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DRUG EVALUATION

Melflufen for relapsed and refractory multiple myeloma

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ABSTRACT

Introduction: The overall survival of patients with multiple myeloma has improved with the advent of novel agents; however, multiple myeloma remains incurable. Combinations of standard-of-care agents such as immunomodulators, proteasome inhibitors, and anti-CD38 monoclonal antibodies are increasingly used in earlier lines of therapy. Patients with disease that is refractory to multiple novel agents represent a population with high unmet medical need and for whom therapies with new mechanisms of action could be beneficial. Melphalan flufenamide (melflufen) has demonstrated encouraging activity in patients with relapsed and refractory multiple myeloma.

Areas covered: This review provides an overview of the mechanism of action of melflufen, a first-in-class peptide-drug conjugate that targets aminopeptidases and rapidly delivers alkylating agents into tumor cells. It reviews key Phase I and II clinical trial data for melflufen in combination with dexamethasone as well as in triplet combinations with daratumumab or bortezomib. The safety profile of melflufen, which is characterized primarily by clinically manageable hematologic adverse events, is described.

Expert opinion: Melflufen has potential to fill a gap in the myeloma treatment landscape by providing a new mechanism of action with clinically meaningful efficacy and a favorable safety profile in patients refractory to multiple novel agents.

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Melflufen; melphalan flufenamide; relapsed/refractory multiple myeloma

1. Introduction

Multiple myeloma (MM), is a plasma cell neoplasia, characterized by an abnormal proliferation of aberrant plasma cells in the bone marrow and the production of a clonal immunoglobulin [1]. Median age at diagnosis is 69 years with a third of patients diagnosed over the age of 75 years [2]. MM is associated with bone lesions and fractures, infections, and end-organ damage [1,3]. Despite new treatment options that have improved outcomes for patients with MM, the disease remains incurable [4,5]. Approved and commonly used treatments for MM include immunomodulatory drugs (IMiDs), proteasome inhibitors, alkylators, and monoclonal antibodies (mAbs) [6–10]. In addition, histone deacetylase inhibition using panobinostat in combination with bortezomib and dexamethasone as well as IMiDs confers meaningful clinical benefit in the relapsed and refractory setting [11–13]. Currently, patients who relapse after receiving prior IMiDs, proteasome inhibitors, anti-CD38 mAbs such as daratumumab, and anti-signaling lymphocytic activation molecule F7 (SLAMF7) mAbs such as elotuzumab have limited treatment options [14]. The combination of agents with distinct mechanisms of action (MOAs) has the potential to enhance efficacy and overcome resistance mechanisms by exerting complementary antimyeloma effects [5,15]. Chemotherapy has historically been a mainstay of treatment, but aside from melphalan as a conditioning agent prior to transplant or the use of alkylator-based regimens in older patients in certain regions, chemotherapy usage is decreasing based on the superiority of novel targeted agents [6,16]. Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) being evaluated in clinical trials in patients with relapsed/refractory MM (RRMM, Box 1) [17–20]. Agents such as melflufen with distinct MOAs are needed to address growing unmet needs in RRMM.

1.1. Unmet needs in RRMM

In the last decade, combinations based on IMiDs, proteasome inhibitors, anti-CD38 mAbs such as daratumumab, and anti-SLAMF7 mAbs such as elotuzumab have significantly improved outcomes and prolonged survival in patients with MM [21–25]. In the frontline setting, new combination strategies with anti-CD38 mAbs have shown clinical benefit, including triplet and quadruplet regimens that contain IMiDs, proteasome inhibitors, and steroids to complement older modalities of therapy and stem cell transplant [26,27]. While

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Article Highlights

- Patients with multiple myeloma that are refractory to multiple agents with distinct mechanisms of action have limited treatment options, face universally poor outcomes, and are in urgent need of novel therapeutics.
- Melphalan flufenamide (melflufen) is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and rapidly releases alkylating agents into tumor cells.
- Melflufen has demonstrated potent cytotoxic activity *in vitro* in multiple myeloma cells, including those with resistance to other treatments (e.g., immunomodulatory drugs, proteasome inhibitors, and alkylators), and induces irreversible DNA damage and apoptosis.
- Melflufen in combination with dexamethasone has demonstrated clinically meaningful efficacy in patients with heavily pretreated relapsed/refractory multiple myeloma, including in patients with triple-class–refractory disease and those with extramedullary disease.
- Melflufen has demonstrated a well-established safety profile with clinically manageable hematologic adverse events being most common.

