Current Hematologic Malignancy Reports (2022) 17:306–318
https://doi.org/10.1007/s11899-022-00682-4

MULTIPLE MYELOMA (PRASHANT KAPOOR, SECTION EDITOR)

The Role of Belantamab Mafodotin, Selinexor, and Melflufen in Multiple Myeloma

Arleigh McCurdy[1] · **Alissa Visram**[1]

Accepted: 11 September 2022 / Published online: 22 November 2022

Abstract

Purpose of Review Multiple myeloma (MM) is a hematologic malignancy of plasma cells that remains incurable with currently available therapies including proteosome inhibitors, immunomodulators, monoclonal antibodies, corticosteroids, and alkylators, in addition to autologous stem cell transplantation in patients who are eligible. Novel therapeutics are therefore required to improve patient outcomes. The goal of this paper is to review the role of three new agents in the MM treatment landscape: belantamab mafodotin, selinexor, and melflufen.

Recent Findings All three agents have demonstrated clinical activity in patients with MM. Belamaf is the first FDA-approved anti-BCMA targeted agent, showing single-agent response rates of 60% and higher response rates of 48–100% in combinations. The majority of patients treated with belamaf experience corneal toxicity which remains the main challenge with its use; however, fortunately, the vast majority of patients recover. Selinexor is also FDA approved for the treatment of relapsed MM, with single-agent response rates of 26% and combination rates of 48–65%. Gastrointestinal side effects are common with selinexor use, with roughly 65% of patients experiencing nausea, 50% anorexia, 35% vomiting, and 42% diarrhea, the majority of which are grades 1–2. Both agents have a plethora of ongoing clinical trials with data forthcoming on various combinations with standard backbone agents as well as additional novel treatments. While melflufen showed promising initial data showing single-agent response rates of about 30%, inferior survival outcomes in patients previously treated with ASCT in the phase 3 OCEAN study lead to early termination of the trial and subsequent removal from the US market.

Summary Belamaf, selinexor, and melflufen are active agents to treat myeloma. Belamaf and selinexor are current options for the treatment of relapsed multiple myeloma with improved response rates and durability when used in triplet combinations. The optimal timing of use and treatment combinations of both agents in the context of additional immunotherapeutics entering the MM landscape requires further study. Many prospective studies are in development and promise to afford further clarity in the near future.

Keywords Multiple myeloma · Treatment · Selinexor · Belantamab mafodotin · Melflufen

Introduction

Multiple myeloma (MM) is a common malignant neoplasm of plasma cells. The treatment of MM has evolved rapidly over the last two decades, with the advent of novel therapeutics leading to significant increases in patient survival. Despite substantial improvement in patient outcomes, MM remains incurable in the vast majority of cases and disease relapse is expected. The mainstays of treatment for newly diagnosed and relapsed patients include various combinations of proteosome inhibitors (PIs) (bortezomib, carfilzomib, ixazomib), immunomodulatory drugs (IMIDs) (lenalidomide, pomalidomide, thalidomide), monoclonal anti-CD3 antibodies (mABs) (daratumumab, isatuximab),

This article is part of the Topical Collection on *Multiple Myeloma*

✉ Alissa Visram
alisvisram@toh.ca

Arleigh McCurdy
amccurdy@toh.ca

[1] Division of Hematology, Department of Medicine, The Ottawa Hospital Research Institute & The University of Ottawa, Box 704-501 Smyth Rd, Ottawa, ON K1H 8L6, Canada

and autologous stem cell transplantation (ASCT) in select fit patients.

Ultimately, patients become triple-class refractory (refractory to a PI, IMID, MAB) or, increasingly, penta-refractory (refractory to bortezomib, carfilzomib, lenalidomide, pomalidomide, and daratumumab), and new therapeutic options are required. The review focuses on belantamab mafodotin, selinexor, and melflufen as treatment for relapsed/refractory multiple myeloma (RRMM). Published clinical trial data for these agents is summarized in Table 1 (study designs), Table 2 (efficacy data), and Table 3 (toxicity data).

Belantamab Mafodotin

Belantamab mafodotin (belamaf) is a first-in-class afucosylated humanized anti-BCMA IgG1 monoclonal antibody conjugated to microtubule disrupting monomethyl auristatin F (MMAF). It binds to FcγRIIIa on plasma cells resulting in activation and recruitment of immune effector cells and enhanced antibody-dependent cell-mediated cytotoxicity (ADCC) [10].

The initial phase 1/2 trial (DREAMM-1) in patients with heavily pre-treated RRMM administered belamaf monotherapy in a dose escalation from 0.03 to 4.60 mg/kg over 1 h by intravenous (IV) every 3 weeks for up to 16 cycles [6]. While no maximum tolerated dose (MTD) was reached in phase 1, the trend towards the increased frequency of grade 3/4 corneal events at higher doses and lower clinical activity at doses ≤ 2.5 mg/kg led to a recommended dose of recommended phase 2 dose (RP2D) of 3.4 mg/kg^2. The overall response rate (ORR) in the phase 2 portion was 60% (95% CI: 42.1–76.1); 46.2% (95% CI: 19.2–74.9) in patients who had previously had > 5 prior therapies and 68.2% (95% CI: 45.1–86.1) in those with ≤ 5 prior lines [6]. Notably, single-agent belamaf had a 38.5% (95% CI: 13.9–68.4) in patients refractory to an IMID and PI and daratumumab exposed [7]. At a median follow-up of 12.5 months, the median progressive-free survival (PFS) was 12 months (95% CI: 3.1–not estimable), 6.2 months in those refractory to IMID PIs and daratumumab exposed, 7.9 months in those refractory to IMIDs and PIs, and 15.7 months in those not previously treated with daratumumab [7].

The DREAMM-2 study was a randomized phase 2 trial of single-agent belamaf (2.5 mg/kg vs. 3.4 mg/kg every 3 weeks) in patients with RRMM refractory to a PI, IMID, and anti-CD38 mAB [8]. Approximately one-third of patients in each cohort received an anti-CD38 mAB as the last prior therapy. The ORR was 31% (97.5% CI: 20.8–42.6) at the 2.5 mg/kg dose and 34% (23.9–46.0) at the 3.4 mg/kg dose, with 60% and 59% of responders achieving ≥ VGPR in each cohort, respectively [8]. At a median follow-up of 6.3 months (2.5 mg/kg group)/6.9 months (3.4 mg/kg group), the median PFS was 2.9 months (95% CI: 2.1–3.7) and 4.9 months (2.3–6.2), with OS not yet reached. Longer term median follow-up of 13.0 months was recently reported for the 2.5 mg/kg group, showing a median PFS of 2.8 months (95% CI: 1.6–3.6) and OS of 13.7 months (95% CI: 9.9–NR) [11]. Both study cohorts had similar clinical efficacy, but the 2.5 mg/kg dose had a favorable safety profile and was therefore recommended for further trials. The promising single-agent activity and PFS demonstrated study has supported the development of further clinical trials of belamaf combination regimens.

The forthcoming belamaf studies are summarized in Table 4. DREAMM-3 is a randomized phase 3 trial of belamaf in combination with pomalidomide and dexamethasone (Pd) versus Pd which is currently enrolling, in which belantamab is being administered in 4 cohorts: 1.92 mg/kg, 2.5 mg/kg single dose, 2.5 mg/kg split on days 1 and 8, or 3.4 mg/kg split on days 1 and 8 [12]. This will build upon the data from the Canadian Myeloma Research Group (CMRG) ALGONQUINN trial, which is a phase 1/2 study of belamaf-Pd exploring multiple doses of belamaf in the triplet combination. This study identified an MTD of belamaf 2.5 mg/kg combined with standard dose Pd, and preliminary data on 60 patients with a median of 3 prior lines of therapy showed a promising ORR of 88.9% with ≥ VGPR 62% and median PFS 24.2 months [13]. The combination of belamaf-Pd is also being studied in the DREAMM-8 trial, a large randomized study of belamaf-Pd with belamaf dosed at 2.5 mg/kg cycle 1 and 1.92 mg/kg cycle 2 onwards versus pomalidomide, bortezomib, and dexamethasone (PVd), the results of which are eagerly anticipated [14].

