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Review

Proteasome inhibition in combination with immunotherapies: State-of-the-Art in multiple myeloma

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ABSTRACT

Multiple myeloma (MM) is a malignant plasma cell disorder accounting for around 1.8% of all neoplastic diseases. Nowadays, clinicians have a broad arsenal of drugs at their disposal for the treatment of MM, such as proteasome inhibitors, immunomodulatory drugs, monoclonal antibodies, bispecific antibodies, CAR T-cell therapies and antibody-drug conjugates. In this paper we briefly highlight essential clinical elements relating to proteasome inhibitors, such as bortezomib, carfilzomib and ixazomib. Studies suggest that the early use of immunotherapy may improve outcomes significantly. Therefore, in our review we specifically focus on the combination therapy of proteasome inhibitors with novel immunotherapies and/or transplant. A high number of patients develop PI resistance. Thus, we also review new generation PIs, such as marizomib, oprozomib (ONX0912) and delanzomib (CEP-18770) and their combinations with immunotherapies.

1. Introduction

1.1. Incidence and risk factors

Multiple myeloma (MM) is a malignant plasma cell disorder accounting for around 1.8% of all neoplastic diseases [1]. Median age at diagnosis is 70 years. There are several risk factors to consider, including age (risk increases with age), low socioeconomic status, place of residence (higher incidence rate in Australasia, Western Europe and North America), gender (more prevalent in men), race (two-fold more common in Blacks), obesity, chronic inflammation, and exposure to biological, physical, or chemical mutagens [2]. An inherited susceptibility to MM has also been demonstrated, first degree relatives of MM patients having a two-fold higher risk of disease development [3,4].

1.2. Disease biology

Plasma cells are mature, terminally differentiated, antibody-secreting B-lymphocytes. Primary mutations of these cells during physiologic development, mostly translocations and hyperdiploidy, are the initiating events of MM. The genetic, epigenetic, and tumor microenvironmental changes that contribute to the pathogenesis of MM have all been extensively studied [5,6]. Classically, there have been two asymptomatic MM precursor conditions described in the literature: a premalignant monoclonal gammopathy of unknown significance (MGUS) followed by a malignant smoldering multiple myeloma (SMM). Over the age of 40, MGUS and SMM affect 5% and 0.5%, respectively, of the general population. MGUS patients are more prone to develop hematological malignancies such as Waldenström's macroglobulinemia (relative risk (RR) of 47.5, 95% CI 25.3-81.3), MM (RR of 23.8, 95% CI 19.3-

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29.1), plasmacytoma, AL amyloidosis and non-Hodgkin lymphoma [7,8]. The risk of developing one of these is cumulative: 10% at 10 years, 18% at 20 years, 28% at 30 years and 36% at 40 years [7]. Overall survival of MGUS patients is lower compared to aged- and gender-matched controls [7].

1.3. Diagnosis

International diagnostic criteria of all three conditions (MGUS, SM, MM) are available and recommended to use [9]. The European Myeloma Network also summarized the tools available for early diagnosis of MM, even before appearance of end-organ damage [10].

1.4. Prognosis

Prognosis depends on patient characteristics (age, comorbidities, performance status), disease characteristics (tumor burden, tumor cell genetics) and depth of response to treatment [11]. Novel prognostic biomarkers have also been reviewed by Wallington et al. [12]. Best prognosis is obtained in sustained (>12 months) minimal residual disease (MRD)-negativity [13]. The International Myeloma Working Group defined MRD criteria and reviewed novel diagnostic tools [14]. In our review we will discuss MRD-negativity endpoints of trials measured either by next-generation flow cytometry (NGF) or next-generation sequencing (NGS) [15]. In transplant eligible patients the median OS is at around 10 years [16]. In transplant ineligible individuals median OS is around 5 years [2]. Relapses are common with each subsequent remission period being shorter and shorter. Multilineage-treatment-resistant relapses or treatment-related complications eventually lead to the death of these patients.

1.5. Treatment

Further findings in mechanisms of myelomagenesis may lead to discovery of novel therapeutic agents. Clinicians, however, already have a broad arsenal of drugs at their disposal for the treatment of MM (Table 1). Autologous hematopoietic stem cell transplantation (ASCT) remains the gold standard of MM treatment after a proper induction therapy in fit patients since multiple studies showed its superiority compared with novel generation triplet or quadruplet combinations alone [17]. The current backbone of induction therapy of newly diagnosed MM (NDMM) is daratumumab, immunomodulatory drugs and proteasome inhibitors (PIs) [18]. Immunotherapies, such as monoclonal antibody therapies, antibody-drug conjugates, and chimeric antibody receptor T-cell therapies, are novel drug classes with FDA-approved representatives. Although teclistamab, for example, has already received FDA authorization, other agents, such as elranatamab, have also demonstrated promising effects and are awaiting approval [19]. All these immunotherapies, except of daratumumab, are indicated only in relapsed/refractory disease yet (RRMM). Patients with RRMM are frequently exposed to high doses of PI-containing regimens, which suppress the immune system [20] and increase the risk of infection, including the reactivation of the varicella-zoster virus [21]. Immunotherapies, in the meantime, mobilize and activate the immune system to fight myeloma cells, requiring a proper function of the immune system. In order to explore how the immune suppression caused by PIs overlaps with the efficacy of immunotherapies, the focus of this review is on the combination of PIs with immunotherapies (immunomodulatory drugs, monoclonal antibodies, bispecific antibodies, antibody-drug conjugates, and ASCT) both in newly diagnosed and relapsed/refractory settings. We reflect on safety, real-life data, and quality of life (QoL) assessment too. We also intend to highlight areas where clinical data is lacking, thereby facilitating the development of new clinical trials and collaborations. Finally, we focus on novel, non-FDA-approved PIs as potential alternatives for MM patients resistant to currently used PIs.

Table 1
Drugs approved for treatment of multiple myeloma.

Drug family	Drug
Corticosteroids	Dexamethasone
	Prednisone
Immunomodulatory drugs	Thalidomide
	Lenalidomide
	Pomalidomide
Proteasome inhibitors	Bortezomib
	Carfilzomib
	Ixazomib
Monoclonal antibodies	Daratumumab (anti-CD38)
	Isatuximab (anti-CD38)
	Elotuzumab (anti-SLAMF7)
Alkylating agents	Melphalan
	Cyclophosphamide
	Bendamustine
	Carmustine
	Cisplatin
Anthracyclines	Doxorubicin (adriamycin)
Topoisomerase inhibitors	Etoposide
Histone deacetylase inhibitor	Panobinostat
Selective inhibitors of nuclear export	Selinexor
Antibody-drug conjugates	Balantamab Mafodotin
Chimeric antigen receptor t-cell therapy	Idecabtagene Vicleucel
Bispecific antibodies	Teclistamab

2. Proteasome inhibitors

The constant production and degradation of proteins maintains cellular protein homeostasis. Lysosomes and proteasomes are the two main protein degradation systems in eukaryotic cells. Proteasomes are cytosolic molecular catalytic systems firstly identified by Etlinger and Goldberg in 1977 [22]. The structural characteristics of proteasomes, which are beyond the scope of this review, have been excellently summarized by several reviews [23,24]. Various cellular processes, including cell cycle control, immune modulation, cellular signaling in the microenvironment, as well as tumor suppression, depend on proteasome integrity. Although all cells rely on the ubiquitin-proteasome system, which was described and characterized by one of the paper's senior author, Nobel Prize laureate Professor Aaron Ciechanover, myeloma cells are especially reliant on its integrity due to their high rate of gammaglobulin production [25]. Other factors that contribute to oncogenesis include the degradation of tumor suppressor proteins and cell cycle checkpoint inhibitors in the proteasomes, which gives malignant cells an advantage in terms of survival and proliferation. Thus, inhibiting proteasomes eventually lead to cell damage and death. Multiple mechanisms are involved, these are summarized in Fig. 1. Several papers reviewed these in greater depth [26,27].

3. Pharmacokinetics of proteasome inhibitors

Wang et al. reviewed the pharmacokinetics of PIs in detail, which is beyond the scope of this article [28]. In this chapter, we highlight essential clinical elements relating to administration routes and treatment plans of bortezomib, carfilzomib and ixazomib.

3.1. Standard dose

A phase 1 trial of bortezomib (NCT00080405) determined that 1.3 mg/m^2 is a highly efficient dose, inducing a proteasome inhibition rate of 74% without significant dose-limiting toxicity [29]. The early exploratory trials used intravenous bortezomib twice a week in 21 days cycles, up to 8 cycles. This approach led to a high rate of adverse effects, 52% of patients presenting grade ≥3 events, mostly peripheral neuropathy (PN) [30]. Reeder et al. reported that weekly administration of bortezomib obtains similar efficacy (ORR of 93% *versus* 88% in the

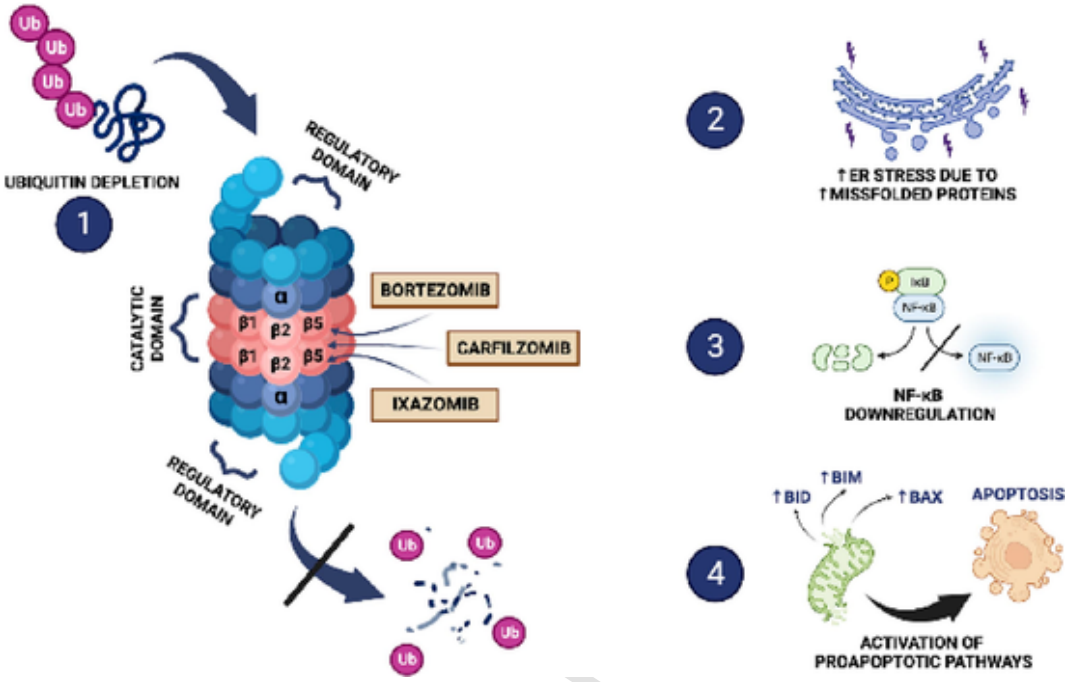

Fig. 1. Mechanisms of action of proteasome inhibitors.

twice-weekly arm) but with a more tolerable safety profile (grade ≥3 PN of 0% *versus* 6%, any grade PN of 57% *versus* 64%) [31]. The phase 1 NCT01812096 and the phase 3 MMY-3021 studies (NCT00722566) demonstrated that subcutaneous administration could further decrease the risk of severe PN (grade ≥3 6% versus 16%, p = 0.026, any grade 38% versus 53%, p = 0.044) with no difference in median PFS (9.3 *versus* 8.7 months in the intravenous arm, p = 0.319) and OS (28.7 months for both arms) [32]. In conclusion, current guidelines recommend starting subcutaneous administration of 1.3 mg/m^2 bortezomib either on days 1, 8, 15, 22 if the duration of a cycle is 28-days or on days 1, 4, 8, 11 in 21-day cycles. Carfilzomib preclinical studies demonstrated that a 30-min infusion lowers maximum plasma concentrations, thus decreasing the risk of adverse effects but with a maintained efficacy [33]. The phase 3 A.R.R.O.W. study (NCT02412878) reported that once-weekly 70 mg/m^2 administration prolongs PFS from 7.6 months (95% CI, 5.8-9.2) to 11.2 months (95% CI, 8.6-13, HR 0.69, p = 0.0029) compared to 27 mg/m^2 twice-weekly administration [34]. The same benefits of once-weekly induction were seen in high-risk patients in a pooled analysis, but once-weekly maintenance did not result in a longer PFS [35]. Most clinical trials split total weekly dose in 2 consecutive days, and administer carfilzomib on days 1, 2, 8, 9, 15, 16, 22 and 23 of the 28-day cycles. Recent preclinical studies also suggest that PI resistance could be overcome by the co-inhibition of β5/β2 proteasome domains reached only by higher concentrations (56 mg or 70 mg/m^2) of carfilzomib (lower concentrations inhibit β5 only). Thus, especially in RRMM, higher doses may be more efficient, but further clinical studies are required to confirm these findings [36]. Ixazomib is an orally administered bortezomib analog. Although it can be administered intravenously, most countries approved the orally bioavailable form only. A standard 4 mg dose of ixazomib has been identified as an effective and safely controllable dose because, in contrast to bortezomib and carfilzomib, body surface has minimal effect on exposure and clearance [37].

3.2. Hepatic impairment

A phase 1 study (NCT00091117) demonstrated that bortezomib is mainly metabolized by hepatic cells, thus a dose reduction to 0.7 mg/m^2 is required in moderate/severe hepatic impairment, defined by bilirubin levels >1.5x upper limit of normal [38]. In vivo rat studies showed that ixazomib is also partially metabolized by hepatocytes, requiring a decrease of the dose to 3 mg in moderate/severe hepatic injuries [39]. In contrast to bortezomib and ixazomib, degradation of carfilzomib is independent of hepatic enzymes, thus, no dose adjustment is required [40].