Box 1. Drug summary.

Drug name (generic)	Melphalan flufenamide (melflufen)
Phase (for indication under discussion)	I, II, and III study
Indication (specific to discussion)	Multiple myeloma
Pharmacology description/mechanism of action	Peptide-drug conjugate
Route of administration	40 mg IV (on day 1 of each 28-day cycle)
Chemical formula	$C_{24}H_{30}Cl_2FN_3O_3$
Pivotal trial	HORIZON [16]

IV: intravenous.

these combinations have potential to further improve patient outcomes, their use in frontline can result, at relapse, in patients with disease that is refractory to several drugs with different MOAs. Moreover, the choice of second-line treatment is largely dependent on prior therapy and prior response to therapy, and a class switch is often prioritized [28,29].

MM is characterized by the emergence of therapy-resistant clones driven by selective pressure of treatment throughout the disease course [4,5,27]. Patients with RRMM with disease refractory to multiple novel agents represent a population with high unmet medical need and limited effective treatment options as well as poor outcomes. In the retrospective MAMMOTH study, 275 patients with RRMM refractory to an anti-CD38 mAb had received a median of four and a maximum of 16 lines of therapy [30]. Survival was dismal overall and for the subgroups of 'not triple-refractory' (refractory to 1 anti-CD38 mAb and not both of a proteasome inhibitor and an IMiD), 'triple- and quad-refractory' (refractory to 1 anti-CD38 mAb plus 1 proteasome inhibitor or IMiD plus 1 or 2 therapies of the other class), and 'penta-refractory' (refractory to 1 anti-CD38 mAb plus 2 proteasome inhibitors plus 2 IMiDs) patients. Median overall survival (OS) was 8.6 months for all patients, 11.2 months for patients who were not triple-refractory, 9.2 months for those with triple- or quadruple-refractory disease, and 5.6 months for those with penta-refractory disease. Similarly, poor survival outcomes for patients refractory to an IMiD and a proteasome inhibitor were reported in 2017, with a median OS of 13 months [31]. Among 249 patients in the MAMMOTH study who received therapy after becoming refractory to daratumumab or isatuximab, the overall response rate (ORR) declined from 31% for the second line of treatment to 18% for the sixth [30]. This lack of efficacy highlights the urgent need for additional therapies to treat patients with advanced RRMM.

1.2. Therapies with new MOAs for RRMM

Several novel drugs with new MOAs have been approved or are in development for RRMM, including selective inhibitors of nuclear export (selinexor), B-cell maturation antigen (BCMA)-directed immunotherapies, and the PDC melflufen [23,32,33]. Selinexor is approved in the US in combination with dexamethasone to treat patients with RRMM who have received at least four prior therapies and who have disease that is refractory to at least two proteasome inhibitors, two IMiDs, and an anti-CD38 mAb [34,35]. Selinexor plus dexamethasone was evaluated in the Phase II STORM study in patients with RRMM and triple-class refractory disease [34]. In STORM, patients (N = 122) had received a median of seven (range, 3–18) prior treatment regimens, 65 (53%) had high-risk cytogenetics, including 32 (26%) with del(17p) [34]. In the primary analysis, the ORR was 26% with a median progression-free survival (PFS) and median OS of 3.7 months and 8.6 months, respectively [34]. Common grade ≥3 adverse events (AEs) with selinexor and dexamethasone were thrombocytopenia (59%), anemia (44%), fatigue (25%), hyponatremia (22%), and neutropenia (21%). Among patients with grade ≥3 thrombocytopenia, grade ≥3 bleeding events were observed in 6 patients (5%) [34].