Preliminary data from part 1 of the DREAMM-4, a phase 1/2 trial of belamaf in combination with pembrolizumab, was recently presented [15]. Patients were dosed at either belamaf 2.5 mg/kg or 3.4 mg/kg with pembrolizumab 200 mg IV every 3 weeks. At a median follow-up duration of 6.8 months in the 2.5 mg/kg group and 4.2 months in the 3.4 mg/kg group, keratopathy was the most common AE with similar AE profiles in both groups and no DLTs [15]. ORR was 67% in the 2.5 mg/kg group and 43% in the 3.4 mg/kg group, with the 2.5 mg/kg dose selected for part 2 [15]. At a median follow-up of 14.7 months, preliminary efficacy results of 34 patients (6 in part 1 and 28 in part 2) who had a median of 5 prior lines of therapy, 29% high-risk cytogenetics and 26% extramedullary disease, showed a median ORR of 47% with 63% of responders achieving ≥ VGPR [16]. Median PFS was months with no new safety signals observed [16].

The DREAMM-5 study is a large phase 1/2 platform study currently accruing in patients post ≥ 3 prior therapies (including a PI, IMID, and anti-CD38 MAB), evaluating the combination of belamaf with GSK3174998 (OX 40 agonist), feladilimab (GSK3359609, ICOS agonist), nirogacestat

Table 1 Study design of pivotal phase 2/3 trials of melflufen, selinexor, and belantamab mafodotin-based regimens

	Study design, primary endpoint	Key inclusion criteria	Intervention (*n*)	Comparator (*n*)
Melflufen				
HORIZON (2021) [1]	• Phase 2 • 1° endpoint: ORR	• ≥ 2 prior therapies • PI and IMID exposed • Refractory to pomalidomide ± antiCD38 mAb	Md until progression, death, or intolerable toxicity (*n* = 157): • Melflufen 40 mg IV q4 weeks • Dexamethasone 40 mg PO qweekly	-
OCEAN (2022) [2]	• Phase 3 • Open label • 1° endpoint: PFS	• 2–4 prior lines (inc. PI and lenalidomide) • Refractory to lenalidomide (within 18 months of randomization) and last line of therapy	Md until progression, death, or intolerable toxicity (*n* = 246): • Melflufen 40 mg IV q4 weeks • Dexamethasone 40 mg PO qweekly	Pd until progression, death, or intolerable toxicity (*n* = 249): • Pomalidomide 4 mg PO daily × 21/28 days • Dexamethasone 40 mg PO qweekly
Selinexor				
STORM Part 2 (2019) [3]	• Phase 2 • 1° endpoint: ORR	• Penta-exposed[a] • Triple refractory[b] • Refractory to last line of therapy	Sd until progression, death, or intolerable toxicity (*n* = 122): • Selinexor 80 mg PO twice/week • Dexamethasone 20 mg PO twice/week	-
STOMP (2018) [4]	• Phase 1b/2 • 1° endpoint: MTD, ORR, DOR, CBR	• ≥ 1 prior line • Not progressing on bortezomib in most recent therapy line	SVd • Selinexor 80 mg once weekly–80 mg twice weekly (based on cohort) • Dexamethasone 20 mg twice weekly–40 mg weekly (based on cohort) • Bortezomib 1.3 mg/m^2 once weekly or twice weekly (based on cohort)	-
BOSTON (2020) [5]	• Phase 3 • Open label • Randomized • If progression on Vd, crossover to SVd allowed	• 1–3 prior lines • ≥ 6 months since last PI, and ≥ PR with PI-based therapy, and no grade ≥ 3 toxicity leading to bortezomib discontinuation	SVd until progression, death, or intolerable toxicity (*n* = 195): • Selinexor 100 mg PO qweek • Bortezomib 1.3 mg/m^2 twice/week × 24 weeks, then once weekly • Dexamethasone 20 mg 4 times/week × 24 weeks, then twice/week	Vd until progression, death, or intolerable toxicity (*n* = 207): • Bortezomib 1.3 mg/m^2 twice/week × 24 weeks, then once weekly • Dexamethasone 20 mg 4 times/week × 24 weeks, then twice/week
Belantamab mafodotin				
DREAMM-1 (2018) [6, 7]	• Phase 1/2 • Open label • Single agent, single arm	• PI, IMID, alkylator exposed • Refractory to last line	Phase 1 (*n* = 38): Dose escalation belamaf (0.03–4.6 mg/kg) IV q3wk (until progression or unacceptable toxicity, maximum 16 cycles) Phase 2 (*n* = 35): Belamaf 3.4 mg/kg IV q3wk (until progression or unacceptable toxicity, maximum 16 cycles)	-

Table 1 (continued)

	Study design, primary endpoint	Key inclusion criteria	Intervention (*n*)	Comparator (*n*)
DREAMM-2 (2020) [8, 9]	• Phase 2 • Open label • Single agent, randomized to dose level	• ≥ 3 prior lines • Refractory: PI/IMID • Refractory or intolerant: antiCD38 mAb	Arm 1 (*n* = 97): Belamaf 2.5 mg/kg IV, q3 weeks until progression/toxicity	Arm 2 (*n* = 99): Belamaf 3.4 mg/kg IV, q3 weeks until progression/toxicity

Bold data: Investigational agents

Abbreviations: PI, proteosome inhibitor; *PR*, partial response; *SV*, selinexor, bortezomib, dexamethasone; *DOR*, duration of response; *CBR*, clinical benefit rate; *mAb*, monoclonal antibody; *Md*, melflufen + dexamethasone; *ORR*, overall response rate; *Pd*, pomalidomide + dexamethasone; *Sd*, selinexor + dexamethasone; *SVd*, selinexor + bortezomib + dexamethasone; *Vd*, bortezomib + dexamethasone

[a]Prior treatment with bortezomib, carfilzomib, lenalidomide, pomalidomide, daratumumab, glucocorticoids, and an alkylating agent

[b]Refractory to at least one IMID, one PI, and daratumumab

(gamma-secretase inhibitor), and dostarlimab (anti-PD1 MAB) [17]. Preliminary results of the feladilimab group showed a promising ORR of 48% and a manageable safety profile among 23 heavily pre-treated patients (median 5 prior lines of therapy) [18]. The initial results of 10 patients, with a median of 4.5 prior lines, treated with low-dose belamaf (0.95 mg/kg Q3W) and nirogacestat 100 mg BID in the dose escalation phase of this substudy were recently presented [19]. The ORR was 60% with one-third of responders achieving VGPR, with 70% of patients experiencing grade 1–2 keratopathy, diarrhea, and hypophosphatemia [19].

DREAMM-6 is an ongoing two-part phase 1/2 study of belamaf combined with either lenalidomide or bortezomib for RRMM after ≥ 1 prior treatment. Preliminary results of 18 patients on the belamaf (2.5 mg/kg single dose cohort), bortezomib, and dexamethasone arm showed an ORR of 78% with ≥ VGPR rate of 50%, with universal ocular toxicity that was manageable [20]. An interim analysis of 45 patients with median 3 prior lines treated on the belamaf (1.9 mg kg Q8W or Q4W; 2.5 mg/kg Q4W or Q4W split dose) (50% days 1 and 8) with lenalidomide and dexamethasone cohort was recently presented [21]. The ORR was 75% in the belamaf 1.9 mg/kg Q4W group (*n* = 12), 42% in the 1.9 mg/kg Q8W group (*n*-4), 63% in the 2.5 mg/kg group (*n* = 16), and 69% in the 2.5 mg/kg Q4W split group (*n* = 13), with median PFS not yet reached at the time of data cutoff [21]. No new safety signals were identified. The phase 3 DREAMM-7 study is ongoing, randomizing patients with relapsed MM and ≥ 1 prior therapy to belamaf in combination with bortezomib and dexamethasone (BVd) vs. daratumumab, bortezomib, and dexamethasone (DVd) [22].