3.3. Renal impairment

Hemodialysis timing and administration of the three PIs are independent variables; PIs can be given before or after hemodialysis. A phase 1 clinical trial (NCT01830816) reported that a decreased dose of 3 mg ixazomib is safer and recommended to use in severe renal impairment [41]. In case of bortezomib and carfilzomib, however, no dose adjustment is needed [42,43].

3.4. Drug interactions

The use of vitamin C and green tea during bortezomib treatment is not advised since they diminish the effects of the drug [44,45]. Another clinically relevant finding is that food consumption can decrease bioavailability of ixazomib, thus administration on an empty stomach is recommended [46].

4. PI trials in smoldering multiple myeloma (SMM)

SMM is a hot topic among clinicians, and whether high-risk SMM patients benefit from early treatment is subject to debate yet. We identified PI combination therapy trials for these patients. One of them is the phase 2 NCT01572480 trial that assessed the safety and efficacy of carfilzomib-lenalidomide-dexamethasone (KRd) combination in 54 patients. An MRD-negativity rate of 70.4% was achieved (95% CI, 56.4-82.0) regardless of age, race, gender, or tumor cell genetics. There was a median CR duration of 66.5 months (95% CI, 44.6-not reached) indicating deep and sustained responses to treatment if it is initiated early before MM appears. The triplet was well tolerated, only 2 individuals discontinued carfilzomib due to cardiac toxicity [47]. We also identified the phase 2 iStopMM (NCT03815279) that is currently recruiting

high-risk SMM patients in Iceland and administers them a 12-cycle KRd induction followed by a 1-year lenalidomide maintenance. NCT03673826 is also a phase 2 trial recruiting high-risk SMM patients but instead of a 12-cycle induction, only 9 cycles are given followed by lenalidomide maintenance. Other phase 2 trials investigated the same triplet combined with ASCT (GEM-CESAR study - NCT02415413) or daratumumab (ASCENT study - NCT03289299) in high-risk SMM patients. Compared to the triplet alone, adding these therapies does not significantly increase treatment efficacy but increases the rate of adverse events [48,49]. Also, phase 2 studies added daratumumab to a bortezomib-lenalidomide-dexamethasone backbone in the PRIMS trial (NCT04775550) or to carfilzomib-dexamethasone in the NCT04933539 trial. No results have been published yet. Ixazomib-dexamethasone doublet has also been tested in the phase 1 NCT02697383 trial. Out of the 14 enrolled high-risk SMM patients 9 achieved an objective response (ORR = 64%) after 12 cycles. Two patients progressed to MM in the median follow-up period of 17 months [50]. Another approach evaluated is the 9-cycle ixazomib-lenalidomide-dexamethasone induction followed by an ixazomib-lenalidomide maintenance for another 15 cycles. The combination seems to be promising, achieving an ORR of 89% out of the 59 patients enrolled in the phase 2 NCT02916771 trial [51].

5. Bortezomib

Even though research on proteasome inhibitors began in the 1980s, the first paper on proteasome inhibition for MM was published in 2001. The paper discussed the cytotoxic effect of PS-341, lately named bortezomib, on a MM cell line [52]. Velcade® (V) was approved later by the FDA in 2003 for RRMM and in 2008 for NDMM based on the results of several clinical trials. The bortezomib studies with published data are listed in Table 2. We also included a supplementary material with tables also including the trials without published data.

5.1. Immunomodulatory drug (IMiDs)-bortezomib combinations

IMiDs are frequently used in both NDMM and RRMM. Their mechanism of action is multimodal: costimulation and activation of T- and NK-cell, production of cytokines, and antitumoral changes in the tumor microenvironment (anti-angiogenetic, anti-inflammatory, and anti-osteoclastogenic effects), respectively [53,54]. Their synergistic effects with PIs have been demonstrated by several clinical trials. Supplementary Table 1. summarizes all the bortezomib trials we identified in combination with IMiDs.

5.1.1. Bortezomib-thalidomide-dexamethasone (VTd)

VTd has been assessed in several combinations for transplant-ineligible NDMM patients. Such an example is VTd induction continued by melphalan-prednisone-thalidomide consolidation in the phase 2 NCT00320476 trial. The study enrolled 35 patients, a 2-year PFS of 64% and 2-year OS of 70% has been reached. Although results were initially promising, due to the high rate of adverse events, that frequently needed therapy discontinuation, melphalan-thalidomide-prednisone consolidation following VTd is not anymore recommended [55]. Another phase 2 trial (NCT00531453) compared VTd induction to VCTd. Outcomes after 4 cycles were promising, the VTd arm achieved a median PFS of 56.3 months (no 95% CI reported). Following sensitivity analysis and censoring, however, median PFS was only 34.1 months (95% CI, 23.5-NR) and 5-year OS rate only 69.1% (95% CI, 51.41-80.1). Out of the 42 patients who achieved CR, 34 were MRD-negative by flow cytometry (threshold 10^{-5}) [56]. A phase 3 study, entitled UPFRONT (NCT00507416), compared VTd to bortezomib-dexamethasone (Vd) and bortezomib-melphalan-prednisone (VMp) in elderly with a median age of 73 years. All three regimens achieved similar PFS and OS as Vd and VMp. A slightly increase in rate of any-grade adverse events and decrease in quality of life when using VTd was, however, reported in the elderly cohort [57]. VTd showed remarkable successes in transplant-eligible NDMM too. IFM2007-02 (NCT00910897) was the first prospective trial demonstrating superiority of VTd compared to Vd alone. Although no differences in ORR have been observed, complete remission + very good partial response rates were significantly higher in case of VTd (74% *versus* 58%, p = 0.02). After a median follow-up of 32 months, there was no difference in PFS and OS. In terms of safety, however, VTd proved to cause a lower rate of both any grade (53% *versus* 70%, p = 0.01) and grade 4 (3% *versus* 11%, p = 0.03) peripheral neuropathy [58]. The prospective, phase 3 IFM2013-04 trial (NCT01971658) demonstrated that VTd induction is more efficient compared to VCd. Although no significant differences in CR rates have been observed (13% *versus* 8.9%, p = 0.22), analyzing ORR (92.3% *versus* 83.4%, p = 0.01) and the number of patients achieving at least very good partial response (VGPR) (66.3% *versus* 56.2%, p = 0.05) VTd showed an increased efficacy with a similar safety profile compared to VCd. No significant difference in OS was reported [59]. Also, case matching comparison of VTd (in the GIMEMA-MMY-3006 - NCT01134484 trial) *versus* VCd induction (in the EMN02/HOVON95 - NCT01208766 trial) demonstrated superiority of VTd achieving a CR rate of 19% *versus* 6% (N = 236, p < 0.001) [60]. Subsequently, VTd induction is preferred over VCd except in patients with renal insufficiency, where VCd is remains recommended [18]. Results of the phase 3 PETHEMA/GEM05 study (NCT00461747) have shown that induction with 6 cycles of VTd instead of 4 cycles (like in IFM2007-02) results in a significantly longer PFS (52 *versus* 28 *versus* 32 months, p = 0.01) when compared with Td or combination chemotherapy (VBMCP/VBAD/V). However, no significant differences in OS have been observed [16]. In the phase 3 GIMEMA-MMY-3006 trial (NCT01134484) VTd consolidation after a double ASCT 3-6 months after an identic VTd induction proved to be more efficient compared to the Td regimen, reaching a CR rate of 61% from 49% before starting consolidation therapy. Median PFS for VTd was 60 months (95% CI 53–74) *versus* 41 months (95% CI 37–50) with an OS at 10 years of 60% (95% CI 54–67) *versus* 46% (95% CI 40–54) [61].

5.1.2. Bortezomib-thalidomide-prednisone (VTp)

VTp consolidation following a 3-cycle VCd induction was tested in the phase 3 VCAT study (NCT01539083) on transplant-eligible NDMM patients. There was no statistical difference in terms of overall response, PFS and safety when compared to TP alone [62].

5.1.3. Bortezomib-melphalan-thalidomide-dexamethasone (VMTd)

The NCT01063179 phase 3 study added melphalan to the classical VTd induction regimen in transplant-ineligible NDMM patients and obtained higher efficacy in terms of PFS (35.3 *versus* 24.8 months, HR 0.58, p < 0.001) and 5 year-OS (61% *versus* 51%, HR 0.70, p < 0.01). In terms of survival after relapse, however, no difference has been observed and VMTd led to significantly higher rate of grade ≥3 adverse events, such as neutropenia (38% *versus* 28%, p = 0.01), cardiac events (11% *versus* 5%, p = 0.02), deep-vein thrombosis/pulmonary embolism (5% *versus* 2%, p = 0.05) and neuropathy (11% *versus* 5%, p = 0.02) [63]. The question whether VMTd or VMTp is superior as induction or salvage therapy is unanswered, but it is unlikely to be resolved anytime soon because more effective quadruplet combinations have been discovered and are already in use.

5.1.4. Bortezomib-thalidomide-doxorubicin (VTD)

A frail patient population that would not tolerate high-dose steroids exist in real-world settings. Thus, a steroid-free regimen trial was initiated. There were 43 patients enrolled in the study. An ORR of 78% was achieved with a median time to progression of 29.5 months (95% CI 18.6-NR). Regarding safety, no treatment-related death was reported, all adverse events were safely manageable [64].

Table 2
Bortezomib trials.

regimen	treatment	ASCT	trial ID	study phase	study population	N	ORR (%)	median PFS (months)	median survival (months)
Immunomodulatory drugs									
VTd	induction	no	NCT00320476 [55]	2	NDMM	35	no data	not reached	not reached
VTd	induction	yes	NCT00531453 [56]	2	NDMM	49	no data	56.3	not reached
VTd *versus* Vd versus VMp	induction	no	NCT00507416 [57]	3	NDMM	502	80	15.4	51.5
VTd *versus* Vd	induction	yes	NCT00910897 (IFM2007-02) [58]	3	NJDMM	205	89	26	no data
VTd	induction	yes	NCT01971658 (IFM2013-04) [59]	3	NDMM	358	92.3	no data	no data
VTd	induction	yes	NCT01134484 (GIMEMA-MMY-3006) [61]	3	NDMM	480	no data	60	not reached
VTp	consolidation	yes	NCT01539083	3	NDMM	254	71.6	22.3	not reached
VCTd	induction	yes	NCT00531453 [56]	2	NDMM	49	no data	36.3	not reached
VMTd	induction	yes	NCT01063179 [63]	3	NDMM	511	no data	35.3	not reached
VTD	induction	yes	NCT00523848 [64]	2	NDMM	46	78	no data	
VRd	induction	yes	NCT00378105 [65]	1/2	NDMM	66	100	not reached	not reached
VRd	induction	yes	NCT02441686 [66]	2	NDMM	45	95	no data	
VRd	induction	yes	NCT02219178 [67]	2	NDMM	42	91.9	no data	
VRd	induction	yes	NCT01685814 [68]	3	NDMM	476	no data	53.7	not reached
VRd	induction	yes	NCT01916252 (PETHEMA /GEM2012) [69]	3	NDMM	458	83.4	no data	no data
VRd	induction	no	NCT01191060 (IFM 2009) [71]	3	NDMM	764	no data	36	not reached
VRd	induction	no	NCT00644228 (SWOG S0777) [72]	3	NDMM	525	82	43	75
VRd *versus* ASCT	induction consolidation	yes	NCT01208662 (DETERMI-NATION) [73]	3	NDMM	873	95	46.2	not reached
VRd	salvage	yes	NCT00378209 [76]	2	RRMM	64	64	9.5	30
VRCd	salvage	yes	NCT00507442 (EVOLUTION) [79]	1/2	RRMM	140	80	not reached	not reached
VRDd	induction	yes	NCT00724568 [80]	1/2	NDMM	74	96	not reached	not reached
VRDd	salvage	yes	NCT01160484 [81]	2	RRMM	39	48.7	9	not reached
VPd	salvage	yes	NCT01212952 [82]	1/2	RRMM	50	86	13.7	not reached
VPd	salvage	yes	NCT01497093 [83]	1	RRMM	34	75	no data	no data
VPd	induction	yes	NCT01734928 (OPTIMISMM) [84]	3	RRMM	559	82.2	11.2	not reached
Mezigdomide (CC-92480) + Vd	salvage	yes	NCT03989414 [85]	1/2	RRMM	384	73.7	no data, **recruiting**	
Monoclonal antibodies									
Dara-Vd	salvage	yes	NCT02497378 [91]	1	RRMM	8	100	no data	
Dara-Vd	salvage	yes	NCT02977494 [92]	2	RRMM	22	67	10.4	not reached

(*continued on next page*)