Idecabtagene vicleucel (bb2121; ide-cel), an investigational autologous BCMA chimeric antigen receptor (CAR) T-cell therapy [36], was evaluated in a Phase I study (CRB-401) in 33 patients with RRMM who had received at least three prior therapies, including an IMiD, a proteasome inhibitor, or both, and in the expansion phase, patients had prior daratumumab, and were refractory to their most recent therapy [36]. The ORR was 85% and, with a median follow-up of 11.3 months (range, 6.2–22.8), the median PFS was 11.8 months [36]. Common grade 3/4 AEs with ide-cel were anemia (45%/0%), leukopenia (18%/39%), thrombocytopenia (15%/30%), and neutropenia (6%/79%) [36]. Grade ≥3 cytokine release syndrome and neurotoxicity events were reported in 6% (n = 2) and 3% (n = 1) of patients treated with ide-cel, respectively, and no grade 4 cytokine release syndrome was reported [36]. One death (cardiopulmonary arrest) considered to be unrelated to treatment was reported [36]. Results from the CRB-401 study suggest ide-cel is safe and yields high response rates in patients with RRMM with at least three prior therapies [36]. KArMMA, an ongoing, multicenter Phase II study of ide-cel, examining the efficacy and safety of a 150-to-450x10^6 dose of ide-cel, has enrolled 128 patients with triple-exposed RRMM [37]. After a median follow up of 11.3 months, the study has met its primary endpoint, with an ORR of 73.4% [37]. The next-generation anti-BCMA CAR T–cell therapy bb21217, which adds a phosphoinositide 3-kinase inhibitor to enrich for

memory-like T cells, is currently in Phase I clinical studies [38].

The anti-BCMA antibody-drug conjugate belantamab mafodotin (GSK857916) was evaluated in a two-arm, randomized, open-label, Phase II study in patients with RRMM who had received three or more prior lines of therapy and who were refractory to IMiDs, proteasome inhibitors, and refractory or intolerant (or both) to an anti-CD38 mAb (DREAMM-2) [33]. In DREAMM-2, 196 patients were randomized to receive 2.5 mg/kg (n = 97) or 3.4 mg/kg (n = 99) doses of belantamab mafodotin [33]. As of the 21 June 2019 data cutoff, ORR was 31% and 34% in patients treated with the 2.5-mg/kg and 3.4-mg/kg dose of belantamab mafodotin, respectively. Median PFS was 2.9 months and 4.9 months at the 2.5-mg/kg and 3.4-mg/kg dose of belantamab mafodotin, respectively, and survival data were not mature at the data cutoff [33]. Common grade 3/4 AEs in the safety population receiving the 2.5-mg/kg (n = 95) or 3.4-mg/kg (n = 99) dose of belantamab mafodotin, were keratopathy (27% and 21%), thrombocytopenia (20% and 33%), and anemia (20% and 25%) [33]. Serious AEs (SAEs) occurred in 40% and 47% of patients treated at the 2.5-mg/kg and 3.4-mg/kg dose of belantamab mafodotin, respectively, and two treatment-related deaths were reported (1 with the 2.5-mg/kg dose [due to sepsis] and 1 with the 3.4-mg/kg dose [due to hemophagocytic lymphohistiocytosis]) [33]. In DREAMM-2, belantamab mafodotin showed clinically meaningful activity consistent with that of previously reported data for the DREAMM-1 study. Despite higher-risk patients being more numerous in DREAMM-2 than in DREAMM-1, the AE profile of DREAMM-2 was acceptable and no new safety signals were identified [33,39].

1.3. Emerging agents

Bispecific antibodies are still in the earliest stages of development, yet they have the potential to be a viable treatment option for patients with RRMM. Clinical data have been reported for three BCMA:CD3 bispecific agents: AMG 420, CC-93269, and REGN5458 [40–42]. In a first-in-human study of AMG 420, among 42 patients who received 400 micrograms/day of AMG 420, the ORR was 70%, with only one patient (2.4%) being treated for grade 3 cytokine release syndrome [43]. In a first-in-human study of CC-93269, 12 patients were treated with at least 6 mg of CC-93269 every week or biweekly which resulted in an ORR of 83.3% [44]. In this study, one of 19 patients (5.3%) died of cytokine release syndrome. A Phase 1 study of REGN5458 used a similar dosing regimen (6 mg every week/biweekly) in 4 patients, 75% of whom responded [45]. No cases of grade ≥3 CRS were reported in seven patients.