Belamaf is also being evaluated in patients with newly diagnosed MM. Preliminary results of a phase 1/2 study of the combination of belamaf, lenalidomide, and dexamethasone in newly diagnosed patients ineligible for transplant showed no new safety signals with the first 18 patients enrolled [23]. DREAMM-9 is an ongoing phase 3 study in newly diagnosed transplant-ineligible patients which randomizes patients to different dose intensities and schedules of belamaf in combination with bortezomib, lenalidomide, and dexamethasone (VRd). A preliminary report on 12 patients showed no new or unexpected safety signals [24].

Toxicity

The most challenging adverse event observed with belamaf is corneal toxicity, which has been described previously with monomethyl auristatin F (MMAF) antibody combinations [25], and is attributable to MMAF, possibly due to non-specific drug uptake by dividing cells in the basal epithelial layer of the cornea [26]. Corneal examinations including a slit-lamp examination for keratopathy and best-corrected visual acuity (BCVA) assessment are currently considered

Table 2 Efficacy outcomes of melflufen, selinexor, and belantamab mafodotin based on selected phase 2/3 pivotal clinical trials

	Med. prior lines	Prior PI (%), IMID (%), antiCD38 mAb (%)	mFU (months)	Responses (ORR%, ≥*CR%)*	mPFS (months)	Median time to first response (months)
Melflufen						
HORIZON [1]		Prior ref.:				
Md ($n=157$)	5 (r. 2–12)	64, 97, 80 13% ref. to melphalan	14	29%, *1%*	4.2 (95% CI 3.4–4.9)	Median time to ≥ PR: 1.9 (r. 1–7.4)
OCEAN [2]		Prior exposure:				
I: Md ($n=249$) C: Pd ($n=249$)	I: 3 (IQR 2–3) C: 3 (IQR 2–3)	I: 66, 100, 20 C: 65, 100, 16	I: 19.8 C: 18.6	I: 33%, *3%* C: 27%, *1%*	I: 6.8 (95% CI 5.0–8.5) C: 4.9 (95% CI 4.2–5.7)	I: 2.1 (IQR 1.1–3.7) C: 2.0 (IQR 1.1–2.9)
Selinexor						
STORM [3] Sd ($n=122$)	7 (range 3–18)	Prior ref.: 100, 100, 100	-	26%, 2%	3.7 (95% CU 3–5.3)	-
STOMP [4] SVd ($n=42$)	3 (range 1–11)	PI ref.: 50% PI + IMID ref.: 45%	-	63%, 8%	9 ($n=40$ evaluable patients)	1.2 (IQR 1.2–1.7)
BOSTON [5]	1 prior line (%):	Prior exposure:				If ≥ PR:
SVd ($n=195$) Vd ($n=207$)	I: 51% C: 48%	I: 82, 45, 6 C: 87, 43, 3	I: 13.2 C: 16.5	I: 76%, 17% C: 62%, 10%	I: 13.9 (11.7–NE) C: 9.5 (8.1–10.8)[a]	I: 1.1 (IQR 0.8–1.6) C: 1.4 (IQR 0.8–1.6)
Belantamab mafodotin						
DREAMM-1 [7]	≥ 5 prior lines (%)	Prior ref.:				
P1($n=38$): 0.03–4.6 mg/kg P2 ($n=35$): 3.4 mg/kg	P1: 76% P2: 57%	P1: 0, 0, 0 P2: 97, 91, 37	P2: 12.5 (r. 0.7–23.2)	P2: 60%, *14%*	P2: 12 (95% CI 3.1–NE)	P2: 1.2 (95% CI 0.7–1.4)
DREAMM-2 [9]		Prior ref.:				
Arm 1 ($n=97$): 2.5 mg/kg Arm 2 ($n=99$): 3.4 mg/kg	Arm 1: 7 (range 3–21) Arm 2: 6 (range 3–21)	Arm 1: 76, 90, 100 Arm 2: 75, 89, 92	Arm 1: 12.4 (r. 0.1–17.9) Arm 2: 6.9 (IQR 4.8–7.9)	Arm 1: 32%, *7%* Arm 2: 34%, *3%*	Arm 1: 2.8 (95% CI 1.6–3.6) Arm 2: 4.9 (95% CI 2.3–6.2)	- -

Bold data: Investigational agents

Abbreviations: *belamaf*, belantamab mafodotin; *Ref*, refractory; *int*, intolerant; *P1*, phase 1 trial; *P2*, phase 2 trial; *ORR*, overall response rate; *I*, intervention; *C*, comparator; *r.*, range; *IQR*, interquartile range

[a]Of the 30% of patients progressing on Vd that crossed over and received SVd, only 19% responded with the addition of selinexor

standard for monitoring patients receiving belamaf, with examination findings combined and graded for toxicity [27]. The keratopathy and visual acuity (KVA scale) has been developed for identifying and grading corneal events [11]. Corneal examination findings range from mild to severe superficial keratopathy with or without microcysts, subepithelial haze, or stromal opacity, as well as corneal epithelial defects such as ulcers [27]. Symptomatically, ocular manifestations include dry eyes, photophobia, blurry vision, and reduced visual acuity [6]. The majority of patients experience corneal toxicity, and it is the most common reason for dose delays and reductions [27]. Fortunately, the vast majority of patients recover with a median time to recovery of 86.5 days (range 8–358) [7–9, 11].

The mainstay of management of corneal events is dose reduction/modification [11]. The original trial protocols recommended prophylactic corticosteroid eye drops four times daily for 7 days and preservative-free lubricating drops 4–8 times daily [6, 8]. An ocular substudy of DREAMM-2 evaluated corticosteroid eye drops given in one eye only and showed no difference in ocular events between the two eyes. This suggests that corticosteroid eyedrops are not effective prophylaxis for preventing corneal complications [8]. Currently, it is recommended that patients use preservative-free

Table 3 Adverse effects of melflufen, selinexor, and belantamab mafodotin based on selected phase 2/3 pivotal clinical trials