Table 2 (*continued*)

regimen	treatment	ASCT	trial ID	study phase	study population	N	ORR (%)	median PFS (months)	median survival (months)
Dara-Vd	salvage	yes	NCT02136134 (CASTOR) [87]	3	RRMM	498	85	16.7	63.4
Dara-Vd	induction	yes	NCT03234972 (LEPUS) [90]	3	RRMM	211	no data	not reached	not reached
Dara-VCd	induction	yes	NCT02955810 [93]	1	NDMM	18	94	no data	
Dara-VCd	induction	yes	NCT04166565 [95]	2	NDMM RRMM	41	78	18	not reached
Dara-VCd	induction	yes	NCT02951819 (LYRA) [94]	2	NDMM	101	97 (ASCT-arm)	not reached	not reached
Dara-VMp	induction	no	NCT03217812 (OCTANS) [97]	3	NDMM	167	90.4	not reached	not reached
Dara-VMp	induction	yes	NCT02195479 (ALCYONE) [203]	3	NDMM	706	90.0	36.4	not reached
Dara-VRd	induction	yes	NCT03412565 (PLEIADES) [100]	2	NDMM	67	97	no data	no data
Dara-(V)Rd	consolidation	no	NCT04566328 (EQUATE) [102]	3	NDMM	1450	**recruiting**		
Dara-VRd	induction	yes	NCT02874742 (GRIFFIN) [99]	2	NDMM	292	99	not reached	not reached
Isa-VRd	induction	no	NCT02513186 [104]	1	NDMM	44	100	not reached	not reached
Isa-VRd	induction	yes	NCT03617731 (GMMG-H7) [105]	3	NDMM	662	no data		
Mezagitamab (TAK-079) + VRd	salvage	yes	NCT03439280 [106]	1	RRMM	50	no data	not reached	no data
Elo-VRd (anti-SLAMF7 mAb)	induction	yes	NCT01668719 (SWOG-1211) [107]	1/2	NDMM	134	no data	31.47	68
Elo-VRd (anti-SLAMF7 mAb)	induction	yes	NCT02375555 [108]	2	NDMM	41	100	no data	
Elo-VRd (anti-SLAMF7 mAb)	induction	yes	NCT02495922 (GMMG-HD6) [109]	3	NDMM	564	81.5	not reached	not reached
Elo-VPd (anti-SLAMF7 mAb)	induction	yes	NCT02718833 [110]	2	RRMM	33	52	no data	
Siltuximab (anti-IL6 mAb) + VMp	induction	yes	NCT00911859 [111]	2	RRMM	118	88	19	no data
KW-2478 (anti-HSP90 mAb) + V	salvage	yes	NCT01063907 [112]	1/2	RRMM	95	39.1	6.4	no data
AVE1642 (anti-IGF1R mAb) + V	salvage	yes	NCT01233895 [115]	1	RRMM	26	45	no data	no data
Plerixafor (anti-CXCR4 mAb) + V	chemo-sensitization	yes	NCT00903968	1/2	RRMM	25	48.5	11.7	no data
Tabalumab (anti-BAFF mAb) + V	salvage	yes	NCT00689507 [119]	1	RRMM	48	42	no data	no data
Tabalumab (anti-BAFF mAb) + V	salvage	yes	NCT01556438 [120]	1	RRMM	16	56.3	no data	no data
Antibody-drug conjugates									
VRd + Belantamab Mafodotin (GSK2857916)	salvage	yes	NCT03544281 (DREAMM-6) [121]	1/2	RRMM	61	no data	not reached	no data
Transplant-related									

(*continued on next page*)

Table 2 (*continued*)

regimen	treatment	ASCT	trial ID	study phase	study population	N	ORR (%)	median PFS (months)	median survival (months)
V (1 mg/m^2) + HDM (200 mg/m^2)	ASCT conditioning	yes	NCT00642395 [123]	2	NDMM	54	70	not reached	not reached
V (1 mg/m^2) + HDM (200 mg/m^2)	ASCT conditioning	yes	NCT00793650 [124]	2	NDMM	39	87	15.3	36.7
V (1 mg/m^2) + HDM (200 mg/m^2)	ASCT conditioning	yes	NCT02197221 (IFM2014-02) [125]	3	NDMM	300	no data	34	not reached
V + melphalan + fludarabine	allo-HSCT conditioning	yes	NCT00948922 [128]	2	NDMM	63	68	not reached	not reached
V + busulfan	second ASCT conditioning	yes	NCT01009840 [204]	2	RRMM	30	38	191	not reached
V + busulfan + melphalan	ASCT conditioning	yes	NCT01255527 [205]	1/2	NDMM	53	assessed toxicity only		
V + PK-directed busulfan + melphalan	ASCT conditioning	yes	NCT01605032 [126]	2	NDMM	18	100	not reached	not reached
V + thalidomide + melphalan	ASCT conditioning	yes	NCT01242267 [127]	1/2	RRMM	32	69	9.3	not reached

V – bortezomib, **R –** lenalidomide, **d** – dexamethasone, **D** – doxorubicin, **p** – prednisone, **C** – cyclophosphamide, **M** – melphalan, **P** – pomalidomide, **I** – iberdomide, **Dara –** daratumumab, **Isa** – isatuximab, **ASCT –** autologous stem cell transplantation.

5.1.5. Bortezomib-lenalidomide-dexamethasone (VRd)

The first phase 1/2 prospective trial (NCT00378105) investigating VRd induction in NDMM patients (N = 66 in phase 1, N = 35 in phase 2) has shown favorable outcomes both with/without ASCT: 19 (29%) patients in the phase 1 and 13 (37%) individuals in the phase 2 population achieved CR with an estimated 18-month PFS of 75% (95% CI 63-84) [65]. Similar efficacy (95% ORR) was achieved in the phase 2 NCT02441686 trial, also for transplant-eligible NDMM patients, the difference being the subcutaneous administration of bortezomib [66]. Subcutaneous bortezomib was also assessed in the phase 2 NCT02219178 trial both for transplant-eligible and -ineligible NDMM patients. ORR was 91.9%, demonstrating similar efficacy to intravenous administration [67]. We also identified data demonstrating higher efficacy of using PIs instead of chemotherapy for induction in NDMM patients. The phase 3 NCT01685814 trial, for example, compared VRd to lenalidomide-doxorubicin-dexamethasone. The trial included 476 patients. Median PFS was higher in the VRd arm, 53.7 months (95% CI, 46.2-63.1) *versus* 41.7 months (95% CI, 35.4-48.5, p = 0.0439) [68]. We found no prospective trial comparing VRd to VTd induction. A retrospective, indirect, retrospective comparison suggests that VRd is more efficient compared to VTd obtaining a VGPR or better of 70% *versus* 60% [69]. Indirect, matching-adjusted comparison of VRd *versus* Dara-VTd, however, showed increased PFS and OS (p < 0.001) for Dara-VTd in transplant-eligible patients [70]. The phase 3 IFM 2009 (NCT01191060) trial investigated if ASCT is still necessary following a 3 cycle VRd induction in young (< 65 years) and transplant-eligible NDMM patients. The ASCT group achieved significantly longer median PFS compared to VRd alone (50 months *versus* 36 months, p < 0.001). The median OS rates, however, did not show statistically significant differences [71]. ASCT was neither intended in the phase 3 SWOG S0777 study (NCT00644228) which recruited 525 NDMM patients to compare lenalidomide-dexamethasone with VRd. While IFM 2009 enrolled younger patients, SWOG S0777 enrolled 43% of patients over the age of 65. Results have shown both an increased median PFS (43 *versus* 30 months, p = 0.0037) and higher median OS (75 *versus* 64 months, p = 0.0250) [72]. Another phase 3 study (DETERMINATION - NCT01208662) also investigated VRd *versus* ASCT. An impressive number of 873 NDMM patients with an age of < 65 years were enrolled. Following a 3-cycle VRd induction, patients received either 5 more VRd cycles or ASCT. Risk of disease progression in the VRd-alone arm was significantly higher (53%, HR = 1.53, 95% CI, 1.23-1.91, p = 0.001). Also, a 21.3-month PFS-benefit in the ASCT cohort has been observed. Thus, the DETERMINATION trial confirms the findings of IFM 2009 and SWOG S0777 [73]. Another intriguing topic is the optimal number of VRd cycles for induction. PETHEMA/GEM2012 (NCT01916252) used 6 cycles rather than 3 cycles in IFM 2009 or 8 cycles in SWOG S0777. Another difference between PETHEMA/GEM2012 and SWOG S0777 or IFM 2009 was the duration of treatment with lenalidomide (21 days in 4-week cycles *versus* 14 days in 3-week cycles) and the reduced dose intensity of bortezomib (same dosing on day 1,4,8,11 but with 28-day cycles *versus* 21-day cycles). CR was achieved in 33.4% of the 458 enrolled patients, 66.6% obtaining VGPR or better. Although cross-trial comparison has its limitations, the 4-week cycle approach seems to obtain an increased efficacy (66.6% VGPR or better *versus* 46% in IFM2009 *versus* 43% in SWOG S0777) with reduced toxicities [69]. Fewer cycles may result in a higher safety profile, while more cycles may result in a deeper response. As a result, the optimal number of cycles remains an open question. In the EMN02/HOVON95 (NCT01208766) phase 3 prospective trial the efficacy of VRd consolidation has been demonstrated, the VRd group obtaining a significantly higher PFS (59.3 *versus* 42.9 months, P = 0.016) [74]. The phase 3 STaMINA trial (NCT02322320) compared VRd consolidation with a second ASCT as consolidation. Results showed no significant difference in long-term outcomes in the intention-to-treat cohort, achieving 6-year PFS and OS of 43.9% *versus* 39.7% (p = 0.6) and 73.1% *versus* 74.9% (p = 0.8) [75]. No data regarding the safety profile of double ASCT versus VRd consolidation have been reported in the trial but VRd may be a safer option, especially for elderly patients. Further studies are required to determine the role and safety of double ASCT consolidation in comparison to novel immunotherapy combinations, such as VRd. VRd proved to be safe and active in RRMM as well. The phase 2 NCT00378209 study achieved an ORR of 64% and a median PFS and OS of 9.5 (95% CI, 7.2-11.7), and 30 months (95% CI, 24-37), respectively [76]. Real-world data also attest the efficacy of VRd. Joseph et al. reported a median PFS of 65 months (95% CI, 58.7-71.3) and a median OS of 126 months (95% CI 113.3-139.8) [77]. Gaballa et al. reported a median PFS and OS of 50 months (95% CI 37.3-64.6) and 101.7 months (95% CI 84.5 – NR), respectively [78]. Differences in outcomes may be attributed to the fact that Joseph et al. used a risk-adapted maintenance with either lenalidomide for standard-risk or VRd for high-risk patients, whereas Gaballa et al. used only lenalidomide maintenance.

5.1.6. Bortezomib-lenalidomide-cyclophosphamide-dexamethasone (VRCd)

The phase 2 EVOLUTION trial (NCT00507442) evaluated the bortezomib-dexamethasone backbone in three combinations: VRd, VCd or VRCd. The one-year PFS obtained in the VCd group was 100% compared to 86% in the VRCd, and 83% in the VRd group. The four-drug

combination seems to obtain similar results compared to the other regimen. Due to increased hematological toxicity (58% grade ≥3 in the VRCd *versus* 26% in the VRD group), however, VRCd does not show any clinical benefit [79].

5.1.7. Bortezomib-lenalidomide-doxorubicin-dexamethasone (VRDd)

The NCT00724568 phase 1 trial evaluated the safety and efficacy of VRDd in 74 NDMM patients. The combination obtained a 18-month PFS and OS probability of 81.6% (95% CI, 65.5-90.6) and 98.6% (95% CI, 90.5-99.8) [80]. NCT01160484, a phase 2 study investigated if a lower dose of 1 mg/m^2 of bortezomib instead of the traditional 1.3 mg/m^2 could improve outcomes and safety profile of VRDd in RRMM patients. An ORR of 48.7% (N = 39) has been achieved with a median PFS of 9 months (95% CI, 1-22) [81]. In the era of immunotherapies, however, CD38 targeting monoclonal antibodies are preferred over doxorubicin. This quadruplet is not included in the list of NCCN recommended regimens.

5.1.8. Bortezomib-pomalidomide-dexamethasone (VPd)

Pomalidomide, a novel-generation analogue of thalidomide, has been investigated in RRMM in the phase 1/2 NCT01212952 study. Results showed no statistically significant increase in ORR and PFS [82]. The phase 1 MM5 trial (NCT01497093) also investigated VPd in RRMM patients, results, however, seemed more optimistic, an ORR of 65% with a median duration of response of 7.4 months have been achieved (95% CI, 4.4–9.6) [83]. Based on the findings of MM5, the phase 3 MM-007-OPTIMISMM (NCT01734928) trial has been initiated. VPd achieved significantly higher PFS compared to Vd alone, 11.2 months (95% CI, 9.66-13.73) *versus* 7.1 months (95% CI, 5.88-8.48, HR = 0.65, p = 0.0008). Efficacy was maintained in high-risk, lenalidomide- or PI-resistant subgroups as well. Although median OS was not yet reached, risk of disease progression and death seems to be significantly lower in the VPd arm [84]. Another trial is ongoing for NDMM patients with renal injury (NCT05432414).

5.1.9. Bortezomib-mezigdomide or iberdomide-dexamethasone

Mezigdomide (formerly CC92480) is a potent cerebron modulator, showing activity even in lenalidomide- and pomalidomide-resistant patients. The CC-92480-MM-002 study (NCT03989414) is currently investigating efficacy of bortezomib-mezigdomide-dexamethasone both in NDMM and RRMM. Preliminary results in RRMM patients (N = 19) demonstrated an ORR of 73.7% with median duration of response of 10.4 months (95% CI, 5.5-NR) [85]. A phase 3 trial has been also initiated for RRMM patients (SUCCESSOR-1, NCT05519085). Iberdomide, formerly CC20, is another novel cerebron E3 ligase immunomodulator, showing greater efficacy than pomalidomide, lenalidomide and thalidomide [86]. The phase 1/2 NCT02773030 trial is currently investigating safety and efficacy of VId in transplant-ineligible NDMM and RRMM, while the phase 2 NCT05272826 study is currently recruiting transplant-eligible NDMM patients.

5.2. CD38-targeting monoclonal antibody-bortezomib combinations

Supplementary Table 2. summarizes all the bortezomib trials we identified in combination with CD38-targeting monoclonal antibodies.