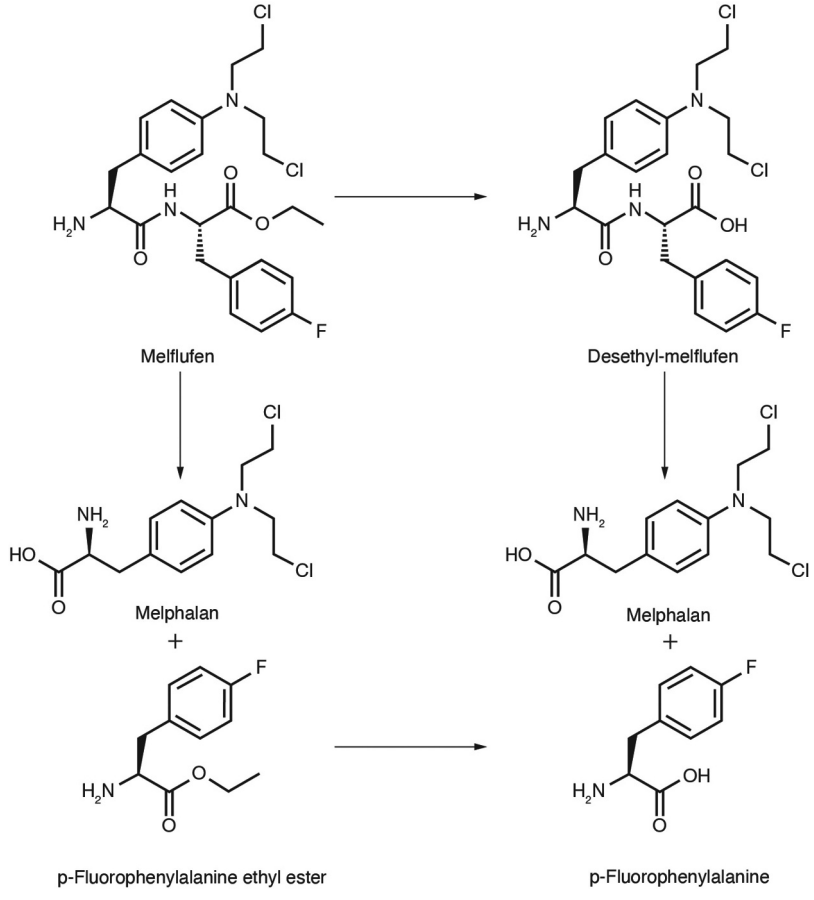

Figure 1. Clinical structure of melflufen hydrochloride and its metabolites melphalan and desethylmelflufen.
Figure reproduced with permission from Schjesvold F, Robak P, Pour L, et al. Future Oncol. 2020;16(11):631–41 [32].

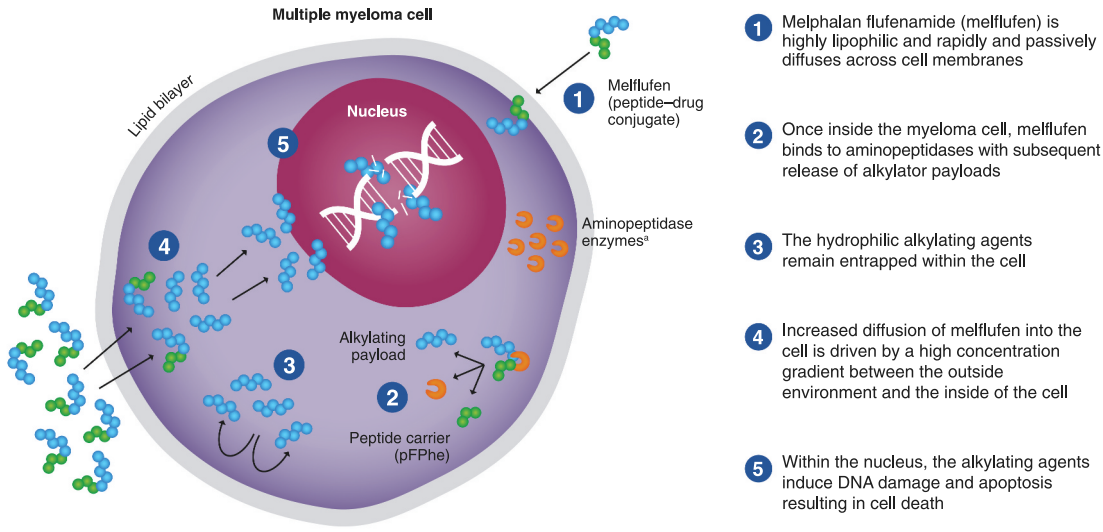

Figure 2. Melflufen mechanism of action.