	Melflufen			**Selinexor**				**Belantamab mafodotin**		
	HORIZON [1]	**OCEAN** [2]		**STORM** [3]	**STOMP** [4]	**BOSTON** [5]		**DREAMM-1** [7]	**DREAMM-2** [8, 9]	
	Md ($n=157$)	**Md** ($n=246$)	**Pd** ($n=249$)	**Sd** ($n=123$)	**SVd** ($n=42$)	**SVd** ($n=195$)	**Vd** ($n=207$)	Phase 2 ($n=35$)	2.5 mg/kg ($n=95$)	3.4 mg/kg ($n=99$)
Hematologic AE (*Gr.3,* Gr. 4)										
Anemia	*42%, < 1%*	*40%, 2%*	*17%, 1%*	*43%, 1%*	*12%, 0%*	*36%, 16%*	*23%, 10%*	*14%, 0%*	*20%, 0%*	*22%, 3%*
Thrombocytopenia	*25%, 51%*	*32%, 31%*	*6%, 4%*	*36%, 33%*	*17%, 29%*	*60%*[†]*, 39%*[†]	*27%, 17%*	*26%, 9%*	*8%, 12%*	*11%, 22%*
Neutropenia[a]	*32%, 47%*	*36%, 30%*	*32%, 18%*	*18%, 3%*	*32%, 2%*	*15%, 9%*	*6%, 3%*	*9%, 3%*	*5%, 4%*	*12%, 3%*
Non-hematologic AE *all grade,* Gr. ≥ 3)										
Infusion reactions	-	-	-	-	-	-	-	*23*[d]*%, 6%*	*21%, 3%*	*16%, 1%*
Peripheral neuropathy	-	-	-	-	*10%, 0%*	*32%, 5%*	*47%, 9%*	-	-	-
GI side effects										
Nausea	*32%, < 1%*	*13%, < 1%*	*7%, < 1%*	*72%, 10%*	*62%, 5%*	*50%, 8%*	*10%, 0%*	*23%, 0%*	*24%, 0%*	*32%, 1%*
Vomiting	*13%, 0%*	-	-	*38%, 3%*	*31%, 2%*	*21%, 4%*	*4%, 0%*	*6%, 0%*	*7%, 2%*	*20%, 0%*
Diarrhea	*27%, 0%*	*14%, 1%*	*8%, < 1%*	*46%, 7%*	*43%, 7%*	*32%, 6%*	*25%, < 1%*	*17%, 3%*	*13%, 1%*	*15%, 1%*
Weight loss	-	-	-	*50%, 1%*	*19%, 0%*	*26%, 2%*	*12%, 1%*	-	-	-
Fatigue[e]	*29%, 3%*	*14%, 0%*	*17%, 1%*	*73%, 25%*	*60%, 15%*	*42%, 13%*	*18%, 1%*	*20%, 0%*	*16%, 2%*	*28%, 5%*
Asthenia	*27%, 3%*	*15%, 2%*	*11%, 2%*	-	-	*25%, 8%*	*13%, 4%*	-	*4%, 0%*	*8%, 2%*
Infections										
Pneumonia[b]	*13%, 10%*	*15%, 11%*	*20%, 15%*	*17%, 11%*	-	*18%, 12%*	*17%, 10%*	*15%, 6%*	*9%, 6%*	*21%, 16%*
URTI[c]	*16%, 2%*	*18%, 3%*	*21%, 2%*	*22%, 2%*	-	*18%, 3%*	*15%, < 1%*	*17%, 0%*	*7%, 0%*	*17%, 1%*
Ocular AE	-	-	-	-	-	-	-			
Keratopathy	-	-	-	-	-	-	-	*9%, 3%*	*72%, 46%*	*71%, 21%*
Blurred vision	-	-	-	*11%, 2%*	-	-	-	*46%, 0%*	*25%, 4%*	*30%, 2%*
Dry eye	-	-	-	-	-	-	-	*34%, 3%*	*15%, 1%*	*23%, 0%*
Eye pain	-	-	-	-	-	-	-	*6%, 3%*	-	-
Photophobia	-	-	-	-	-	-	-	*23%, 0%*	-	-
Decreased visual acuity	-	-	-	-	-	-	-	*3%, 3%*	*54%, 31%*	-
Hyponatremia	-	-	-	*37%, 22%*	*10%, 5%*	-	-	*3%, 0%*	*5%, 2%*	*7%, 4%*

[†]Thrombocytopenia occurred despite 18% of patients in the SVd arm being treated with thrombopoietin receptor agonists (compared to 1% of patients in the Vd arm)

[a]Includes neutropenia, decreased neutrophil count, and febrile neutropenia

[b]Includes pneumonia, COVID-19 pneumonia, lower respiratory tract infection, respiratory tract infection, influenzal pneumonia, pneumonia legionella, and pneumonia respiratory syncytial viral

[c]Includes upper respiratory tract infection and bronchitis

[d]Per protocol, pre-medication was not allowed for the first infusion

[e]Includes fatigue and lethargy

Table 4 Active* clinical trials including belantamab mafodotin (where recruitment is ongoing or anticipated)

Trial	Phase	*N*	Inclusion	Intervention	Primary endpoint	Status
NDMM						
NCT04808037	½	66	Transplant ineligible	Belamaf + Rd until progression (belamaf doses vary, study evaluates dose modification guidelines for corneal AE)	Safety (DLT, AE, SAE) and ORR	Recruiting
NCT05280275	½	36	Transplant ineligible	Belamaf + DVRD until progression	Safety (DLT, AE, SAW, ocular toxicity), ORR	NYR (start: March 2022)
NCT04091126 (DREAMM-9)	3	144	Transplant ineligible	Belamaf + VRD until progression (differing dose intensity and schedule)	Safety (DLT, AE)	Recruiting
NCT04802356	2	50	Transplant eligible	Belamaf + VRD induction, ASCT intensification, belamaf + VRD consolidation, belamaf + lenalidomide maintenance	Safety (death, AE, biochemical abnormalities, ocular events)	Recruiting
NCT04680468	2	47	Transplant eligible within < 12 m diagnosis	Pre-/post-ASCT belamaf + lenalidomide maintenance	MRD(-) by NGS at 12mo post-ASCT	Recruiting
NCT05091372	2	94	Post-ASCT	Belamaf maintenance*versus* Lenalidomide maintenance	MRD(+) to MRD(-) CR conversion	NYR (start: April 2022)
NCT05208307	2	34	≥ PR post-ASCT with high-risk[a] disease	Belamaf + Pd maintenance until progression	CR rate (best response on maintenance)	NYR (start: March 2022)
NDMM + RRMM						
NCT04822337	1/2	70	P1: RRMM (1–3 prior lines) P2: High-risk NDMM[b]	Belamaf + KRD	MTD and ≥ CR post induction	Recruiting
NCT04892264	1/2	76	P1: RRMM (≥ 1 prior line, IMID/PI exposed) P2: NDMM	Belamaf + DR induction, belamaf + DR maintenance until progression *versus* Belamaf + DRd induction, belamaf + DR maintenance until progression	P1: MTD P2: CR after induction	Recruiting
NCT04876248	2	20	MRD(+) or < CR post-ASCT	Belamaf + lenalidomide consolidation post-transplant	MRD(-) post consolidation	NYR (start: March 2022)
RRMM						
NCT05065047	1	20	Post-salvage ASCT	Belamaf maintenance	Safety/tolerability	NYR (start: March 2022)
NCT05060627	1/2	60	1–3 prior lines	Belamaf + Kd	ORR and AE	Recruiting
NCT03732703 (MyDRUG)	1/2	228	1–3 prior lines with early relapse	Belamaf + ixazomib + Pd *versus*7 other treatment arms	ORR	Recruiting
NCT03715478 (ALGONQUIN)	½	96	≥ 2 prior lines (PI and IMID exposed)	Belamaf + Pd	P1: RP2D P2: ORR	Recruiting
NCT04398680 (DREAMM-13)	1	28	> 2 prior lines	Belamaf (dose varies based on hepatic function)	PK, safety, tolerability	Recruiting

Table 4 (continued)

Trial	Phase	*N*	Inclusion	Intervention	Primary endpoint	Status
NCT04398745 (DREAMM-12)	1	36	≥3 prior lines, PI and IMID exposed	Belamaf (dose varies based on renal function)	PK, safety, tolerability	Recruiting
NCT05064358 (DREAMM-14)	2	180	≥3 prior lines	Belamaf (different dose and schedule, to optimize safety)	Grade ≥2 ocular AE	Recruiting
NCT04896658	1/2	64	≥3 prior lines, triple refractory	Belamaf + Cd	P1: AE incidence and severity P2: ORR (≥PR)	Recruiting
NCT04126200 (DREAMM-5)	1/2	464	≥3 prior lines (PI, IMID, antiCD38 mAb exposed)	Belamaf platform study (belamaf monotherapy or in combination with feladilimab, nirogacestat, dostarlimab, isatuximab, GSK3174998)	Safety (DLT, AE, SAE, abnormal vital signs, biochemical/lab abnormalities), ORR	Recruiting
NCT04643002 (UMBRELLA)	1/2	66	≥3 prior lines, non-refractory to antiCD38 mAb	Belamaf + isatuximab + dexamethasone *versus* 2 other isatuximab-based treatment arms	Safety, ≥VGPR rate	Recruiting
NCT02343042 (STOMP)	1b/2	518	PI/IMID refractory, antiCD38 mAb exposed, belamaf naïve	Belamaf + Selinexor + dexamethasone *versus* 10 other selinexor-based treatment arms	Safety, duration of response, ≥MR	Recruiting
NCT05117008	2	45	≥3 lines pre-CART, non-relapsed post anti-BCMA CAR-T therapy	Belamaf maintenance post-CART	PFS (at 12mo)	NYR (March 2022)
NCT05002816	2	24	≥3 prior lines	Belamaf + elotuzumab	Safety (MTD, DLT)	NYR (Feb 2022)
NCT04162210 (DREAMM-3)	3	380	≥3 prior lines	Belamaf *versus* Pd	PFS	Recruiting
NCT04484623 (DREAMM 8)	3	450	>1 prior line, IMID exposed	Belamaf + Pd *versus* PVd	PFS	Recruiting