5.2.1. Daratumumab-bortezomib-dexamethasone (Dara-Vd)

The phase 3 CASTOR study (NCT02136134) investigated if adding daratumumab to the Vd backbone would increase efficacy of treatment for 498 RRMM transplant-eligible patients. Daratumumab treatment showed a significant clinical advantage, 14% of patients achieving MRD-negativity compared to 2% in the Vd group (p < 0.000001). Daratumumab achieved best results at first relapse but showed increased PFS in all patient subgroups. Median PFS for all patients included in the study was 16.7 months for the Dara-Vd *versus* 7.1 months for the Vd group (p < 0.0001) [87]. Health-related QoL of MM patients remained stable or slightly improved during Dara-Vd. Another finding of Hungria et al. was that side effects of daratumumab were not cumulative, thus a long-term administration seems to be safe [88]. These findings support the continuation of other trials investigating dara-R maintenance therapy. Sonneveld et al. published an impressive median OS of 63.4 months among the patients included in CASTOR (95% CI, 51.2-72.4) [89]. A phase 3 Chinese study (NCT03234972) confirmed the results, achieving a 12-month PFS rate of 62.4% with median time to progression significantly increased compared to Vd alone (HR = 0.26, 95% CI 0.15-0.46, p < 0.00001) [90]. A phase 1 trial (NCT02497378) on Japanese patients achieved similar results as CASTOR [91]. Dara-Vd in transplant-ineligible NDMM is also tested in the phase 2 NCT03695744 trial. No results have been published yet. Elderly (median age of 70) RRMM patients with renal impairment achieved an ORR of 67% (N = 20) with a median PFS of 10.4 months (95% CI not reported). These data suggest that the combination can be safely used in renally impaired patients as well [92].

5.2.2. Daratumumab-cyclophosphamide-bortezomib-dexamethasone (Dara-CyBorD)

Immunomodulatory-drug sparing regimens could be a promising approach to increase the therapeutic window and efficacy in relapsed/refractory disease. The 16-BCNI-001/CTRIAL-IE 16-02 phase 1 trial (NCT02955810) administered Dara-CyBorD induction to 18 NDMM transplant eligible patients. Results were promising with an ORR of 94%, while 10 of 18 patients (56%) achieved MRD-negativity with a threshold of 10^{-5} [93]. Thus, further studies were started, such as the phase 2 LYRA (NCT02951819). LYRA investigated Dara-CyBorD induction in 101 transplant-eligible NDMM patients. While estimated 36-month PFS was higher in the non-transplant group (72.6%, 95% CI, 54-84.70) compared to the transplanted arm (69.3% with 95% CI, 43-85.3), estimated OS was higher in the ASCT-arm (94.9%, 95% CI, 81.0–98.7 *versus* 84.3%, 95% CI, 69.8–92.2) [94]. The differences are statistically not significant. Further follow-up is required to compare the two cohorts. The patients, regardless of the ASCT status, underwent daratumumab maintenance. The phase 2 EMN-19 (NCT04166565) assessed the combination in extramedullary disease both in NDMM and RRMM cases. ORR was 78%, median PFS of 18 months (95% CI, 7-NR) and median OS not reached after a follow-up of 12 months (95% CI not specified) [95]. Thus, Dara-CyBorD seems to be safe and active in extramedullary disease too.

5.2.3. Daratumumab-bortezomib-melphalan-prednisone (Dara-VMp)

The addition of daratumumab in the ALCYONE phase 3 trial (NCT02195479) provided an impressive PFS and OS advantage when compared to VMp alone. The Dara-VMp treated patients achieved a median PFS of 50.4 months (95% CI, 32.1-45.9) and a 3-year OS rate of 78% compared to 68% in the VMp group (p < 0.0005). Dara-VMp led to a 40% reduction in risk of death [96]. The phase 3 OCTANS trial (NCT03217812) investigated Dara-VMp in transplant-ineligible Chinese NDMM patients. MRD-negativity was 29.8% compared to 5.7% (p < 0.0003) in the VMp arm. Median PFS was not reached but also significantly higher (HR = 0.41, 95% CI, 0.21-0.78, p = 0.0049) [97].

5.2.4. Daratumumab-bortezomib-thalidomide-dexamethasone (Dara-VTd)

The phase 3 CASSIOPEIA trial investigated safety and efficacy of Dara-VTD induction (4 cycles) and consolidation (2 cycles) compared to VTd alone. Dara-VTd proved to obtain MRD-negativity rate both by flow cytometry (64% *versus* 44%, p < 0.0001) and NGS (57% *versus* 37%, p < 0.0001). Median PFS and OS have not been reached but 18-month PFS was 93% (95% CI, 90-95) compared to 85% (95% CI, 81-88) with a HR of 0.47 (95% CI, 0.33-0.67, p < 0.0001) [98]. Dara-VTd induction in NDMM patients with kidney failure is also assessed in the currently ongoing phase 3 NCT03319667 trial.

5.2.5. Daratumumab-bortezomib-lenalidomide-dexamethasone (Dara-VRd)

The GRIFFIN phase 2 trial (NCT02874742) analyzed safety, and efficacy of intravenous daratumumab and VRd compared to VRd alone. The patients received 4 induction cycles, ASCT and two consolidation cycles followed by maintenance with lenalidomide monotherapy. Dara-VTd showed superior results in terms of ORR (99% *versus* 91.8%, $p = 0.016$), MRD-negativity at 22 months follow-up (51% *versus* 20.4%, $p < 0.0001$). At 24-months follow-up, PFS was reported to be 95.8% (95% CI, 89.2-98.4) for the Dara-VRd arm *versus* 89.9% (95% CI, 77.1-95.7) for VRd alone [99]. The phase 2 PLEIADES study confirmed efficacy of the 4-cycle induction in NDMM achieving an ORR of 97% (95% CI, 90.9-99.5) [100]. In the traditional Dara-VRd regimen, frail, transplant-ineligible patients are more likely to experience serious side effects. As a result, a dose-adjusted 4 cycle "Dara-VRd-lite" regimen was established in the phase 2 NCT01782963 trial and it demonstrated comparable efficacy to the standard dose combination with an ORR of 85% versus 84% (indirect comparison) and median PFS of 41.9 months (95% CI, 31.2 - NR), a more manageable safety profile and a low rate (4%) of drug discontinuation [101]. Another phase 2 study (DRAMMATIC - NCT04052880) is now ongoing and is investigating efficacy of a 12 cycle Dara-dose attenuated VRd induction followed by daratumumab ± lenalidomide or ixazomib maintenance in frail, transplant ineligible NDMM patients. The phase 2 NCT04140162 trial starts with Dara-Rd induction in NDMM patients followed with a Dara-VRd consolidation in case of MRD-positivity. Following consolidation, Dara-R maintenance will be initiated. There are no results published yet but MRD-driven strategy seems promising. Another interesting MRD-driven strategy is 8 cycles of daratumumab as induction and based on MRD-status either a Dara-Rd (if MRD-negative) or Dara-VRd (if MRD-positive) continued with a dara-R maintenance. This approach is investigated in transplant-eligible NDMM patients in the currently ongoing phase 3 EQUATE (NCT04566328) trial [102]. Dara-VRd is also tested in transplant-eligible NDMM patients but without initial intent of ASCT in the phase 3 CEPHEUS (NCT03652064) trial.

5.2.6. Isatuximab-bortezomib-lenalidomide-dexamethasone (Isa-VRd)

Isatuximab, formerly SAR650984, is novel generation IgG1-kappa anti-CD38 antibody. Its advantage compared to daratumumab is that it can be detected separately on serum protein electrophoresis, thus allowing precise dosing of endogenous M-protein concentration [103]. The phase 1 NCT02513186 study compared Isa-VRd to Isa-VCd induction in 44 transplant-ineligible NDMM patients. Both combinations seem to be efficient and safe with an ORR of 93% for Isa-VCD and 100% for Isa-VRd and 2-year PFS probability of 93% and 96%, respectively [104]. The phase 3 GMMG-HD7 trial (NCT03617731) compared safety and efficacy of Isa-VRd induction *versus* VRd alone in transplant eligible NDMM patients. MRD-negativity was reached in 50.1% if isatuximab was added *versus* 35.6% in the VRd arm (OR-1.83, 95% CI 1.34-2.51, $p < 0.001$). Although CR rates were not significantly different, VGPR or better was 77.3% *versus* 60.5% ($p < 0.001$). Thus, Isa-VRd showed superiority compared to VRd alone while toxicity rates were similar between the two arms of the study [105]. IFM2020-05 (NCT04751877) and IMROZ (NCT03319667) are other phase 3 trials are currently ongoing in transplant-ineligible NDMM elderly.

5.2.7. Mezagitamab-bortezomib-lenalidomide-dexamethasone

Mezagitamab (TAK-079) is a fully human, IgG1 anti-CD38 monoclonal antibody. In the phase 1 NCT03439280 trial, its combination with a VRd backbone is assessed in RRMM patients. Preliminary data ($N = 34$) at a 7.5-month median follow-up show that the combination is well tolerated (no treatment-related death, neither any events that led to treatment discontinuation) and active (median PFS not reached) [106]. Further studies are required.

5.3. Other monoclonal antibody-bortezomib combinations

Supplementary Table 3. summarizes all the bortezomib trials we identified in combination with monoclonal antibodies, except of CD38-targeting ones that have already been discussed above.

5.3.1. Elotuzumab-bortezomib-lenalidomide or pomalidomide-dexamethasone (Elo-VRd/Elo-VPd)

The phase 1/2 SWOG-1211 trial (NCT01668719) investigated safety and efficacy of adding elotuzumab, a SLAMF7-antibody to the classical VRd regimen in high-risk NDMM patients defined by presence of t(14;16), t(14;20), del(17p) or amp 1q21. No significant difference in efficacy has been observed compared to VRd alone [107]. NCT02375555 is a phase 2 trial that evaluated Elo-VRd in 41 NDMM patients. ORR was 100% after 4 cycles. Although two patients died (septicemia and respiratory failure) due to complications, the combination seemed to have a manageable safety profile [108]. A further phase 3 trial (GMMG-HD6 - NCT02495922) investigated efficacy of Elo-VRd either as induction therapy only or as induction + consolidation therapy in transplant-eligible NDMM patients. The combination showed no superiority, VGPR or better being obtained in 80.2% in the Elo-VRd *versus* 78.2% in the VRd arms ($p = 0.95$). Neither PFS nor OS were reported to be significantly different [109]. The phase 2 NCT02718833 added pomalidomide to the Elo-Vd backbone. Preliminary results evaluated response in 31 patients, obtaining a best ORR of 52% with a median length of follow-up of 3.3 months [110]. Further studies are required to conclude the efficacy of this approach.

5.3.2. Other monoclonal antibody-bortezomib combinations

The phase 2 NCT00911859 assessed adding **siltuximab** to the classical VMP triplet. Outcomes, however, were not improved by adding siltuximab. Median PFS was 19.1 months in the siltuximab arm compared to 17.1 months in the VMp-alone arm, demonstrating no significant difference in long-term efficacy. Same results have been obtained in the 1-year OS, which was 88% in both arms [111]. **KW-2478** is a monoclonal antibody targeting HSP90, a chaperone involved in stabilization of proteins needed for tumor growth. Its combination with bortezomib in the phase 1/2 NCT01063907 trial for RRMM didn't obtain significant effects, however [112]. **Dacetuzumab** is a humanized IgG1 CD40-targeted monoclonal antibody. CD40 is a surface receptor of the tumor necrosis factor superfamily. It is expressed on both normal and malignant B-cells [113]. A phase 1 trial (no NCT identified) assessed Dacetuzumab-VR in RRMM and achieved modest outcomes with an ORR of 39% [114]. The insulin-like growth factor (IGF) system may contribute to the development of myeloma, and an elevated IGF-1 receptor on the surface of myeloma cells is associated with a poor prognosis. We identified a phase 1 study combining bortezomib and **AVE1642**, an anti-IGFR1R monoclonal antibody, in RRMM but the ORR of 45% (5 out of 11 patients), with only one patient achieving complete response, led to termination of the trial [115]. **Plerixafor (AMD3100)** is a CXCR4-targeting antibody and its main effect is de-adhesion of tumoral cells and a decreased dependence on the bone marrow microenvironment. Thus, a phase 1/2 study (NCT00903968) analyzed if chemosensitization with plerixafor could increase efficacy of bortezomib in RRMM without increasing the incidence of severe adverse events. Even though 78% of the patients were bortezomib refractory, an ORR of 48.5% has been reached ($N = 16/33$) with a median PFS of 11.7 months (95% CI, 5.5-18.9). Further studies are required to assess if this approach could overcome resistance to proteasome inhibitors [116]. **Ulocuplumab** is another anti-CXCR4 monoclonal antibody with the role of inducing apoptosis in tumoral cells. Its addition to the Vd backbone in the phase 1 NCT01359657 trial proved to be safe in RRMM and achieved an ORR of 40% with 6 out of 15 patients responding to treatment [117]. **AO-176** targets CD47, thus promotes phagocytosis but also other killing mechanisms (programmed and immunogenic cell death) since the

CD47-signal regulatory protein α (SIRPα) axis favors tumor cell escape by inhibition of the innate immune system. In case of solid tumors, AO-176 proved to be well tolerated [118]. A phase 1/2 trial (NCT04445701) in RRMM is ongoing to investigate if the same effect can be observed in MM. **Tabalumab (LY2127399)** is a B-cell activating factor targeted monoclonal antibody, promoting myeloma cell death. Two phase 1 studies investigated safety and efficacy of tabalumab with bortezomib ± dexamethasone. NCT00689507 included 48 patients and achieved an ORR of 42% with only 3 complete responses. NCT01556438 administered the regimen to 16 Japanese RRMM patients [119]. A similar ORR of 56.3% has been reached, most of them, however, are only partial responses. No patient achieved complete response. Currently, more efficient salvage therapies outperform this combination [120].

5.4. Bispecific antibody-bortezomib combinations

Supplementary Table 4. summarizes all the bortezomib trials we identified in combination with bispecific antibodies, CAR T-cell therapies, antibody-drug conjugates, immunocytokines and checkpoint-inhibitors.

Teclistamab is the first humanized FDA-approved BCMA-targeting bispecific antibody for RRMM. The MajesTEC-2 phase 1 study (NCT04722146) is currently investigating the safety and efficacy of the teclistamab-daratumumab-bortezomib-dexamethasone combination in both NDMM and RRMM patients. A phase 3 study (MajesTEC-3, NCT05083169) has been also initiated in RRMM. The study is currently recruiting patients. Linvolseltamab (formerly REGN5458) is also a BCMAxCD3 bispecific antibody but with a fully human construct. A phase 1 study (NCT05137054) assessing efficacy of Linvolseltamab in addition to bortezomib or carfilzomib is now ongoing for RRMM patients.