Melflufen targets aminopeptidases and rapidly releases alkylating agents into tumor cells. Peptidases are expressed in several types of cancer cells, including those of MM. Melflufen is rapidly taken up by mylema cells due to its high lipophilicity. Once inside the multiple myeloma cell, the activity of melflufen is dependent on its immediate hydrolysis by peptidases, which unleashes its more hydrophilic alkylator payloads that remain entrapped within the cell.

2. Melflufen

2.1. Mechanism of action

Melflufen is a first-in-class peptide-drug conjugate (PDC) that targets aminopeptidases and rapidly releases alkylating agents into tumor cells (Figure 1) [17,46]. Peptidases are expressed in several types of cancer cells, including those of MM [47–49]. Melflufen is rapidly taken up by myeloma cells due to its high lipophilicity [17,46]. Once inside the myeloma cell, the activity of melflufen is dependent on its immediate hydrolysis by peptidases, which unleashes its more hydrophilic alkylator payloads that remain entrapped within the cell (Figure 2) [17,50,51]. Melflufen rapidly induces irreversible DNA damage and apoptosis via an alkylator-like, yet distinct mechanism of cytotoxicity that is independent of p53 function in MM cells [46,52,53]. Melflufen is 50-fold more potent than melphalan in MM cells *in vitro* because the combined effects of its high lipophilicity and intracellular binding to aminopeptidases results in increased intracellular alkylator exposure with melflufen (vs melphalan) [17,46,54]. Melflufen also has significant anti-myeloma activity, comparing favorably with melphalan *in vivo* with traditional xenografts [46] or genetically engineered transgenic models of the disease [55].

2.2. Overview of clinical trials

2.2.1. O-12-M1

O-12-M1 was a Phase I/II study to establish the dose and dosing schedule of melflufen in combination with dexamethasone and to investigate initial treatment responses in patients with RRMM with disease refractory to the last line of therapy [18]. The Phase I portion of the study originally employed a 21-day cycle with no dose-limiting toxicities occurring at the melflufen 40-mg dose level. However, in the Phase II dose-expansion portion of the study, the cycle length was increased from 21 to 28 days, providing additional time for recovery of the platelet and neutrophil counts, reducing the need for cycle delays and dose modifications, and allowing patients to remain on treatment longer [18]. Thus, O-12-M1 identified the maximum tolerated dose of melflufen of 40 mg and the minimum acceptable cycle length of 28 days in combination with dexamethasone as the recommended regimen for further evaluation in patients with RRMM [18]. Prior to the O-12-M1, a study of melflufen plus dexamethasone on patients with solid tumors demonstrated that the pharmacokinetic parameters of melflufen were not significantly influenced by weight, thus, a fixed dosing schedule was used in subsequent studies [56].

Table 1. Melflufen clinical trials summary table.

Trial name	No. of patients	Key inclusion criteria	Treatment(s)	Efficacy
0–12-M1: Phase II study of melflufen + dexamethasone in RRMM [18]	45	RRMM ≥2 prior lines of therapy Prior lenalidomide and bortezomib Refractory to last line of therapy (relapsed ≤60 days after completing treatment)	Melflufen + dexamethasone	Median follow-up: 27.9 mo ORR: 31% CBR: 49% mDOR: 8.4 mo mPFS: 5.7 mo mOS: 20.7 mo
HORIZON (OP-106): Pivotal phase II study of melflufen + dexamethasone in RRMM refractory to pomalidomide anti-CD38 mAb, or both [19]	154	RRMM ≥2 prior lines, including an IMiD and a PI Refractory to pomalidomide, anti-CD38 mAb, or both	Melflufen + dexamethasone	Follow-up (n = 125): ≥20 wks ORR: 29% CBR: 44% mDOR: 4.4 mo mPFS: 4.2 mo mOS: 11.6 mo
ANCHOR (OP-104): Phase I/II study of melflufen + dexamethasone + bortezomib or daratumumab in RRMM [20]	33	RRMM 1–4 prior lines of therapy Refractory (or intolerant) to IMiDs, PIs, or both	Melflufen + dexamethasone + daratumumab	Median follow-up: 6.6 mo ORR: 76% CBR: 79% mPFS: 14.3 mo
	6	RRMM 1–4 prior lines of therapy Refractory (or intolerant) to IMiDs, PIs, or both	Melflufen + dexamethasone + bortezomib	Median follow-up: 13.4 mo ORR: 67% CBR: 83%
OCEAN (OP-103): Phase III study of melflufen + dexamethasone in RRMM refractory to lenalidomide [32]	~450	RRMM 2–4 prior lines of therapy Relapsed and refractory or refractory to last line of therapy Refractory to lenalidomide administered ≤18 mo prior to randomization	Melflufen + dexamethasone vs pomalidomide + dexamethasone	–
LIGHTHOUSE [57]	170 (planned)	RRMM Double refractory (or intolerant) to an IMiD and a PI *or* ≥3 prior lines of therapy including an IMiD and a PI	Melflufen + daratumumab vs daratumumab (2:1)	–