Bold data: Disease status at trial inclusion

Abbreviations: *belamaf*, belantamab mafodotin; *NDMM*, newly diagnosed multiple myeloma; *Rd*, lenalidomide + dexamethasone; *DVRD*, daratumumab + bortezomib + lenalidomide + dexamethasone; *DLT*, dose-limiting toxicity; *AE*, adverse event; *SAE*, serious adverse events; *ORR*, overall response rate being ≥ partial response; *VRD*, bortezomib + lenalidomide + dexamethasone; *MRD*, minimal residual disease; *ASCT*, autologous stem cell transplant; *CR*, complete response; *NYR*, not yet recruiting; *RRMM*, relapsed refractory multiple myeloma; *KRD*, carfilzomib + daratumumab + dexamethasone; *DR*, daratumumab + lenalidomide; *MTD*, maximum tolerated dose; *Kd*, carfilzomib + dexamethasone; *Pd*, pomalidomide + dexamethasone; *PK*, pharmacokinetics; *IMID*, immunomodulatory drug; *PI*, proteosome inhibitor; *Cd*, cyclophosphamide + dexamethasone; *PR*, partial response; *CART*, chimeric antigen receptor T-cell; *BCMA*, B-cell maturation antigen; *PVd*, pomalidomide + bortezomib + dexamethasone

[a]High-risk MM defined as primary plasma cell leukemia, del17p, t(4;14), t(14;16), t(14;20)

[b]High-risk MM defined as the presence of del1p, gain1q, del13q, t(4;14), t(14;16), t(14;20)

*This table was up to date as of at the date of manuscript submission

lubricating eye drops at least 4 times daily for the duration of their treatment [11].

It is currently unclear how ocular toxicity and necessary dose interruption affect patient response and outcomes. A study of 38 consecutive heavily treated patients (median 8 prior lines) who received ≥ 1 dose of belamaf 2.5 mg/kg evaluated this question, with a median duration of belamaf treatment of 2 months and median 11 months of follow-up [28]. The ORR for the overall cohort was 20% and the median PFS was 2 months [28]. As expected, 75% of patients in this cohort experienced corneal toxicity, with 58% having decreased BCVA and 69% keratopathy, occurring at a median time of 1.4 months into therapy and improving after withholding belamaf for median 2.4 months [28]. In this study, belamaf was permanently discontinued or delayed due to keratopathy in 10 of the 38 patients (26%), with 7 of those patients experiencing MM progression within 3 months while off belamaf [28]. This study raises the issue of belamaf feasibility in the context of advanced MM in the real world, though larger studies are needed to evaluate this question.

Thrombocytopenia is commonly reported [6, 8] and is also consistent with previous reports associated with MMAF [25]. It can be significant, but it recovers between doses and bleeding events are rare [7, 8].

Selinexor

Selinexor is an oral selective inhibitor of nuclear export (SINE) small molecule that inhibits exportin 1 (XPO1) function, preventing the export of tumor suppressor proteins, oncoprotein mRNAs, and the glucocorticoid receptor [29, 30]. The nuclear retention of tumor suppressors, in addition to suppression of BCL-2 and MYC [31], leads to myeloma cell death [32].

The initial phase 1 study of selinexor in patients with hematologic malignancies, including heavily treated MM, explored a range of selinexor doses (45–160 mg) twice weekly [33]. The ORR was 23%, and based on tolerance and efficacy, the dose of 60 mg twice weekly was selected as the RP2D for hematologic malignancies [33]. Subsequently, part 1 of the STORM phase II trial of 79 MM patients (median of 7 prior lines, 48 and 31 of whom were quad- and penta-refractory, respectively), using selinexor 80 mg and dexamethasone 20 mg twice weekly was performed [34]. The ORR was 21% in quad-refractory patients and 20% in penta-refractory patients, with median PFS of 2.3 months and median OS of 9.3 months [34].

Part 2 of the STORM trial evaluated selinexor 80 mg and dexamethasone 20 mg twice weekly in a heavily treated patient population, with inclusion criteria requiring exposure to lenalidomide, pomalidomide, bortezomib, carfilzomib, glucocorticoids, an alkylator, and daratumumab. Patients also had to be triple refractory (refractory to a PI, IMID, and anti-CD38 mAb) and refractory to the last line of therapy [3]. One hundred and twenty-two patients were enrolled with a median of 7 prior lines of therapy, 68% penta-refractory and 96% refractory to carfilzomib, pomalidomide, and daratumumab [3]. The overall response rate was 26% with ≥ VGPR rate of 5%, median PFS 3.7 months, and OS 8.6 months [3].

With respect to combination trials, a phase 1 study of 21 patients, median 4 prior lines of therapy and 81% refractory to an IMID and PI, treated with selinexor in combination with carfilzomib and dexamethasone (SKd) established a recommended RP2D of selinexor 60 mg, carfilzomib 20/27 mg/m^2, and dexamethasone 20 mg, all twice weekly [35]. ORR was 48% with ≥ VGPR rate of 14% for the entire cohort; for 13 patients treated at the RP2D, the ORR was 38% with ≥ VGPR rate 15% [35]. A phase I study of the all-oral combination of selinexor, ixazomib, and dexamethasone (SId) was performed in 18 patients with 5 prior lines of therapy, establishing an MTD of selinexor 80 mg weekly in combination with dexamethasone 20 mg weekly and ixazomib 4 mg on days 1, 8, and 15 of a 28-day cycle, with an ORR of 22% in the cohort [36].

The phase 1b/2 STOMP study is an ongoing trial evaluating the safety and efficacy of selinexor in 10 combinations and 11 treatment arms. The combination arm of selinexor, bortezomib, and dexamethasone (SVd) has been reported, which included 42 patients with median 3 prior lines of treatment, of whom 50% were PI refractory and 45% were PI + IMID refractory [4]. The RP2D of SVd was determined at selinexor 100 mg, bortezomib 1.3 mg/m^2, and dexamethasone 40 mg all given once weekly in 35-day cycles, dosing at which no grade 3 or 4 nausea of vomiting was observed [4]. The ORR of the overall SVd cohort was 63% with 31% achieving a ≥ VGPR; ORR was 58% and 21% ≥ VGPR in those treated at the RP2D [4]. Median PFS was 9.0 months for the entire cohort, 6.1 months for the 21 patients who were PI refractory, and 17.8 months for the 19 patients who were not [4].

Preliminary results of the selinexor, pomalidomide, and dexamethasone (SPd) arm of STOMP were recently reported [37]. Twenty patients were treated with the selinexor 60 mg weekly and 19 patients with 40 mg weekly, both in combination with standard pomalidomide 4 mg on days 1–21 and weekly dexamethasone 40 mg. This group is less heavily pre-treated, with median 2 prior lines of therapy, 85% PI and 79% IMID refractory. In the 60 mg group, ORR was 65% with median PFS 8.9 months, whereas the ORR in the 40 mg group was 42% with median PFS not yet reached; no new safety concerns were identified [37].

The phase III Boston trial of 402 patients with relapsed MM compared SVd to Vd in patients treated with 1–3 prior lines of therapy [5]. At a median follow-up of 13.2 months for

the SVd group, the median PFS was 13.9 months as compared to the Vd cohort who had a median of 16.5 months of follow-up and a median PFS of 9.46 months [5]. A summary of active and accruing trials for selinexor is summarized in Table 5.