5.5. CAR-T cell therapy-bortezomib combinations

5.5.1. Idecabtagene vicleucel

Idecabtagene vicleucel-bortezomib-pomalidomide-dexamethasone is a novel concept, and hopefully it will provide encouraging results to treat RRMM patients with anti-BCMA CAR-T cell therapy in combination with other FDA-approved therapies. The phase 1/2 KarMMa-7 (NCT04855136) study is ongoing. No results have been published yet.

5.5.2. Ciltacabtagene autoleucel

The phase 3 CARTITUDE-6 (NCT05257083) is comparing ASCT to ciltacabtagene autoleucel in NDMM. In both arms a VRd induction will be performed. CARTITUDE-5 (NCT04923893) is also a phase 3 trial in NDMM patients, but un this trial ASCT is not initially planned and it compares Rd *versus* VRd induction followed by Ciltacabtagene autoleucel. Both trials are currently recruiting patients. CARTITUDE-5 may contribute in the future to generation of a new ASCT-free era for NDMM patients. Ciltacabtagene autoleucel anti-BCMA CAR T-cell therapy following a Dara-VRd induction in NDMM patients is currently investigated in a cohort of the phase 2 CARTITUDE-2 (NCT04133636) trial. VPd induction compared to Dara-Pd in RRMM followed by Ciltacabtagene autoleucel is being investigated in the phase 3 CARTITUDE-4 (NCT04181827) trial. All these trials will offer crucial information regarding utility of CAR-T cell therapy earlier, even in combination with other myeloma therapies, such as PIs.

5.6. Immune checkpoint inhibitor-bortezomib combinations

Pembrolizumab is an FDA-approved checkpoint inhibitor targeting programmed cell death protein-1 (PD-1). Its combination with bortezomib in RRMM is currently studied in the phase 1/2 AMBUSH trial (NCT05514990).

5.7. Antibody-drug conjugate (ADC)-bortezomib combinations

Balantamab Mafodotin is an FDA approved BCMA-targeting antibody-drug conjugate. Balantamab Mafodotin-Vd may be a feasible salvage therapy for RRMM patients. The DREAMM-7 phase 3 trial (NCT04246047) trial investigates its efficacy. Trials are also investigating if combining balantamab with a VRd backbone could increase efficacy. The DREAMM 6 phase 1/2 study (NCT03544281) reported that the combination is safe and active in RRMM patients. Interim results showed that after a median follow-up of 17.4 months a highest ORR of 75% (N = 4) has been reached with a dose of 1.9 mg/kg and 63% (N = 16) with 2.5 mg/kg. Median PFS and OS have not been reached yet [121]. While DREAMM-6 assessed efficacy in RRMM, the phase 1 DREAMM-9 study (NCT04091126) is currently recruiting transplant-ineligible NDMM patients [122]. In the phase 3 DREAMM-8 trial (NCT04484623) for RRMM Balantamab is combined with a VPd backbone. Combination of antibody-drug conjugates with PI-containing regimens remains a major unanswered question yet.

5.8. Immunocytokine-bortezomib combinations

Modakafusp Alfa (formerly TAK-573) is a humanized anti-CD38 antibody-cytokine fusion protein. This immunocytokine is delivering interferon-alfa to CD38 + cells, thus causing direct and indirect cytotoxicity to myeloma cells. A phase 1 study (NCT05556616) is now testing the combination of Modakafusp alfa with bortezomib or bortezomib-pomalidomide in RRMM.

5.9. Transplant-associated bortezomib therapy

Adding bortezomib to classical conditioning regimens for ASCT (bortezomib-melphalan, bortezomib-thalidomide-melphalan or bortezomib-busulfan-melphalan) seemed to achieve durable remissions without increasing the risk of complications in phase 1 or 2 trials. NCT00642395 is a phase 2 trial that evaluated bortezomib (1 mg/m2)-high dose melphalan (200 mg/m^2) conditioning in NDMM patients. Out of the 53 treated patients 37 (70%) achieved a very good partial response (VGPR) or better with median PFS and OS not reached after a 22-month median follow-up (95% CI, 12-28). The 2-year PFS in patients not achieving complete response was 63%, compared to 88% in those achieving CR [123]. Another phase 2 trial (NCT00793650) confirmed safety and efficacy of bortezomib-high dose melphalan (200 mg/m^2), achieving an ORR of 87% with a median PFS and OS of 15.3 and 36.7 months (95% CI not specified) [124]. The NCT01453088 phase 2 study addresses bortezomib-melphalan conditioning for elderly (age ≥60 years). No results have been published yet. The phase 3 IFM2014-02 trial, which included 300 NDMM patients, showed no significant differences in PFS and OS of bortezomib-high-dose melphalan compared to melphalan alone. Median PFS was 34 months for the bortezomib-melphalan arm compared to 29.6 months in the melphalan alone subgroup (HR = 0.82, 95% CI 0.61-1.13, p = 0.244) while 3-year OS was 89.5% for both arms (HR = 1.28, 95% CI, 0.62-2.64, p = 0.374) [125]. Pharmacokinetics (PK) directed administration of busulfan as a bortezomib-busulfan-melphalan triplet proved to be safe and active (ORR = 100%) in 18 NDMM patients according to the outcomes of the phase 2 NCT01605032 trial [126]. Another phase 1/2 study (NCT01242267) assessing bortezomib-thalidomide-melphalan obtained an ORR of 69% with a median PFS of 9.3 months (95% CI not published). Median OS was not reached after a median follow-up of 17.8 months. Safety profile was not modified compared to melphalan-only conditioning [127]. A bortezomib-fludarabine-melphalan-total marrow irradiation trial (NCT01163357) is also ongoing. Bortezomib post-HSCT maintenance has been also studied both in NDMM (NCT00288028, NCT02308280) and RRMM (NCT00084747, NCT00504634). Combination maintenance therapy trials were also done but no results have been

published yet (VCd - NCT01706666, VTd - NCT00792142). We also identified allogeneic HSCT studies, like the phase 2 NCT00948922 trial that compared allo-HSCT with ASCT as consolidation therapy in NDMM. In both cases a bortezomib-melphalan-fludarabine conditioning was administered. Results were promising with a 2-year PFS and OS of 74.8% (95% CI, 44.6–90.1) and 77.5% (95% CI, 49.7–91.1). Regarding efficacy of allo-HSCT versus ASCT further studies are required. The bortezomib-melphalan-fludarabine conditioning seems to be, however, safe in both options [128]. In the Supplementary Table 5. we summarized all the transplant-related bortezomib trials we identified.

6. Carfilzomib

Carfilzomib, formerly PX-171-006, is a second-generation proteasome inhibitor. Kyprolis® (K) was approved by the FDA in 2012 for the treatment of RRMM. Jayaweera et al. reviewed all relevant chemical and biological features of carfilzomib. Carfilzomib is more specific to the proteasome β5 subunit, resulting in significantly lower toxicities when compared to bortezomib [129]. We discuss in this section the results of carfilzomib combination therapy trials with immunomodulatory drugs, CD38-targeting monoclonal antibodies, SLAMF-7 targeting antibodies, bispecific antibodies, ADCs, immune checkpoint inhibitors, and immunocytokines. The trials with published data are listed in Table 3. We identified no trials combining carfilzomib with CAR-T cell therapy.

6.1. Immunomodulatory drug (IMiD)-carfilzomib combinations

Supplementary Table 6. summarizes all the carfilzomib trials we identified in combination with IMiDs.

6.1.1. Carfilzomib-thalidomide-dexamethasone (KTd)

The phase 2 NCT03140943 trial assessed safety and efficacy of a 12-cycle induction and 4-cycle maintenance approach as salvage therapy in RRMM patients but no results have been published yet.

6.1.2. Carfilzomib-cyclophosphamide-thalidomide-dexamethasone (CYKLONE)

The CYKLONE regimen has been investigated in the phase 1/2 NCT01057225 trial in NDMM. The main goal of this four-drug combination is to decrease neurotoxicity and early myelosuppression. Thus, patients with initial neuropathies may benefit from this approach. The study enrolled 64 patients achieving an ORR of 91% after four cycles. In terms of efficacy, CYKLONE seems to be highly active in NDMM achieving a 2-year PFS of 76% and OS of 96%. In terms of safety, all peripheral neuropathies were grade 1 and all adverse events were well manageable [130].

6.1.3. Carfilzomib-lenalidomide (KR)

The phase 2 FORTE trial (NCT02203643) compared KR post-transplant maintenance to lenalidomide alone. KR proved to be more efficient in prolonging 3-year PFS (75% *versus* 66%, HR 0.63, p = 0,026) both in standard- and high-risk patients. At a 3-year follow up no difference in OS has been observed [131]. VRd and KR are recommended maintenance options for high-risk MM in the NCCN guidelines. To identify which approach could improve outcomes more, controlled trials comparing VRd and KR are necessary. Optimal duration of maintenance should also be determined.

6.1.4. Carfilzomib-lenalidomide-dexamethasone (KRd)

KRd was first tested in RRMM patients. The phase 1/2 NCT00603447 demonstrated that the maximum planned dose of 20 mg/m^2 for the first two days and 27 mg/m^2 thereafter is well tolerated and active, achieving an ORR of 76.4% (N = 52 in the maximum planned dose arm) and a median PFS of 15.4 months (95% CI, 7.9-34.1) [132]. Another phase 1 trial (NCT02335983) investigated weekly administration of high-dose carfilzomib (56 or 70 mg/m^2) instead of the usual twice-weekly administration in RRMM. Preliminary results of the trial show that weekly administration doesn't increase toxicity and 56 mg/m^2 *versus* 70 mg/m^2 achieved similar ORR without any difference in the incidence of adverse events [133]. The phase 3 ARROW-2 trial (NCT03859427) also investigated once-weekly *versus* twice-weekly administration of carfilzomib. No results have been published yet. The phase 3 ASPIRE study (NCT01080391) compared KRd to Rd in RRMM. KRd, with a median duration of treatment of 88 weeks (95% CI, 1-185) proved to improve outcomes significantly in terms of ORR (87.1% *versus* 66.7%, p < 0.0001), median PFS (26.1 months *versus* 16.6 months, HR = 0.66; 95% CI, 0.55-0.78; p < 0.001) and median OS (48.3 months *versus* 40.4 months, HR = 0.79; 95% CI, 0.67-0.95; p = 0.0045) [134,135]. A secondary analysis of ASPIRE revealed that continuous KRd treatment may improve outcomes, as complete remission rates increased through the first 18 cycles [136]. An observational study (NCT05495620) was also initiated in an Asian cohort evaluating efficacy of KRd induction in RRMM. The phase 1/2 NCT01029054 trial administered 28-day cycles of KRd to NDMM patients. After a median follow-up of 25 months (95% CI, 5-37) with a median of 22 cycles administered, 2-year PFS and OS rate were 94% and 98%. There was no treatment discontinuation or death due to adverse events [137]. The NCT01402284 phase 2 trial also combined 8 cycles of carfilzomib with the lenalidomide-dexamethasone backbone and administered it to 45 NDMM young, fit patients. The combination resulted in a 18-months PFS rate of 93% (95% CI, 75%-99%) in MRD-negative patients and 84% in MRD-positive patients (95% CI, 55%-96%). Although differences in outcomes based on MRD-status determined by NGS (93% vs 84%) were not statistically significant, the combination proved to be safe and beneficial in extending survival in NDMM [138]. The phase 2 FORTE (NCT02203643) trial investigated if 4 KRd cycles, ASCT and 4 consolidation KRd cycles or 8 KRd cycles alone is more efficient. MRD-negativity as primary endpoint was higher in the transplanted group (62% *versus* 56%, P = 0.001). 4-year PFS was 69% (95% CI, 62-77) for the ASCT group compared to 56% (95% CI, 48-64) in the KRd only arm [139]. Based on the results, KRd + ASCT is superior and ASCT remains the gold standard even with new generation PIs. The phase 2 IFM trial (NCT02405364) confirmed the results of FORTE. Patients received 4 cycles of KRd induction, ASCT and 4 KRd consolidation cycles followed by lenalidomide maintenance to 46 NDMM patients. Out of these 17 obtained MRD-negativity according to NGS data and 25 patients by flow cytometry. Median PFS was 56.4 months (95% CI 43.5-NE) with an estimated 5-year OS of 77.8% (95% CI 62.7-87.4). No adverse events-related death was reported [140]. The NCT01816971 phase 2 study conducted by the Multiple Myeloma Research Consortium (MMRC) explored outcomes in further extended KRd, patients receiving 4 cycles induction, ASCT, 4 cycles consolidation and 10 cycles of KRd maintenance followed by lenalidomide monotherapy. MRD-negativity increased from 60% after 8 cycles to 70% after 18 cycles, with 81% as best response. An MRD-test following 3 years of lenalidomide maintenance showed that 76% (22 of 29) of patients remained MRD-negative. In the overall cohort a 5-year PFS of 72% (95% CI, 60-81) and OS of 84% (95% CI, 71-92) has been estimated. As a conclusion, an extended KRd protocol following ASCT suggests a deepened response and improved outcomes [141]. Direct, prospective comparative trials, however, are still required. Another phase 2 trial (NCT02891811) assessed efficacy of K monotherapy maintenance and investigated if KRd induction is superior to KTd. Preliminary results (N = 75) reported a combined (KRd + KTd arms) ORR of 100%, a median PFS of 22.3 months (no 95% CI reported) and a 2-year OS of 78% [142]. Results regarding superiority of KRd and efficacy of carfilzomib maintenance have not been published yet. The phase 3 ENDURANCE trial (NCT01863550) compared KRd with VRd in NDMM standard-risk patients without initial intent to ASCT. Results have shown no superiority of KRd regimen