CBR: clinical benefit rate; IMiD: immunomodulatory agent; mAb: monoclonal antibody; mDOR: median duration of response; mOS: median overall survival; mPFS: median progression-free survival; ORR: overall response rate; PI: proteasome inhibitor; RRMM: relapsed/refractory multiple myeloma.

Table 2. Most common treatment-emergent AEs with melflufen and dexamethasone in O-12-M1 [18].

	Melflufen in combination with dexamethasone (n = 45)		
Adverse events, n (%)	All grades	Grade 3–4	Grade 5
Thrombocytopenia	33 (73)	28 (62)	0 (0)
Neutropenia	31(69)	27 (60)	1 (2)
Anemia	29 (64)	20 (44)	0 (0)
Pyrexia	18 (40)	2 (4)	0 (0)
Asthenia	14 (31)	3 (7)	0 (0)
Fatigue	13 (29)	2 (4)	0 (0)
Nausea	12 (27)	0 (0)	0 (0)
Diarrhea	11 (24)	1 (2)	0 (0)
Pneumonia*	7 (16)	3 (7)	2 (4)

*There was one case each of a grade 3 and a grade 5 pneumonia overlapping with a grade 4 neutropenia.

In 45 patients treated in the Phase II portion of O-12-M1, melflufen and dexamethasone demonstrated durable responses with a manageable safety profile. Patients had received a median of four prior lines of therapy (interquartile range, 3–5), 24 (53%) had received prior alkylator therapy, 30 (67%) were double-refractory (proteasome inhibitor and IMiD), nine (20%) had International Staging System (ISS) stage III disease, 20 (44%) had high-risk cytogenetics by fluorescence in situ hybridization, and 26 (58%) had a prior autologous stem cell transplant [18]. ORR by investigator assessment was 31%, including 5 patients who achieved very good partial response (VGPR) and 9 who achieved partial response (PR), and the clinical benefit rate (CBR; ≥minimal response) was 49% (Table 1) [18]. After a median follow-up of 27.9 months, the median duration of response (DOR) was 8.4 months, and median PFS and OS were 5.7 months and 20.7 months, respectively (Table 1) [18]. The most common AEs (all grades), regardless of relationship to study drug, included thrombocytopenia (73%), neutropenia (69%), anemia (64%), pyrexia (40%), and asthenia (31%) (Table 2) [18]. Grade ≥3 AEs, regardless of cause, occurred in 91% of patients, and melflufen-related grade ≥3 AEs occurred in 58%. The most common melflufen-related grade 3/4 AEs were thrombocytopenia (58%) and neutropenia (58%) [18]. Overall, seven bleeding events, all grade 1, were reported in association with grade 4 thrombocytopenia [18]. Treatment-emergent SAEs were reported in 38% of patients, with pneumonia being the most common (11%) and febrile neutropenia being observed in 4% of patients [18]. Overall, four deaths occurred in patients with rapidly progressing disease within 30 days of the last dose of melflufen, two of which (neutropenic sepsis and *Escherichia coli* sepsis) were assessed as possibly treatment related.

