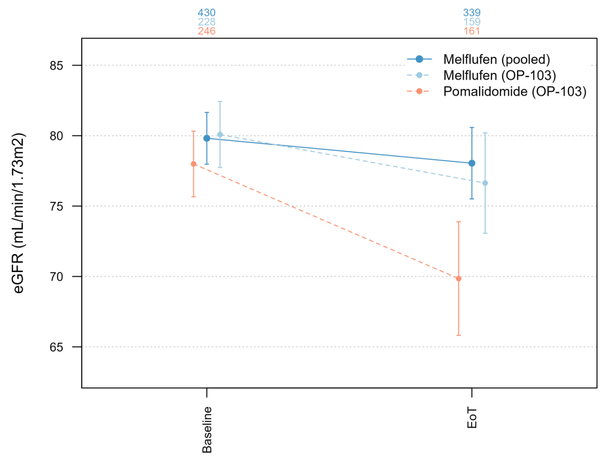
	Pooled		OCEAN	
	Melflufen N=430	Melflufen, eGFR <60 (n=74)	Melflufen (n=228)	Pomalidomide (n=246)
Age, median (range)	66 (35-91)	68 (41-84)	68 (41-91)	68 (39-87)
Age group, n (%)				
<65	187 (43.5)	22 (29.7)	89 (39.0)	82 (33.3)
65-74	178 (41.4)	37 (50.0)	102 (44.7)	125 (50.8)
75+	65 (15.1)	15 (20.3)	37 (16.2)	39 (15.9)
Male, n (%)	249 (58)	42 (57)	130 (57)	138 (56)
ASCT, n (%)	248 (58)	37 (50)	112 (49)	118 (48)
Number of prior lines, median (range)	3 (2-14)	4 (2-14)	3 (2-4)	3 (2-4)
High risk cytogenetics, n (%)	154 (36)	26 (35)	75 (33)	84 (34)
ISS, n (%)				
I	194 (45.1)	17 (23.0)	116 (50.9)	124 (50.4)
II	151 (35.1)	29 (39.2)	84 (36.8)	93 (37.8)
III	76 (17.7)	26 (35.1)	28 (12.3)	29 (11.8)
Missing/Unknown	9 (2.1)	2 (2.7)	0	0
Baseline eGFR, median (range)	81.2 (18.5-124.4)	51.0 (18.5-59.9)	81.4 (34.0-121.4)	79.6 (8.7-119.2)
Baseline eGFR, grouped, n (%)				
<60	74 (17.2)	74 (100.0)	35 (15.4)	40 (16.3)
60-90	200 (46.5)	0	110 (48.2)	133 (54.1)
90+	156 (36.3)	0	83 (36.4)	73 (29.7)

ASCT, autologous stem cell transplant; ISS, International Staging System; eGFR, estimated glomerular filtration rate.

RENAL FUNCTION

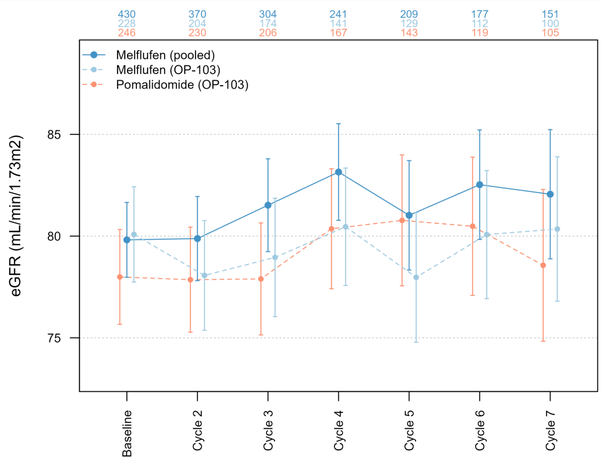
- The result from the pooled melflufen group showed that renal function remained stable throughout the course of treatment.
  - Mean eGFR showed no clinical meaningful change from baseline to EOT (**Figure 2**), or from baseline to Cycle 7 (**Figure 3**),
  - Importantly, patients with baseline eGFR <60 maintained a stable eGFR with no meaningful decline observed during their treatment with melflufen (**Figure 4**).
- In the comparative analysis between melflufen and pomalidomide, no differences in renal function over time were observed between treatments (**Figure 2-4**), but there was a trend towards higher GFR in the melflufen arm at EOT (**Figure 2**).