Table 3
Carfilzomib trials.

regimen	treatment	ASCT eligible	trial ID	study phase	study population	N	ORR (%)	median PFS (months)	median survival (months)
Immunomodulatory drugs									
CYKLONE	induction	yes	NCT01057225 [130]	1/2	NDMM	64	91	not reached	not reached
KRd	salvage	yes	NCT00603447 [132]	1/2	RRMM	84	76.9	15.4	no data
KRd	salvage	yes	NCT02335983 [133]	1	RRMM	107	90	no data	no data
KRd *versus* Rd	salvage	yes	NCT01080391 (ASPIRE) [136,206]	3	RRMM	792	87.1	26.1	48.3
KRd	induction	yes	NCT01029054 [137]	1/2	NDMM	53	98	not reached	not reached
KRd	induction	yes	NCT01402284 [138]	2	NDMM	45	98	not reached	not reached
KRd	induction	yes	NCT02405364 [140]	2	NDMM	46	97.7	56.4	not reached
KRd	induction	yes	NCT01816971 [141]	2	NDMM	76	97.4	not reached	not reached
KRd *versus* KTd K maintenance	induction	yes	NCT02891811 [142]	2	NDMM	146 (75)	**100**	**22.3**	not reached
KPd	salvage	yes	NCT01464034 [145]	1	RRMM	136	50	7.2	20.6
Monoclonal antibodies									
Dara-Kd	salvage	yes	NCT01998971 (MMY1001) [147]	1	RRMM	85	86	14.1	no data
Dara-Kd	salvage	yes	NCT03158688 (CANDOR) [148]	3	RRMM	466	84	28.6	not reached
18-cycle Dara-KRd	induction	no	NCT04065789 (KyDaR)	2	NDMM	41	90	15.4	28.2
Dara-KRd	induction	yes	NCT03606577 (IFM 2018-04) [153]	2	NDMM	50	96	not reached	not reached
Isa-Kd	salvage	yes	NCT02332850 [155]	1	RRMM	33	70	10.1	not reached
Isa-Kd	salvage	yes	NCT03275285 (IKEMA) [156]	3	RRMM	302	87	not reached	not reached
Isa-KRd	induction consolidation	yes/no	NCT03104842 (GMMG-CONCEPT) [157]	3	NDMM	246	100	not reached	not reached
Elo-KRd	induction	yes/no	NCT02969837 [158]	2	NDMM	46	no data	not reached	not reached
Checkpoint inhibitors									
Pembrolizumab-Kd	salvage	yes	NCT02036502 (KEYNOTE-023) [161]	1	RRMM	77	50	no data	no data
Transplant related									
K + HDM (200 mg/m^2) conditioning Kd maintenance	ASCT conditioning maintenance	yes	NCT02572492 (CARFI) [164,207]	2	NDMM	200	98	not reached	not reached
KRd *versus* R	post-ASCT maintenance	yes	NCT02659293 (ATLAS) [165]	3	NDMM	180	no data	59.1	not reached

with a median PFS of 34.6 months *versus* 34.4 months (p = 0.74), a 3-year OS of 86% *versus* 84% (p = 0.92). Regarding toxicity, however, differences have been observed, such as 11 deaths in KRd arm compared to 1 death in the VRd treated group, higher rate of cardiopulmonary and renal complications in the KRd arm while a higher rate of peripheral neuropathy in the VRd group [143]. In terms of QoL however, no significant difference has been reported [144]. An exciting clinical question is whether VRd or KRd delivers superior outcomes in NDMM patients. The phase 3 COBRA trial (NCT03729804) is currently recruiting patients to answer this question. We also identified a phase 3 trial (NCT04096066) comparing KRd to Rd in transplant-ineligible NDMM patients aged 65 or older. Recruitment is currently ongoing.

6.1.5. Carfilzomib-pomalidomide-dexamethasone (KPd)

The first phase 1/2 trial (NCT01464034) assessing safety and efficacy of KPd recruited 33 RRMM patients and administered them KPd induction followed by KPd maintenance. A median of 7 cycles were administered and an ORR 50% has been achieved. Median PFS and OS were 7.2 months (95% CI, 3-9) and 20.6 months (95% CI, 11.9-28.7), respectively. The trial proved that KPd is safe and active in RRMM

[145]. Another phase 1/2 trial (NCT01665794) is currently recruiting PI sensitive/naïve RRMM patients to assess the 28-day cycle induction with KPd. Preliminary data (N = 55) show an ORR after 4 cycles of 77% which increased to 84% after a median of 7.2 cycles. Median PFS was 12.9 months (no 95% data reported). Estimated 18-month OS was 86.5%. Thus, the regimen seems to prove the efficacy of KPd in lenalidomide-refractory patients [146]. Results are awaited for the phase 1/2 NCT02185820 trial investigating efficacy of 8 KPd cycles in primary lenalidomide-resistant RRMM patients. NCT05509374, a phase 2 study, investigates efficacy of KPd in KRd-resistant RRMM patients. The trial is currently recruiting patients. Phase 2 trials (SELECT - NCT04191616 and NCT04287855) designed specifically for early (first- or second-) relapse were initiated. Patients will receive continuous once-weekly carfilzomib combined with Pd until disease progression. No results have been published yet.

6.1.6. *Carfilzomib-mezigdomide or iberdomide-dexamethasone*

While SUCCESSOR-1 investigates bortezomib-mezigdomide-dexamethasone, the phase 3 SUCCESSOR-2 (NCT05552976) is currently recruiting RRMM patients to assess efficacy of mezigdomide in combination with Kd. A phase 1/2 study that also enrolls NDMM patients is currently ongoing (NCT03989414). A phase 1/2 study (NCT05199311) assessing safety and efficacy of 4 cycles of carfilzomib-iberdomide-dexamethasone was also initiated and is currently recruiting transplant-eligible NDMM patients. Another phase 1/2 (NCT02773030) is currently recruiting patients for multiple combinations of iberdomide, one of them being the KId induction in both NDMM and RRMM patients. Efficacy of these novel approaches remains to be determined.

6.2. *CD38-targeting monoclonal antibody-bortezomib combinations*

Supplementary Table 7. summarizes all the carfilzomib trials we identified in combination with CD-38-targeting monoclonal antibodies.

6.2.1. *Daratumumab-carfilzomib-dexamethasone (Dara-Kd)*

Dara-Kd may be a feasible option in immunomodulatory drug-resistant patients. We identified the phase 1 MMY1001 (NCT01998971) investigating safety of Dara-Kd for lenalidomide-refractory RRMM. Grade 3/4 adverse events were mostly hematologic, thrombocytopenia (37%), anemia (29%), neutropenia (28%) and lymphopenia (26%). Median PFS was 14.1 months (95% CI, 9.4-NR) but MRD-negativity was reached by no patient at a threshold of 10^{-6} and only by 2% at 10^{-5} [147]. The phase 2 PLEIADES trial (NCT03412565) includes a Dara-Kd arm for RRMM patients. No results have been published yet. The phase 3 CANDOR (NCT03158688) study demonstrated high efficacy of the regimen, obtaining ORR of 84% in RRMM patients even if more than half of the patients were refractory to 2-3 prior lines of treatment. Dara-Kd achieved a year longer median PFS of 28.6 months (95% CI, 22.7-NR) *versus* 15.2 months (95% CI, 11.1-19.9) in the Kd alone arm (HR = 0.59, 95% CI, 0.45-0.78, p < 0.0001). Although cardiac failure and infections led to treatment discontinuation in 28% and to death in 2% of patients treated with Dara-Kd, benefit-risk ratio is higher given the impressively increased median PFS [148]. We have not identified any comparative trials of Dara-Kd *versus* Dara-Vd. However, a matching-adjusted, indirect comparison shows that Dara-Kd reduces the risk of disease progression or death by 36% (HR = 0.64; 95% CI, 0.46-0.90). However, one confounding factor is that Dara-Vd trials typically administered 8 cycles, whereas Dara-Kd was usually continued for more than 8 cycles [149].

6.2.2. *Daratumumab-carfilzomib-lenalidomide-dexamethasone (Dara-KRd)*

The phase 2 MASTER trial (NCT03224507) enrolled 123 transplant-eligible NDMM patients and administered 4 cycles of Dara-KRd induction followed by ASCT and Dara-KRd consolidation. The trial adapted maintenance therapy to MRD-status, two consecutive MRD-negative results leading to lenalidomide maintenance monotherapy cessation. The outcomes are promising with 80% of patients MRD-negativity (10^{-5}), 2-year PFS and OS being 87% and 94%. The study is the first to demonstrate that MRD-assessment is a feasible option to adjust treatment duration [150]. Another phase 2 trial (NCT04113018) assesses MRD-status following a 9 cycle Dara-KRd induction. In case of MRD-positivity, following ASCT in transplant-eligible patients or directly after MRD-assessment in transplant-ineligible patients, up to 12 cycles of KRd consolidation will be given. MRD-negative patients continue lenalidomide monotherapy. The approach seems to be promising, no results have been published yet [151]. The efficacy of Dara-KRd was also demonstrated in the non-randomized MANHATTAN trial (NCT03290950). The study enrolled 41 NDMM patients and administered 8 cycles of Dara-KRd for each of them. MRD-negativity after 8 cycles was achieved in 29 patients with a median time to negativity of 6 cycles. At 11 months PFS was 98% (95% CI, 93-100) with an OS rate of 100%. A limitation of the study, however, is the small number of patients included [152]. There is a currently ongoing phase 3 trial (ADVANCE - NCT04268498) studying an 8-cycle induction with Dara-KRd in NDMM. MRD-driven ASCT and lenalidomide maintenance will be performed. No preliminary results have been published yet. While an ongoing phase 2 (NCT03500445) study investigates a continuous 24-cycle initial treatment with Dara-KRd in NDMM patients regardless of transplant-eligibility and age, another one (KyDaR - NCT04065789) administered only 18-cycles to transplant-ineligible NDMM patients. Cohen et al. reported at ASH 2021 an ORR of 90%, median PFS and OS of 15.4 and 28.2 months (no 95% CI data). We also identified a phase 3 study (NCT03742297) investigating a 18-cycle induction in elderly aged between 65-80 followed by Dara-R maintenance. Induction with 12 cycles is tested in the currently recruiting phase 2 REACH trial (NCT02036502). The optimal number of cycles [4,8,12,18,24] when ASCT is not intended remains an unanswered question both for young and elderly patients. Tandem transplants were also evaluated in combination with Dara-KRd. The phase 2 IFM 2018-04 (NCT03606577) investigated 6-cycles Dara-KRd induction followed by ASCT, 4-cycles of Dara-KRd consolidation, second ASCT and Dara-R maintenance for high-risk NDMM patients. Preliminary data showed an ORR of 96% and an MRD-negativity rate of 62% following induction [153]. A retrospective analysis of Dara-KRd *versus* Dara-VRd in high-risk NDMM didn't show any statistically significant difference in PFS (p = 0.25) and OS (p = 0.3) [154]. Further prospective trials are required to identify patient subgroups where Dara-KRd may improve outcomes *versus* Dara-VRd. Trials for RRMM have also been initiated, such as the phase 2 NCT03556332. Patients received one cycle of Dara-KRd followed by melphalan conditioning and salvage ASCT. Following transplant, 4 additional cycles of Dara-KRd has been administered. No results have been published yet. We identified an observational real-world study of Dara-KRd in RRMM (NCT02970747) too.

6.2.3. *Daratumumab-carfilzomib-pomalidomide-dexamethasone (Dara-KPd)*

Dara-KPd would be a feasible option for lenalidomide-resistant patients. The phase 2 NCT04176718 is currently investigating the combination in RRMM patients who received at least one prior lenalidomide and PI-containing therapy.

6.2.4. *Daratumumab-carfilzomib-iberdomide-dexamethasone (Dara-KId)*

The phase 1/2 COMMANDER trial (NCT05434689) compares 6 cycles of Dara-KId consolidation *versus* Dara-Id in MRD-positive patients following ASCT. The trial is currently recruiting patients.

6.2.5. Isatuximab-carfilzomib-dexamethasone (Isa-Kd)

In the phase 1 NCT02332850 study isatuximab was administered with Kd. The dose of carfilzomib was 20 mg/m^2 followed by 27 mg/m^2. Median PFS was 10.1 months (95% CI, 6.47-16.4), while 2-year OS rate 76% [155]. The success of the phase 1 led to initiation of the 3 IKEMA trial (NCT03275285). It demonstrated superiority of Isa-Kd, achieving a higher very good partial response rate of 73% versus 56% (p = 0.0011) and 2-year PFS of 68.9% (95% CI, 60.7-75.8) *versus* 45.7% (95% CI, 35.2-55.6; HR = 0.58, 99% CI, 0.36-0.92; p = 0.0010) [156].

6.2.6. Isatuximab-carfilzomib-lenalidomide-dexamethasone (Isa-KRd)

NCT04430894 is a phase 2 study currently recruiting transplant-eligible NDMM patients. A maximum of 8 cycles are planned with stem cell collection following cycle 4, ASCT and 2 more consolidation Isa-KRd cycles. If HSCT is deferred, 4 more consolidation cycles are given. The GMMG-CONCEPT phase 3 trial (NCT03104842) recruited high-risk NDMM patients in order to assess efficacy of Isa-KRd. The study included 6 cycles Isa-KRd induction, 4 cycles Isa-KRd consolidation and Isa-KR maintenance. Eligible patients underwent ASCT. Median PFS was not reached after a median follow-up of 24.9 months, 2-year PFS was 75.5% (95% CI, 63.5-86.6). Carfilzomib-related cardiac toxicity was observed in 4 patients and 3 patients died due to infections [157]. We identified another phase 3, randomized trial entitled IsKia (NCT04483739) that investigates Isa-KRd safety and efficacy compared to KRd induction alone in both standard-and high-risk NDMM. No results have been published yet.