2.2.2. HORIZON

HORIZON (OP-106) is a pivotal, single-arm, multicenter, Phase II study evaluating the efficacy and safety of melflufen and dexamethasone in heavily pretreated and poor-risk patients with RRMM refractory to pomalidomide or an anti-CD38 mAb, or both [19]. In an interim analysis of HORIZON, melflufen and dexamethasone had efficacy and was generally safe and well tolerated in 154 patients with RRMM who had exhausted most salvage therapy options (data cutoff 1 October 2019) [19]. Patients had a median age of 64.5 years (range, 35–86) and had received a median of five prior lines of therapy (range, 2–12) with 83% of patients having received prior alkylator therapy; 32% had ISS stage III disease, 38% had high-risk cytogenetics, 32% had extramedullary disease, 71% had triple-class refractory disease, and 69% had received ≥1 prior autologous stem cell transplant. Among 125 efficacy-evaluable patients, the ORR by investigator assessment was 29% (1 stringent complete response [CR], 12 VGPR, and 23 PR) and the CBR was 44% (Table 1) [19]. The median DOR was 4.4 months, median PFS was 4.2 months, and median OS was 11.6 months [19]. In patients with triple-class refractory disease and extramedullary disease, ORR was 24% and 24%, median DOR was 7.5 and 5.1 months, median PFS was 4.0 and 3.0 months, and median OS was 11.3 and 8.1 months, respectively. In the overall population (N = 154), 97% of patients experienced a treatment-emergent AE and 85% experienced a grade 3 or 4 treatment-emergent AE. The most common (≥20%) grade 3/4 treatment-emergent AEs were thrombocytopenia (21%/48%), neutropenia (31%/35%), and anemia (36%/1%) [19]. In addition, febrile neutropenia was also observed (4%/1%), and the incidence of nonhematologic AEs was low [19]. As of the interim analysis data cutoff, five patients (3%) have died due to treatment-emergent AEs and none of these deaths were treatment related [19]. These findings are highly encouraging because patients in whom lenalidomide- and PI-based treatments have failed have limited remaining effective treatment options [28,30].

2.2.3. ANCHOR

ANCHOR (OP-104) is a Phase I/II study evaluating the safety and efficacy of melflufen and dexamethasone in triplet combinations in patients with RRMM [20]. Preliminary data from ANCHOR showed activity of melflufen and dexamethasone with daratumumab or bortezomib. As of the data cutoff (8 October 2019), 33 patients had been treated with melflufen (6 with a 30-mg dose; 27 with a 40-mg dose) in combination with daratumumab and dexamethasone, with a median treatment duration of 6.2 months (range, 0.9–18.0) [20]. Patients had a median of 2.5 (range, 1–3) and 2 (range, 1–4) prior lines of therapy in the 30-mg and 40-mg melflufen treatment groups, respectively [20]. In addition, 83% and 89% of patients had received prior alkylator therapy in the 30-mg and 40-mg melflufen treatment groups, respectively. However, patients must have been naïve to prior anti-CD38 mAb therapy [20]. The ORR (≥PR) was 76% (1 stringent CR, 11 VGPR, and 13 PR), the CBR was 79%, and median PFS was 14.3 months [20]. At data cutoff, six patients had been treated with melflufen (3 with 30 mg; 3 with 40 mg) plus dexamethasone and bortezomib, with a median treatment duration of 9.3 months. Patients had a median of 2.5 prior lines of therapy (range, 2–4), and no patient had achieved CR in any previous line [20]. Further, all patients had previously been exposed to a proteasome inhibitor, but could not have been refractory to proteasome inhibitors, and 5 patients had received prior alkylator therapy [20]. ORR was 67%, and the CBR was 83% in these six patients, including two patients each who achieved VGPR and PR [20]. No dose-limiting toxicities were observed at any of the evaluated dose levels during dose-escalation with either daratumumab or bortezomib combinations. Among patients who received melflufen 30 mg (n = 6) and 40 mg (n = 27) in the

daratumumab combination group, the most common grade 3/4 treatment-related AEs (≥2 patients) were neutropenia (83%/56%), thrombocytopenia (50%/67%), and anemia (50%/7%) [20]. Six patients in this group experienced treatment-related SAEs, including febrile neutropenia (n = 2), abdominal pain, pancytopenia, pyrexia, respiratory failure, sepsis, and upper respiratory tract infection (n = 1 each) [20]. In the six patients in the bortezomib combination group, grade 3/4 treatment-related AEs of thrombocytopenia (n = 5), neutropenia (n = 3), anemia (n = 1), and pneumonia (n = 1) were observed and one patient experienced treatment-related SAEs (neutropenia and pneumonia) [20].

2.3. Safety and tolerability

Patients with RRMM have depleted bone marrow reserves due to the disease as well as side effects of prior therapy, and cytopenias are common [58]. Despite cytopenias being common with melflufen, particularly thrombocytopenia, they are clinically manageable with a low incidence of bleeding events [18]. However, it is important to vigilantly monitor cytopenias with melflufen and to provide appropriate management and supportive care for platelet count recovery including dose reductions, growth factor support, and platelet transfusions [59,60]. Despite working through an alkylator-dependent mechanism, melflufen does not appear to cause alopecia and incidence of mucositis is low, primarily grade 1/2 [18].