Toxicity

The main challenges in safety and tolerability in patients treated in clinical trials with selinexor are gastrointestinal in nature, with the most frequent non-hematologic AEs being nausea (62–73%), vomiting (31–44%), anorexia (49–60%), and diarrhea (42–43%), the majority of which were grades 1–2 [4, 34], with 5–8% of patients having grade 3–4 nausea and 5–7% having grade 3–4 diarrhea [4, 34]. Grade 3 hyponatremia occurred in 22% of patients [3, 34]. The most common grade 3–4 hematologic toxicity is thrombocytopenia (50–59%), followed by anemia (19–44%) and neutropenia (21–26%) [3, 4, 34], with grade 3 bleeding seen in only a minority of patients (3–5%) [3, 34].

Routine use of prophylactic and therapeutic anti-emetics is recommended. Administration of 8 mg of ondansetron (or other 5-HT3 agonists) prior to selinexor dosing, as well as up to three times daily as needed afterwards, is encouraged. We and others have found low-dose olanzapine (2.5 mg) two times daily as needed can also be effective for mitigating nausea for patients treated with selinexor [36]. Additional anti-emetic agents including low-dose benzodiazepines, megestrol, neurokinin-1 receptor antagonists, and cannabinoids have been described in patients treated with selinexor [38].

Thrombocytopenia is predictable and multifactorial, due to the drug in addition to additional factors such as prior myelosuppressive therapy and MM. Close monitoring of platelets is recommended and off-label use of eltrombopag or romiplostim can be considered for severe thrombocytopenia, in additional platelet transfusion if clinically indicated [38].

Melflufen

Melflufen is an alkylating agent and a melphalan prodrug that was developed to reduce drug resistance, increase tumor specificity, and reduce toxicity [39, 40]. It is rapidly incorporated into tumor cells due to its high lipophilicity and is hydrolyzed into melphalan by aminonopeptidase N, an enzyme highly expressed in MM cells, leading to an accumulation of melphalan inside MM cells and resultant cytotoxicity [39]. Pre-clinical studies demonstrated increased potency and the ability to overcome resistance to melphalan and novel agents, endorsing further clinical studies to improve outcomes in patients with RRMM [39, 40].

The initial phase 1/2 study in RRMM which included patients with ≥ 2 prior lines of treatment, PI and IMID exposed, established the maximum tolerated dose (MTD) of melflufen of 40 mg every 21 days with dexamethasone 40 mg weekly [41]. The phase 2 portion showed an ORR of 31% [41], with a median PFS of 5.7 months and overall survival (OS) of 20.7 months at a median follow-up of 46.0 months [42]. The phase 2 HORIZON study followed, which included patients with ≥ 2 prior therapies, also PI and IMID exposed as well as pomalidomide and/or daratumumab refractory [43]. Seventy-six percent of patients included in HORIZON were triple-class refractory, 59% alkylator refractory, and 35% had extramedullary disease [42]. With a median of 5.5 prior treatments, ORR was 29% with a median PFS of 4.2 months and OS of 11.6 months [1], including ORR of 26%, median PFS of 4.0 months, and OS of 11.3 months in patients with triple-class refractory disease [1].

The instructive phase 3 OCEAN study was a large trial of melflufen and dexamethasone versus pomalidomide and dexamethasone (Pd) in patients with RRMM after 2–4 prior lines of therapy. With the most recent update, 474 patients were randomized: 246 to receive melflufen and dexamethasone and 249 to Pd. Median prior therapies was 3 in both groups, with 50% having a prior transplant [2]. At a median follow-up of 15.5 months, the median PFS was 6.8 months in the melflufen group and 4.9 months in the Pd group, with median OS of 19.8 months and 25.0 months, respectively [2]. While exploratory analyses of PFS favored melflufen in most subgroups, Pd showed improved OS in patients who had previously had ASCT. Further analyses specifically evaluating patients with and without prior ASCT were performed. In the no prior ASCT cohort, the median PFS was 9.3 months in the melflufen group compared to 4.6 months in the Pd group, with a median OS of 21.6 months for melflufen and 16.5 months for Pd [2]. In contrast, patients with prior ASCT had a median PFS of 4.4 months for melflufen and 5.2 months for Pd, with median OS of 16.7 months and 31.0 months, respectively [2]. Post hoc multivariate analysis revealed prior ASCT and ECOG PS 1–2 vs. 0 as risk factors affecting OS [2]. The FDA requested suspension of enrollment based on this preliminary data, and subsequently, the sponsor withdrew melflufen from the US market [44].

With this development, two additional studies have since been terminated (the ANCHOR phase 1/2 study evaluating the combination of melflufen with bortezomib or daratumumab in RRMM and the phase 2 BRIDGE trial of patients with RRMM and renal impairment).

Toxicity

Melflufen is generally well tolerated, with the most common grade 3–4 AEs being hematologic and low frequencies of non-hematologic AEs [1, 41, 45, 46]. While rates of neutropenia (54–79%), thrombocytopenia (63–76%), and anemia (43%) were high, grade 3 (1–16%) and 4 (0–3%) bleeding events

Table 5 Active* clinical trials including selinexor (where recruitment is ongoing or anticipated)

Trial	Phase	*N*	Inclusion	Intervention	Primary endpoint	Status
NDMM						
NCT04717700	2	100	Transplant ineligible	Selinexor + V/R (alternating) + dex-*versus* VRD light	ORR	Recruiting
NCT04782687	2	100	Transplant ineligible	Selinexor + DRd	CR, sCR, safety	Recruiting
NDMM + RRMM						
NCT02343042 (STOMP)	1b/2	518	Specific to treatment arm	Selinexor + dexamethasone with: P, V, R, PV, Daratumumab, K, R, ixazomib, P + elotuzumab, belamaf, P + daratumumab	Safety, duration of response, ≥ MR	Recruiting
RRMM						
NCT04891744	1/2	48	≥ 1 prior line	Selinexor + Td	ORR	NYR (start: July 2021)
NCT04925193	2	20	≥ 1 prior line	Selinexor + Pd,*or* Selinexor + Kd,*or* Selinexor + daratumumab + dex	ORR	Recruiting
NCT05170789	2	18	≥ 1 prior line	Selinexor + elotuzumab + dexamethasone	ORR	NYR (start: January 2022)
NCT04877275	2	50	≥ 1 prior line	Selinexor + doxorubicin + dex,*or* Selinexor + cyclophosphamide + dex	ORR	Recruiting
NCT04941937	2	90	≥ 1 prior line	Selinexor + Td or Selinexor + Rd or Selinexor + Pd	ORR	Recruiting
NCT03732703 (MyDRUG)	1/2	228	1–3 prior lines with early relapse	Selinexor + ixazomib + Pd *versus*7 other treatment arms	ORR	Recruiting
NCT02199665	1	100	≥ 2 prior lines	Selinexor + Kd	MTD	Recruiting
NCT03944057 (MARCH)	2	82	IMID and PI refractory	Selinexor + dexamethasone	ORR	Recruiting
NCT04661137	2b	96	K or P refractory	Selinexor + Pd,*or* Selinexor + Kd,*or* Selinexor + daratumumab + dex (exploratory)	ORR	Recruiting
NCT04756401	2	52	1–3 prior lines, high risk[a]	Selinexor + Kd + daratumumab	MRD(-)	NYR (start: August 2022)
NCT04843579	2	26	1–4 prior lines	Selinexor + Pd + clarithromycin	ORR	Recruiting
NCT04414475	2b	134	> 1–5 prior lines (based on treatment arm)	Selinexor + dex (varying doses),*versus* Selinexor + Vd	ORR	Recruiting
NCT05028348	3	280	1–4 prior lines	Selinexor + Pd*versus* Elotuzumab + Pd	PFS	NYR (start: March 2022)
NCT04939142	3	150	1–3 prior lines	Selinexor + Vd,*versus* Vd	PFS	Recruiting
NCT04519476	Pilot	22	≥ 3 prior lines	Selinexor + lenalidomide + methylprednisolone	ORR, CBR	Recruiting
NCT04764942	1/2	81	≥ 2–3 prior lines (based on treatment arm), PI/IMID refractory	Selinexor + Pd ± carfilzomib	MTD, ORR	Recruiting
NCT05201118	1	30	≥ 3 prior lines, extramedullary disease,	Selinexor + CT103A (anti-BCMA CART)	PFS, ORR, DOR	NYR (start: February 2022)
NCT03589222	2	62	≥ 3 prior lines	Selinexor + Vd + daratumumab	ORR	Recruiting