6.2.7. Isatuximab-carfilzomib-pomalidomide (Isa-KP)

Isa-KP is tested in phase 2 NCT04850599 trial and may be a promising approach for RRMM resistant to Dara-VTd or Dara-VRd. It is currently recruiting patients.

6.2.8. Isatuximab-carfilzomib-pomalidomide-dexamethasone (Isa-KPd)

NCT04883242 is a phase 2 trial currently ongoing in order to assess the safety efficacy of Isa-KPd in RRMM patients. A 6-cycle Isa-KPd induction followed by a reduced intensity Isa-KPd maintenance up to 24 months.

6.3. Elotuzumab-carfilzomib combinations

Supplementary Table 8. summarizes all the carfilzomib trials we identified in combination with elotuzumab.

The phase 2 NCT02969837 enrolled 46 NDMM patients regardless of transplant-eligibility and assessed efficacy of an MRD-driven induction/maintenance approach. All patients received 12 cycles of Elo-KRd. Following cycle 12, patients were evaluated. In case of MRD-negativity, carfilzomib was ceased and patients started an Elo-Rd maintenance. If MRD-positive, patients continued Elo-KRd for up to 6 additional cycles. ASCT was not intended in the trial. MRD-negativity (10^{-5}) increased from 56% at cycle 8 to 70% with further cycles of Elo-KRd administered. The 3-year PFS was higher in the MRD-negative arm (92%) compared to the overall population (72%) [158]. We also identified a phase 3 trial (NCT03948035) initiated in transplant-eligible NDMM patients. The trial compares efficacy of a 6-cycle Elo-KRd induction to KRd alone followed by a 4-cycle consolidation. Elo-KRd is also tested in lenalidomide-resistant RRMM. In the phase 2 NCT03361306 induction with 4 cycles of Elo-KRd has been performed followed by Elo-R maintenance until disease progression. The phase 1 NCT03155100 trial investigated the effects of Elo-Kd in RRMM patients aged 18-75 years. More results are awaiting.

6.4. Bispecific antibody-carfilzomib combinations

Supplementary Table 9. summarizes all the carfilzomib trials we identified in combination with bispecific antibodies, antibody-drug conjugates, immunocytokines and checkpoint-inhibitors.

Elranatamab is a BCMAxCD3 bispecific antibody, that proved safe and efficient in the MagnetisMM-1 (NCT03269136) trial, 100% of the evaluable patients reaching MRD-negativity (N = 55) [159]. A novel approach combining elranatamab with carfilzomib and dexamethasone is currently investigated in the phase 1 MagnetisMM-20 (NCT05675449) trial in RRMM patients. Talquetamab is a bispecific T-cell engager targeted against G protein–coupled receptor, family C, group 5, member D (GPRC5D). Although even monotherapy in RRMM achieved impressive outcomes in the MonumenTAL-1 trial (NCT03399799), further trials were initiated in NDMM too [160]. MonumenTAL-2 (NCT05050097) is a phase 1 trial investigating multiple combinations of Talquetamab in NDMM, one arm investigating its combination with Dara-K. The study is currently recruiting patients. Linvolseltamab, as also described in case of bortezomib, is being combined with several drugs in the phase 1 LINKER-MM2 study (NCT05137054), with one arm currently recruiting RRMM patients to assess its efficacy with carfilzomib.

6.5. Immune checkpoint-inhibitor-carfilzomib combinations

Pelareorep is a wild-type oncolytic reovirus, tested for several solid tumors, such as breast cancer and melanoma. A novel combination with nivolumab, an anti-PD-1 immune checkpoint inhibitor, is tested in combination with Pelareorep and the Kd backbone in the phase 1 NCT03605719 trial. There were enrolled RRMM patients but no results have been published yet. The phase 1 KEYNOTE-023 (NCT02036502) study, although terminated earlier due to business reasons, investigated pembrolizumab in combination with the Kd backbone. Patients achieved an ORR of 50% while the lenalidomide-refractory subgroup only 36%. No data regarding PFS and OS have been published [161]. These findings are not encouraging, and it is likely that no further research will be conducted in the future. A transmembrane protein called CD47, often referred to as integrin associated protein, primarily serves as an anti-phagocytic ("do not eat me") signal, allowing cells that express CD47 to escape from by macrophages. Magrolimab is a monoclonal antibody, a macrophage checkpoint inhibitor, targeting CD47 [162]. In the phase 2 NCT04892446 trial magrolimab is combined with a Kd backbone for RRMM. Patients are now being enrolled in the study.

6.6. Antibody-drug conjugate-carfilzomib combinations

As with bortezomib, balantamab mafodotin is investigated in combination with Kd in lenalidomide-resistant RRMM patients. The phase 1/2 NCT05060627 trial aims to determine maximum tolerated dose and toxicities of the combination. For lenalidomide sensitive/naïve RRMM patient a phase 1/2 study (NCT04822337) was initiated to determine optimal dose and safety profile of the balantamab-KRd quadruplet. The study is currently recruiting patients.

6.7. Immunocytokine-carfilzomib combinations

As already described, Modakafusp Alfa is investigated in several combinations for RRMM (NCT05556616). There are two carfilzomib-containing arms, one with carfilzomib only, the other one adds daratumumab to the immunocytokine-carfilzomib combination.

6.8. Transplant-associated carfilzomib therapy

Supplementary Table 10. summarizes all the transplant-related carfilzomib trials we identified.

Doublet conditioning with carfilzomib and high-dose melphalan has been evaluated both in NDMM patients (CARAMEL - NCT01842308) and in RRMM patients undergoing salvage ASCT (in the phase 1/2 NCT01690143 trial). The combination proved to be safe and well tolerated in RRMM. Out of the 45 recruited patients, 59.1% (95% CI, 44.1-72.3) achieved a very good partial response or better [163]. Interpretation of results, however, is debatable, comparative trials are necessary. A carfilzomib-busulfan-melphalan triplet conditioning is evaluated in currently ongoing phase 1/2 NCT03795597 trial. Carfilzomib is administered in 4 doses on days -9, -8, -2 and -1 with dose escalation from 20 mg/m^2 in the first two doses to 27 mg/m^2 and 56 mg/m^2 in the last two administrations. Reinduction with KRd prior to second ASCT in RRMM is also evaluated in the phase 2 NCT05497102 study. The trial is recruiting patients aged 70 years or younger. Trials evaluating efficacy of carfilzomib-dexamethasone doublet therapy as post-up front ASCT maintenance are missing. Following salvage ASCT, however, carfilzomib prolonged time to progression (TTP) in the CARFI phase 2 trial (NCT02572492) from a median TTP of 18.5 months (95% CI, 14.3-22) in the observation arm to 28.8 months (95% CI, 24.2-NR, p = 0.003) in the carfilzomib treated group [164]. The phase 3 ATLAS trial (NCT02659293) compared up to 36 cycles of KRd post-ASCT maintenance to carfilzomib alone. Preliminary results show that KRd improves outcomes without any significant increase in the incidence of severe adverse events. Median PFS was 59.1 months (95% CI, 54.8-NR) in the KRd arm compared to 41.4 months (95% CI, 33.2-65.4; HR = 0.51, 95% CI 0.31-0.86; p = 0.012), median OS was not reached [165]. KPd maintenance in high-risk MM patients has been assessed in the phase 2 NCT03756896. We are waiting for the results to be published.

7. Ixazomib

Ixazomib or Ninlaro® (N) is the first orally bioavailable PI approved by the FDA in 2015 for treatment of RRMM. Gupta et al. provided an excellent review of the pharmacological properties of ixazomib [166]. Table 4 illustrates ixazomib trials combined with immune therapies with published data. We identified no trials combining ixazomib with elotuzumab or other SLAMF-7 targeting antibodies, bispecific antibodies, CAR-T cell therapies or ADCs.

Table 4
Ixazomib trials.

regimen	treatment	ASCT	trial ID	study phase	study population	N	ORR (%)	median PFS (months)	median survival (months)
Immunomodulatory drugs									
NTd	induction	yes	NCT02410694 [167]	2	RRMM	90	51.1	8.5	not reached
NR	maintenance	no	NCT03941860 (OPTIMUM)	3	NDMM	510	**recruiting**		
12-cycle NRd	induction	yes	NCT01217957 [172]	1/2	NDMM	65	88	35.4	not reached
16-cycle NRd	induction	yes	NCT01383928 [173]	1/2	NDMM	64	92	25.4	not reached
3-cycle NRd + ASCT + 2-cycle NRd (weekly N)	induction consolidation	yes	NCT01936532 (IFM2013-06) [174,208]	2	NDMM	42	92.3	not reached	not reached
3-cycle NRd + ASCT + 2-cycle NRd (twice-weekly N)	induction consolidation	yes	NCT02897830 (IFM2014-03) [175]	2	NDMM	46	91	not reached	not reached
NRd	induction	no	NCT01850524 (TOURMALINE-MM2) [176]	3	NDMM	705	82.1	35.3	54.3
NRd	consolidation	no	NCT03173092 (TOURMALINE-MM6) [177]	4	NDMM	140	78	not reached	not reached
NRd	salvage	yes	NCT01645930 [180]	1	RRMM	43	65	no data	
NRd	salvage	yes	NCT02917941 [181]	2	RRMM	34	84.4	22	not reached
NRd	salvage	yes	NCT01564537 (TOURMALINE-MM1) [182]	3	RRMM	722	no data	no data	53.6
NRd NPd	salvage	yes	NCT02206425 [184]	3	RRMM	45	12.8	2.1	no data
NPd	salvage	yes	NCT02119468 [186]	1/2	RRMM	32	76	8.6	not reached
NPd	salvage	yes	NCT02004275 [187]	2	RRMM	117	51.7	4.4	34.3
NPd	salvage	yes	NCT04094961 [188]	2	NDMM	120	93	no data	no data
Dara-NRd	induction	yes	NCT03669445 (IFM-2018-01) [190]	2	NDMM	45	93.4	not reached	not reached
ixazomib	post-ASCT maintenance	yes	NCT02181413 (TOURMALINE-MM3) [192]	3	NDMM	656	92	26.5	not reached
NR	post-ASCT maintenance	yes	NCT01718743 [193]	2	NDMM	64	no data	73.3	not reached
ixazomib	post-allo-HSCT maintenance	yes	NCT02440464 [194,209]	2	NDMM	57	88.9	not reached	not reached

7.1. Immunomodulatory drug (IMiD)-ixazomib combinations

Supplementary Table 11. summarizes all the ixazomib trials we identified in combination with IMiDs.

7.1.1. Ixazomib-thalidomide-dexamethasone (NTd)

An 8-cycle all-oral NTd induction followed by ixazomib maintenance has been evaluated in RRMM in the phase 2 NCT02410694 trial. ORR was higher in those exposed only to 1 previous line of therapy. Overall median PFS was 8.5 (95% CI, 6.4-10.3). The combination showed equal activity regardless of fitness, ISS status and renal impairment. Although not statistically significant (p = 0.111), median PFS (7 months) was remarkable shorter in patients with gain of 1q21. Ixazomib maintenance, however, led to an increase in ORR [167]. A 9-cycle NTd induction was also investigated in elderly, aged 65 or older, transplant-ineligible NDMM patients in the phase 2 UNITO-EMN10 (NCT02586038) trial. ORR was 84% with a median PFS was 12 months (95% CI, 10-18). MRD-negativity was reached by 8% of the patients [168]. The Australasian Myeloma Research Consortium (AMaRC) 16-02 trial (no NCT identified) achieved similar results, ORR of 56.4% (N = 39) with median PFS of 18.8 months (95% CI, 8.2-22.2) [169]. HOVON-126/NMSG 21.13 (no NCT identified), a phase 2 study, however reported no significant difference between the NTd and placebo-Td arm with a median PFS of 9.5 months *versus* 8.4 months (HR = 0.80; 95% CI, 0.48-1.34; p = 0.39) [170]. Since current data are contradictory, further prospective trials are needed to assess efficacy of NTd in RRMM.

7.1.2. Ixazomib-Lenalidomide (NR)

The OPTIMUM phase 3 trial (NCT03941860) is currently recruiting patients that are already on lenalidomide maintenance but MRD-positive to assess efficacy of adding ixazomib to the maintenance therapy. We also identified a prospective, phase 4 trial (NCT04217967) that is currently recruiting patients to directly compare efficacy of lenalidomide alone, ixazomib alone or their combination as maintenance therapy. Interim analysis reported no significant difference in disease progression rates in the non-ASCT arm (13.5% with N, 10.2% R and 10.8% with NR) while more patients relapsed while on lenalidomide maintenance in the ASCT arm (0% with N, 21.7% with R, 0 with NR) [171].