Figure 2. eGFR values from baseline to end of treatment in patients treated with melflufen + dex or pomalidomide + dex



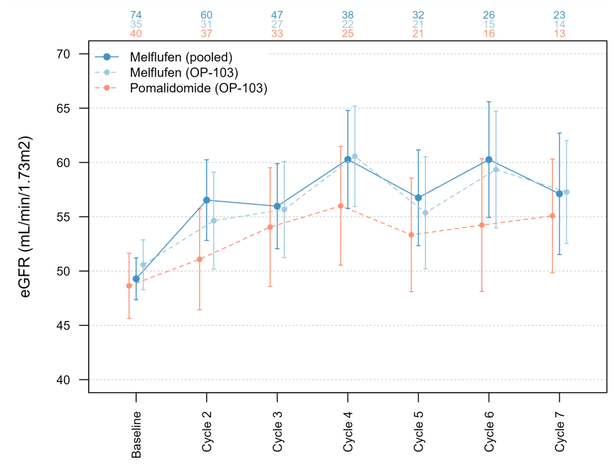
Mean and 95% confidence intervals
Dex, dexamethasone; eGFR, estimated glomerular filtration rate; EoT, end of treatment; OP-103, OCEAN.

Figure 3. eGFR values from baseline to Day 1 in Cycle 7 in patients treated with melflufen + dex or pomalidomide + dex



Mean and 95% confidence intervals
Dex, dexamethasone; eGFR, estimated glomerular filtration rate; OP-103, OCEAN.

Figure 4. eGFR values <60 from baseline to Day 1 in Cycle 7 in patients treated with melflufen + dex or pomalidomide + dex



Mean and 95% confidence intervals
Dex, dexamethasone; eGFR, estimated glomerular filtration rate; OP-103, OCEAN.

ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

- Adverse events were reported in 99.5% of patients in the pooled melflufen group, most commonly thrombocytopenia and neutropenia.
- Renal or urinary adverse events, as defined by the MedDRA System Organ Class, were infrequent (10.7%), with low rates of acute kidney injury (2.3%) and renal failure (1.4%) (**Table 2**).
- Serious adverse events of renal and urinary disorders were reported in 3% (**Table 3**).

Table 2. Renal adverse events in the pooled melflufen group (Any Grade ≥1% of patients)

Adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)
Renal and urinary disorders	23 (5.3)	8 (1.9)	12 (2.8)	0	3 (0.7)	46 (10.7)
Acute kidney injury	2 (0.5)	2 (0.5)	5 (1.2)	0	1 (0.2)	10 (2.3)
Renal failure	1 (0.2)	1 (0.2)	2 (0.5)	0	2 (0.5)	6 (1.4)
Dysuria	6 (1.4)	1 (0.2)	1 (0.2)	0	0	8 (1.9)
Haematuria	4 (0.9)	1 (0.2)	1 (0.2)	0	0	6 (1.4)

AE, adverse event

Table 3. Renal serious adverse events in the pooled melflufen group (Any Grade ≥2 patients)

Serious adverse event	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)	Any Grade n (%)
Renal and urinary disorders	0	2 (0.5)	8 (1.9)	0	3 (0.7)	13 (3.0)
Acute kidney injury	0	1 (0.2)	5 (1.2)	0	1 (0.2)	7 (1.6)
Renal failure	0	0	2 (0.5)	0	2 (0.5)	4 (0.9)

SAE, serious adverse event

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DISCLOSURES

AL: honoraria from Celgene, Janssen, BMS, and Amgen. **AO:** honoraria and advisory board participation for Janssen, Amgen, BMS, Sanofi, and Roche. **FS:** honoraria and consultancy fees and has participated in advisory boards for Amgen, BMS, Janssen, Sanofi and Oncopeptides. **LP:** honoraria and consulting fees from Janssen, Amgen, and BMS. **MAD:** honoraria from participation in advisory boards/satellite symposia from Amgen, Sanofi, Regeneron, Menarini, Takeda, GSK, BMS, Janssen, Beigene, Swixx, Astra Zeneca. **MT & SN:** employees of and receive stock or stock options from Oncopeptides AB. **MTK**: adboard/consultancy from Amgen, BMS/Celgene, J&J, Sanofi, Takeda, GSK, Pfizer, Stemline, Oncopeptides, Kite/Gilead. **MVM:** honoraria from lectures and advisory boards for JJ, BMS, GSK, pfizer, abbvie, amgen, sanofi, kite, stemline, oncopeptides. **PGR**: honoraria/consulting fees from Amgen, Celgene, Bristol Myers Squibb, Janssen, Takeda, Oncopeptides and Karyopharm. **PS**: honoraria/consultancy fees/research funding from Janssen, Amgen, Bristol Myers Squibb, and Takeda. **SB**: Honoraria/ad board participation from Amgen Celgene/BMS, GSK, Janssen, Sanofi, Abbvie, Takeda, Pfizer, Stemline Therapeutics, Oncopeptides. Consultancy fees from Sanofi.

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