Bold data: Disease status at trial inclusion

Abbreviations: *NDMM*, newly diagnosed multiple myeloma; *RRMM*, relapsed refractory multiple myeloma; *ORR*, overall response rate being ≥ partial response; *CBR*, clinical benefit rate; *CR*, complete response rate; *sCR*, stringent complete response; *PFS*, progression-free survival; *DOR*, duration of response; *MTD*, maximum tolerated dose; *MR*, minimal response; *MRD*, minimal residual disease; *NYR*, not yet recruiting; *V*, bortezomib; *R*, lenalidomide; *DRD*, daratumumab + lenalidomide + dexamethasone; *BCMA*, B-cell maturation antigen; *CART*, chimeric antigen receptor T-cell; *Pd*, pomalidomide + dexamethasone; *Kd*, carfilzomib + dexamethasone; *Vd*, bortezomib + dexamethasone; *P*, pomalidomide; *Td*, thalidomide + dexamethasone; *Rd*, lenalidomide + dexamethasone; *IMID*, immunomodulatory drug; *PI*, proteosome inhibitor

[a]High-risk MM defined as at least one of del1p, gain1q (≥ 3 copies), del17p, t(4;14), t(14;16), t(14;20), LDH above upper limit of normal, extramedullary disease, ISS stage 3 at relapse, ≥ 5% circulating plasma cells at relapse, high-risk gene expression profiling, relapse < 18 months on upfront transplant-ineligible regimen, and < 36 months post-ASCT on maintenance

*This table was up to date as of at the date of manuscript submission

are low [2, 42]. Non-hematologic AEs are less common and include pneumonia (3–10%) and other infections (11%–10); gastrointestinal events including diarrhea (12–27%), constipation (7–15%), and nausea/vomiting (13%) are common and mostly grades 1–2 with rare grade 3 events [2, 42].

Conclusions

This review focused on the respective roles of belantamab mafodotin, selinexor, and melflufen as treatment for RRMM. The majority of patients with RRMM will be exposed and/or refractory to PIs, IMIDs, and anti-CD38 MABs, given the increasing use of triplet and quadruplet therapies earlier in the disease course, and this population continues to be one of an unmet clinical need. While there are many novel therapeutics being studied in this space, including bi-specific antibodies and chimeric antigen receptor T cell (CAR-T) therapies, optimal therapy and its sequencing is not yet defined. Belantamab mafodotin and selinexor both have single-agent activity in RRMM with a reasonable safety profile, although the duration of response as single agents remains limited and combination use is recommended for the majority of patients. Evaluation of their respective safeties and efficacy in combinations in both newly diagnosed and relapsed diseases is ongoing. Melflufen has been withdrawn from the US market and currently is not recommended for the treatment of MM. Ongoing studies are needed to define the optimal partners, timing, and sequence for the use of belamaf and selinexor as treatments for MM.

Declarations

Conflict of Interest Arleigh McCurdy has received an honorarium for advisory boards for GSK and Forus Therapeutics. Alissa Visram has no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

References

1. Mateos M-V, et al. Clinical activity of melflufen in patients with triple-class refractory multiple myeloma and poor-risk features in an updated analysis of HORIZON (OP-106), a phase 2 study in patients with relapsed/refractory multiple myeloma refractory to pomalidomide and/or daratumumab. Blood. 2019;134:1883–1883. https://doi.org/10.1182/blood-2019-124825.
2. Schjesvold FH, et al. Melflufen or pomalidomide plus dexamethasone for patients with multiple myeloma refractory to lenalidomide (OCEAN): a randomised, head-to-head, open-label, phase 3 study. Lancet Haematol. 2022;9:e98–110. https://doi.org/10.1016/s2352-3026(21)00381-1.
3. Chari A, et al. Oral selinexor-dexamethasone for triple-class refractory multiple myeloma. N Engl J Med. 2019;381:727–38. https://doi.org/10.1056/NEJMoa1903455.
4. Bahlis NJ, et al. Selinexor plus low-dose bortezomib and dexamethasone for patients with relapsed or refractory multiple myeloma. Blood. 2018;132:2546–54. https://doi.org/10.1182/blood-2018-06-858852.
5. Grosicki S, et al. Once-per-week selinexor, bortezomib, and dexamethasone versus twice-per-week bortezomib and dexamethasone in patients with multiple myeloma (BOSTON): a randomised, open-label, phase 3 trial. Lancet. 2020;396:1563–73. https://doi.org/10.1016/s0140-6736(20)32292-3.
6. Trudel S, et al. Targeting B-cell maturation antigen with GSK2857916 antibody-drug conjugate in relapsed or refractory multiple myeloma (BMA117159): a dose escalation and expansion phase 1 trial. Lancet Oncol. 2018;19:1641–53. https://doi.org/10.1016/s1470-2045(18)30576-x.
7. Trudel S, et al. Antibody-drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: an update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019;9:37. https://doi.org/10.1038/s41408-019-0196-6.
8. Lonial S, et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): a two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020;21:207–21. https://doi.org/10.1016/s1470-2045(19)30788-0.
9. Lonial S, et al. Longer term outcomes with single-agent belantamab mafodotin in patients with relapsed or refractory multiple myeloma: 13-month follow-up from the pivotal DREAMM-2 study. Cancer. 2021;127:4198–212. https://doi.org/10.1002/cncr.33809.
10. Tai YT, et al. Novel anti-B-cell maturation antigen antibody-drug conjugate (GSK2857916) selectively induces killing of multiple myeloma. Blood. 2014;123:3128–38. https://doi.org/10.1182/blood-2013-10-535088.
11. Lonial S, et al. Management of belantamab mafodotin-associated corneal events in patients with relapsed or refractory multiple myeloma (RRMM). Blood Cancer J. 2021;11:103. https://doi.org/10.1038/s41408-021-00494-4.
12. Weisel K, et al. Dreamm-3: a phase 3, open-label, randomized study to evaluate the efficacy and safety of belantamab mafodotin (GSK2857916) monotherapy compared with pomalidomide plus low-dose dexamethasone (Pom/Dex) in participants with relapsed/refractory multiple myeloma (RRMM). Blood. 2019;134:1900–1900. https://doi.org/10.1182/blood-2019-129893.
13. Trudel S, et al. Part 1 results of a dose-finding study of belantamab mafodotin in combination with pomalidomide and dexamethasone for the treatment of relapsed/refractory multiple myeloma (RRMM). Blood. 2021;138:1653–1653. https://doi.org/10.1182/blood-2021-147101.
14. Trudel S, et al. DREAMM-8: a phase III study of the efficacy and safety of belantamab mafodotin with pomalidomide and dexamethasone (B-Pd) vs pomalidomide plus bortezomib and dexamethasone (PVd) in patients with relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136:4–4. https://doi.org/10.1182/blood-2020-139785.
15. Nooka A, et al. DREAMM-4: evaluating safety and clinical activity of belantamab mafodotin (belamaf) in combination with pembrolizumab in patients with relapsed/refractory multiple myeloma. Hematol Rep. 2020;12.
16. Suvannasankha A, et al. Safety and clinical activity of belantamab mafodotin with pembrolizumab in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-4 Study. J Clin Oncol. 2022;40:8018–8018. https://doi.org/10.1200/JCO.2022.40.16_suppl.8018.
17. Nooka AK, et al. Belantamab mafodotin in combination with novel agents in relapsed/refractory multiple myeloma:

DREAMM-5 study design. Future Oncol. 2021;17:1987–2003. https://doi.org/10.2217/fon-2020-1269.
18. Callander NS, et al. DREAMM-5 study: investigating the synergetic effects of belantamab mafodotin plus inducible T-cell costimulator agonist (aICOS) combination therapy in patients with relapsed/refractory multiple myeloma. Blood. 2021;138:897–897. https://doi.org/10.1182/blood-2021-152662.
19. Lonial S, et al. Synergistic effects of low-dose belantamab mafodotin in combination with a gamma-secretase inhibitor (nirogacestat) in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-5 study. J Clin Oncol. 2022;40:8019–8019. https://doi.org/10.1200/JCO.2022.40.16_suppl.8019.
20. Popat R, et al. DREAMM-6: safety, tolerability and clinical activity of belantamab mafodotin (belamaf) in combination with bortezomib/dexamethasone (BorDex) in relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136:19–20. https://doi.org/10.1182/blood-2020-139332.
21. Quach H, et al. Safety and clinical activity of belantamab mafodotin with lenalidomide plus dexamethasone in patients with relapsed/refractory multiple myeloma (RRMM): DREAMM-6 arm-A interim analysis. J Clin Oncol. 2022;40:8017–8017. https://doi.org/10.1200/JCO.2022.40.16_suppl.8017.
22. Rifkin RM, et al. DREAMM-7: a phase III study of the efficacy and safety of belantamab mafodotin (belamaf) with bortezomib, and dexamethasone (B-Vd) in patients with relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136:53–4. https://doi.org/10.1182/blood-2020-139181.
23. Terpos E, et al. A phase 1/2, dose and schedule evaluation study to investigate the safety and clinical activity of belantamab mafodotin administered in combination with lenalidomide and dexamethasone in transplant-ineligible patients with newly diagnosed multiple myeloma. Blood. 2021;138:2736–2736. https://doi.org/10.1182/blood-2021-152241.
24. Usmani SZ, et al. DREAMM-9: phase I study of belantamab mafodotin plus standard of care in patients with transplant-ineligible newly diagnosed multiple myeloma. Blood. 2021;138:2738–2738. https://doi.org/10.1182/blood-2021-153315.
25. Eaton JS, Miller PE, Mannis MJ, Murphy CJ. Ocular adverse events associated with antibody-drug conjugates in human clinical trials. J Ocul Pharmacol Ther. 2015;31:589–604. https://doi.org/10.1089/jop.2015.0064.
26. Zhao H, et al. Modulation of macropinocytosis-mediated internalization decreases ocular toxicity of antibody-drug conjugates. Cancer Res. 2018;78:2115–26. https://doi.org/10.1158/0008-5472.Can-17-3202.
27. Farooq AV, et al. Corneal epithelial findings in patients with multiple myeloma treated with antibody-drug conjugate belantamab mafodotin in the pivotal, randomized, DREAMM-2 study. Ophthalmol Ther. 2020;9:889–911. https://doi.org/10.1007/s40123-020-00280-8.
28. Abeykoon JP, et al. Impact of belantamab mafodotin-induced ocular toxicity on outcomes of patients with advanced multiple myeloma. Br J Haematol. 2022. https://doi.org/10.1111/bjh.18298.
29. Rosebeck S, et al. Synergistic myeloma cell death via novel intracellular activation of caspase-10-dependent apoptosis by carfilzomib and selinexor. Mol Cancer Ther. 2016;15:60–71. https://doi.org/10.1158/1535-7163.Mct-15-0488.
30. Podar K, Pecherstorfer M. Current and developing synthetic pharmacotherapy for treating relapsed/refractory multiple myeloma. Expert Opin Pharmacother. 2017;18:1061–79. https://doi.org/10.1080/14656566.2017.1340942.
31. Chim CS, et al. Management of relapsed and refractory multiple myeloma: novel agents, antibodies, immunotherapies and beyond. Leukemia. 2018;32:252–62. https://doi.org/10.1038/leu.2017.329.
32. Schmidt J, et al. Genome-wide studies in multiple myeloma identify XPO1/CRM1 as a critical target validated using the selective nuclear export inhibitor KPT-276. Leukemia. 2013;27:2357–65. https://doi.org/10.1038/leu.2013.172.
33. Chen C, et al. Safety, efficacy, and determination of the recommended phase 2 dose for the oral selective inhibitor of nuclear export (SINE) selinexor (KPT-330). Blood. 2015;126:258–258. https://doi.org/10.1182/blood.V126.23.258.258.
34. Vogl DT, et al. Selective inhibition of nuclear export with oral selinexor for treatment of relapsed or refractory multiple myeloma. J Clin Oncol. 2018;36:859–66. https://doi.org/10.1200/jco.2017.75.5207.
35. Jakubowiak AJ, et al. Phase 1 study of selinexor plus carfilzomib and dexamethasone for the treatment of relapsed/refractory multiple myeloma. Br J Haematol. 2019;186:549–60. https://doi.org/10.1111/bjh.15969.
36. Salcedo M, et al. Phase I study of selinexor, ixazomib, and low-dose dexamethasone in patients with relapsed or refractory multiple myeloma. Clin Lymphoma Myeloma Leuk. 2020;20:198–200. https://doi.org/10.1016/j.clml.2019.12.013.
37. White DJ, et al. Once weekly oral selinexor, pomalidomide, and dexamethasone in relapsed refractory multiple myeloma. Blood. 2021;138:2748–2748. https://doi.org/10.1182/blood-2021-148759.
38. Gavriatopoulou M, et al. Integrated safety profile of selinexor in multiple myeloma: experience from 437 patients enrolled in clinical trials. Leukemia. 2020;34:2430–40. https://doi.org/10.1038/s41375-020-0756-6.
39. Chauhan D, et al. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. Clin Cancer Res. 2013;19:3019–31. https://doi.org/10.1158/1078-0432.Ccr-12-3752.
40. Ray A, et al. A novel alkylating agent Melflufen induces irreversible DNA damage and cytotoxicity in multiple myeloma cells. Br J Haematol. 2016;174:397–409. https://doi.org/10.1111/bjh.14065.
41. Richardson PG, et al. Melflufen plus dexamethasone in relapsed and refractory multiple myeloma (O-12-M1): a multicentre, international, open-label, phase 1–2 study. Lancet Haematol. 2020;7:e395–407. https://doi.org/10.1016/s2352-3026(20)30044-2.
42. Richardson PG, et al. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. J Clin Oncol. 2021;39:757–67. https://doi.org/10.1200/jco.20.02259.
43. Richardson P, et al. OP-106 Horizon — melflufen therapy for RRMM patients refractory to daratumumab and/or pomalidomide; updated results and first report on PFS. Blood. 2018;132:600–600. https://doi.org/10.1182/blood-2018-99-113095.
44. Olivier T, Prasad V. The approval and withdrawal of melphalan flufenamide (melflufen): implications for the state of the FDA. Transl Oncol. 2022;18: 101374. https://doi.org/10.1016/j.tranon.2022.101374.
45. Bringhen S, et al. PF628 O-12-M1: an evaluation of time to next treatment in melflufen and dexamethasone-treated patients with relapsed/refractory multiple myeloma. HemaSphere. 2019;3:267. https://doi.org/10.1097/01.HS9.0000560796.93881.5c.
46. Mateos M-V, et al. Melflufen therapy for relapsed refractory multiple myeloma (RRMM) patients refractory to daratumumab and/or pomalidomide: a report on early efficacy. Blood. 2017;130:1841–1841. https://doi.org/10.1182/blood.V130.Suppl_1.1841.1841.