2.4. Regulatory status

Melflufen is an investigational drug and has been granted orphan drug designation in the United States and Europe [61]. The US Food and Drug Administration granted priority review to the New Drug Application for melflufen in combination with dexamethasone for the treatment of adult patients with triple-class refractory MM, with a target date for review of the New Drug Application set for February 28, 2021 [62].

3. Conclusions

To date, melflufen has demonstrated durable responses and a manageable safety profile in patients with RRMM. Treatment-related AEs associated with melflufen and dexamethasone are primarily hematologic, and rates of nonhematologic AEs are low. Based on the encouraging activity and acceptable safety profile of melflufen in RRMM, the randomized, head-to-head, superiority, open-label, global, Phase III OCEAN (OP-103) study is evaluating the efficacy and safety of melflufen plus dexamethasone versus pomalidomide plus dexamethasone in patients with RRMM who received two to four prior therapies including lenalidomide within 18 months and are refractory to the last line of therapy (Table 1) [32]. Top-line results for OCEAN are expected in the first half of 2021 [32].

4. Expert opinion

Current standards in the treatment of MM include combinations of IMIDs, proteasome inhibitors, corticoids, and mAbs in frontline and early relapse treatment settings. As a consequence, there is a growing need for novel agents with alternative MOAs for patients with RRMM who are refractory to IMiDs, proteasome inhibitors, and anti-CD38 mAbs. A major proportion of patients who do not enjoy a prolonged response to frontline treatment are expected to be triple-class refractory early in the course of disease, as triplet or quadruplet combinations of effective agents are used both upfront and at first relapse. In contrast, the role of alkylating agents in early MM is becoming relatively limited, except for the use of high dose melphalan in younger patients. The encouraging efficacy of melflufen and dexamethasone in RRMM suggests this combination will provide an important option and translate successfully to real-world practice, strengthened by the convenience of a monthly infusion schedule [63]. Specifically, the activity of melflufen in the triple-class refractory patient population is promising, given the otherwise poor prognosis in these patients. Melflufen as a single agent appears to be not only effective in patients not exposed to alkylating agents but also to overcome prior chemotherapy resistance. Its response rate in extramedullary disease is of interest too, as extramedullary disease represents a major issue in the context of aggressive MM progression. In addition to its distinct MOA, melflufen has a manageable and a toxicity profile nonoverlapping with alternative agents. Although oral drugs are preferred options at early stages of the disease, gastrointestinal toxicity, mainly diarrhea and malabsorption, are present in a relevant proportion exposed to lenalidomide and pomalidomide. Patients with a prior history of gastrointestinal toxicity may not be ideal candidates for selinexor therapy. Similarly, panobinostat may have a limited role due to toxicity issues. Others may have limited options by virtue of prior treatment-related toxicity such as peripheral neuropathy, both features melflufen does not share. Melflufen may also be more suitable than belantamab mafodotin and other investigational agents for a subset of patients given its otherwise limited nonhematologic toxicity, including absence of alopecia and minimal mucositis as well as low rates of infection, an especially important consideration in the current era. Its predictable hematologic toxicity and potency may further position melflufen as a preferred option for bridging therapy for other important emerging treatment strategies such as CAR T-cell therapy. Moreover, significantly greater clinical activity is anticipated from the combination of melflufen with proteasome inhibitors or mAbs in a less advanced setting, with preliminary data strongly supporting this [20]. Furthermore, if the efficacy and safety of melflufen in combination with daratumumab is confirmed, melflufen could also be a potential partner for immunotherapeutic agents such as bispecific antibodies in the near future, providing an ideal combination of drugs with high individual efficacy, MOAs not exhausted in previous treatment lines, and a potentially relatively favorable safety profile.

The remarkable progress observed in MM treatment may be able to provide a very prolonged disease-free period for a significant proportion of patients or even cure some of them. However, it is expected that most individuals still relapsing will present more aggressive and resistant disease. We need to increase our armamentarium to face the needs of such individuals with drugs and combinations with alternative MOAs.

Melflufen may become a preferred choice either in combination with dexamethasone only or with third agents.

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Declaration of interest

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