7.1.3. Ixazomib-lenalidomide-dexamethasone (NRd)

One of the first trials investigating long-term efficacy of an NRd induction and ixazomib maintenance in NDMM is the phase 1/2 NCT01217957. The study enrolled 65 patients achieving CR in 23% of patients with a median PFS of 35.4 months (95% CI, 17.84-44.12) and a 4-year OS rate of 84% [172]. While NCT01217957 administered 12 cycles (28-day/cycle) with once weekly ixazomib, NCT01383928, another phase 1/2 trial, assessed a 16 cycle (21-day/cycle) approach with twice-weekly administration. Although ORR was higher (92%), the CR rate was similar (24%) when compared to 12 cycles. Median PFS was 24.9 months (95% CI, 17.4-40.5) with a 3-year OS of 91% [173]. In the phase 2 IFM2013-06 trial (NCT01936532), also for NDMM patients, a 3-cycle induction was followed by ASCT, 2 additional NRd early-consolidation cycles and 6 NR late-consolidation cycles. Patients started ixazomib maintenance after the consolidation therapy. CR rates increased after each cycle from 12% post-induction to 19% post-ASCT, 32% post-early consolidation, 36% post-late consolidation and 48% following 1-year maintenance. With a median 2-year follow-up PFS rate was 83% while OS rate was 95% [174]. Same approach but with twice-weekly administration of ixazomib was evaluated in the phase 2 IFM2014-03 trial (NCT02897830) achieving a similar CR rate (20.9%; 90% CI, 11.4-33.7). Thus, twice-weekly ixazomib was not superior to weekly administration [175]. The phase 3 TOURMALINE-MM2 (NCT01850524) study compared the all-oral NRd regimen to Rd in transplant-ineligible NDMM patients. Followed by the NRd induction, NR was continued until disease progression. No statistical difference has been observed in ORR (82.1% *versus* 79.7%, p = 0.436) and OS (HR 0.998, 95% CI, 0.790-1.261), neither in PFS (35.3 *versus* 21.8 months, p = 0.073). The statistically nonsignificant increase in PFS suggests, however, that the PFS benefit may be clinically meaningful and further, risk- and age-stratified real-world studies are needed [176]. Transition from a 6-cycle VRd induction to continuous, long-term NRd in transplant-ineligible NDMM patients is tested in the phase 4 TOURMALINE-MM6 trial (NCT03173092). Out of the 140 enrolled patients an ORR of 78% has been achieved with a 2-year PFS and OS of 69% and 85%, respectively. In 14% of patients, the combination caused serious, treatment-related adverse events, but QoL was maintained after the bortezomib-ixazomib transition [177]. NRd post-ASCT consolidation has been evaluated in the NCT02253316 phase 2 trial in NDMM patients aged 18-70. Following transplant 4 cycles of NRd consolidation was administered continued with an either ixazomib or lenalidomide maintenance. Interim results show that after a median follow-up of 12.3 months, 18% of patients had progressive disease [178]. NRd maintenance was assessed in a real-world study. Shen et al. reported favorable results, with a median PFS of 16.2 months following initiation of NRd [179]. Further, randomized, controlled, prospective studies are required to draw any conclusions regarding efficacy of ixazomib-containing maintenance options. In case of RRMM, the first trial to investigate efficacy of NRd was the phase 1 NCT01645930. Out of the 43 East Asian enrolled patients 28 responded to the therapy, NRd achieving an ORR of 65%. The trial assessed pharmacokinetics and safety. The most common grade 3 or higher adverse events were neutropenia, thrombocytopenia, and diarrhea [180]. A phase 2 trial (NCT02917941) on Japanese RRMM reported similar results with a median PFS of 22 months. (95% CI 17.3-NR) [181]. Clinical trial and real-world data, attest the efficacy of NRd regimen in comparison to Rd. In the phase 3 TOURMALINE-MM1 (NCT01564537) study, similarly in TOURMALINE-MM2, no significant difference in non-stratified OS has been observed (53.6 months in the IRd group compared to 51.6 months, p = 0.495) in NDMM patients. Predefined patient subpopulations, mainly high-risk and heavily-pretreated patients obtained greater OS benefit [182]. Real-world data, however, reported a statistically significant increase in both PFS (17.5 *versus* 11.5 months, p = 0.005) and OS (36.6 *versus* 26 months, p = 0.008) [183]. The safety profile and post-treatment QoL of patients in the NRd group was comparable to the Rd regimen both in TOURMALINE-MM1 and in real-life data. In the phase 1/2 NCT02206425 trial, when patients who received traditional bortezomib or carfilzomib combinations (VRd, VMP, VCd, Vd, Kd, KRd, VPd, KRd) relapsed, the PI used in the combination was changed to ixazomib. Unfortunately, ORR was 12.8% and there was no clinical benefit in changing the PI only [184]. Another approach was tested in a phase 4 (NCT03416374) study in RRMM patients who received a 3-cycle VRd or KRd reinduction followed by NRd if no response to reinduction was achieved. No results have been published yet. Real-world, observational studies in RRMM patients are also currently ongoing. These are either investigating quality of life and changes in symptom severity (NCT03903406) or long-term efficacy (NCT03433001). Based on current results, however, NRd, the first all-oral combination may be in the future a feasible therapeutic option for both NDMM and RRMM patients. Biomarkers that may predict response to PIs are intensively studied. NFKB2 rearrangement was reported as a possible resistance mechanism in PI-refractory patients. A phase 2 study (NCT02765854) has been initiated to investigate if NDMM patients without the NFKB2 rearrangement achieve superior response rates and better outcomes following NRd treatment compared to the NFKB2 non-mutated ones. Although statistically not significant, due to the small number of enrolled patients (p = 0.16), the non-mutated arm achieved higher ORR (56.3%; 95% CI, 29.9-80.3 *versus* 16.7%; 95% CI, 0.4-64.1) [185]. Further studies are required but results are promising.

7.1.4. Ixazomib-pomalidomide or iberdomide-dexamethasone (NPd/NId)

NPd salvage therapy was evaluated in the phase 1/2 NCT02119468 and in the phase 2 NCT02004275 trials. In the NCT02119468 trial 76% of patients achieved at least stable disease with a median PFS of 8.6 months (95% CI, 1.8-NR) and a 1-year OS of 82% (95% CI, 59-93) [186]. In NCT02004275 a median PFS and OS of 4.4 months (95% CI, 3.0-18.4) and 34.3 months (95% CI, 19.2-NR) has been achieved with a median follow-up of 28.4 months. Adverse effects were well manageable, most of them being neutropenia and infections [187]. Another phase 2 trial (NCT03202628) added a salvage ASCT to the 4-cycle NPd reinduction, while efficacy of NPd in RRMM with extramedullary disease was investigated in the NCT02547662 trial. No results have been published yet. NCT04790474 is also a phase 2 study that is currently ongoing in daratumumab-, lenalidomide- and bortezomib-resistant patients that will receive NPd as third-line therapy. While most studies chose 28-day cycles, the currently recruiting phase 1/2 NCT04094961 administers NPd in 21-day cycles with twice-weekly ixazomib. Also, a real-world, multicenter, phase 4 study (NCT04989140) is currently recruiting lenalidomide-refractory RRMM patients to investigate long-term efficacy of NPd. We identified only one trial (NCT03376672) assessing a 4-cycle NPd induction in transplant-eligible NDMM patients. An ORR of 93% has been reached without any significant toxicities. Only 8% of patients were flow-MRD-negative before consolidation [188]. NId may be a feasible option for elderly, transplant-ineligible RRMM patients. The phase 2 NCT04998786 trial is currently recruiting elderly, aged 70 or older first relapsed MM patients. Induction consists of 6 cycles of NId followed by NI maintenance until disease progression.

7.2. CD38-targeting monoclonal antibody-ixazomib combinations

Supplementary Table 12. summarizes all the ixazomib trials we identified in combination with anti-CD38 monoclonal antibodies.

7.2.1. Daratumumab-ixazomib (Dara-N)

Ixazomib alone *versus* Dara-N maintenance following a 4 cycle Dara-VTd or Dara-VCd induction and a 2-cycle consolidation with the same quadruplet is currently evaluated in the phase 2 NCT03896737 trial. Maintenance is given up to 24 months or until disease progression.

7.2.2. Daratumumab-ixazomib-cyclophosphamide (Dara-NC)

NCT01415882 is phase 2 trial investigating several combinations of ixazomib in RRMM. One arm of the study investigated a 12 cycle Dara-NC reinduction. No results have been published yet.

7.2.3. Daratumumab-ixazomib-dexamethasone (Dara-Nd)

Dara-Nd is compared to Dara-Vd in fit, transplant-eligible NDMM patients in the phase 2 DeRIVE (NCT03942224) trial. Both arms proceed to Dara-N maintenance following the 8 cycles of induction. We are awaiting the publication of the results. The phase 2 HOVON 143 phase 2 study (no NCT ID identified) included 65 transplant- ineligible NDMM patients and analyzed efficacy and safety of a novel 9 cycle Dara-Nd induction followed by a 2-year long (or until progression) daratumumab + ixazomib maintenance. With an ORR of 71%, median PFS was 17.4 months (95% CI, 10.4-22.6) and 12-month OS 92% (95% CI, 82-97). Although QoL increased during treatment, the number on grade ≥3 adverse events were high (51% for non-hematologic events, such as gastrointestinal issues, central nervous system alteration, infections, or peripheral neuropathy and 12% for hematologic events, mostly neutropenia) [189]. It remains to be determined in further studies if Dara-Nd or Dara-NRd would be a safer and more efficient option for frail patients. Another phase 2 study (DARIA - NCT03746652) administered Dara-Nd as second-line therapy in lenalidomide-refractory RRMM patients. NCT03439293 enrolled RRMM patients that relapsed following ASCT. Patients received 6-cycles of Dara-Nd induction followed by Nd maintenance until disease progression. No results from these trials have been published yet. Another interesting approach, a 3-cycle reinduction with Dara-Vd in RRMM followed by a long-term Dara-Nd consolidation/maintenance until disease progression, is assessed in the currently ongoing phase 2 NCT03763162 trial.

7.2.4. Daratumumab-ixazomib-lenalidomide-dexamethasone (Dara-NRd)

Phase 2 IFM-2018-01 study (NCT03669445) analyzed safety and efficacy of a 6-cycle Dara-NRd induction in transplant-eligible NDMM. The study enrolled younger patients (N = 45) with a median age of 57 years. At a sensitivity of 10^{-5} MRD-negativity rate was 51.4% (95% CI, 82.1-98.8). The PFS at 2-years was 95.2% (95% CI, 82.1-98.8) and the OS 100%. Although indirect comparison has its limitation, MRD-negativity rate seems to be lower in case of Dara-NRd compared to Dara-VTD and Dara-KRd [190]. Another phase 2 trials are currently also recruiting both transplant-ineligible NDMM patients aged 18-75 years (AFT-41 - NCT04009109) or transplant-eligible NDMM patients (NCT03012880) for a 12-cycle Dara-NRd induction followed by a 2-year ixazomib maintenance. Primary outcome measure of these trials is MRD-negativity rate.

7.2.5. Daratumumab-ixazomib-pomalidomide-dexamethasone (Dara-NPd)

In RRMM a novel Dara-NPd approach may lead to increased responses and better outcomes. The phase 2 NCT03590652 trial is currently recruiting daratumumab- and pomalidomide-naïve patients. Preliminary results (N = 14) showed an ORR of 84%, a median PFS of 9.5 months and a median OS of 39 months (no 95% CI reported). The combination was well tolerated without any safety alarms [191].

7.3. Immune checkpoint inhibitor-ixazomib combinations

A novel approach in RRMM, nivolumab-ixazomib-cyclophosphamide-dexamethasone has been investigated in the phase 2 NCT04119336 trial. Patients were given one dose of nivolumab every 28 days (1 cycle). No results have been published yet. In the phase 2 NCT03506360 trial RRMM receive 84-day cycles of pembrolizumab-ixazomib and dexamethasone. In total 13 patients have been enrolled but no results have been published yet.

7.4. Transplant-related ixazomib therapy

Supplementary Table 13. summarizes all the transplant-related ixazomib trials we identified.

We identified only one phase 3 trial (NCT03562169) currently recruiting patients to assess an ixazomib-high dose melphalan combination for ASCT conditioning in NDMM patients. Ixazomib will be given alternatively on day -4 and -1, while melphalan on day -3 and -2. The phase 2 trial NCT02168101 is investigating ixazomib as post-ASCT maintenance in NDMM, whereas the phase 1 study NCT02504359 evaluated ixazomib as post-ASCT maintenance in RRMM. No results have been published. The phase 3 TOURMALINE-MM3 (NCT02181413) trial assessed the efficacy of 2-year fixed post-transplant maintenance with ixazomib in NDMM. The primary endpoint was median PFS, which was significantly prolonged in the ixazomib arm compared to placebo (26.5 *versus* 21.3 months, HR 0.72, 95% CI 0.58-0.89, p = 0.0023). There was no difference in efficacy in high-risk *versus* standard-risk patients, the age <60, however, was a positive prognostic factor with a HR of 0.84 (95% CI 0.62-1.12) in the <60 years subgroup *versus* HR of 0.66 (95% CI 0.48-0.91) in the ≥60 years subgroup [192]. Phase 2 clinical trials are now examining whether ixazomib or lenalidomide alone, in combination, or alternately is a better maintenance strategy. NCT05477797 is a prospective, randomized trial directly comparing Nd maintenance to Rd. NCT02619682 is investigating efficacy of alternating 2 cycles of ixazomib with 2 cycles of lenalidomide. Results of these studies are still pending. The NR doublet combination might be a feasible post-transplant maintenance option in the future. A single arm phase 2 study

(NCT01718743) included 64 patients and showed a median PFS of 73.3 months (95% CI, 59.9 months – NR) and a 3-year OS of 92.2% (95% CI, 85.8-99). Outcomes are significantly better for standard-risk patients with a 5-year PFS of 69% (95% CI, 57-85) versus 34% in high-risk arm (95% CI, 16-72, p = 0.0068) [193]. These findings imply that NR maintenance may be more effective than lenalidomide monotherapy. The fact that both drugs can be taken orally would be a benefit of this combination. However, to confirm these results, additional multicenter, comparative trials are required. Optimal treatment duration should also be determined. The phase 2 NCT037336913 and the phase 3 NCT02406144 trials, for instance, directly compare NR maintenance to lenalidomide alone but no results have been published yet. Adding dexamethasone to NR during the first four cycles of maintenance has also been tested in the phase 2 NCT02389517 trial but no data have been reported yet. In case of allo-HSCT, ixazomib maintenance was also tested in the phase 2 NCT02440464 trial. No statistically significant 21-month PFS (55.3% for ixazomib *versus* 59.1% for placebo) or OS (52% *versus* 85%) benefit has been observed when compared to placebo (p = 0.17) [194].

8. Novel, non-FDA approved proteasome inhibitors

Because of the high number of patients developing PI resistance, the development of new generation PIs and deeper understanding of these mechanisms is required. There are several reviews on the subject [195,196]. There are three not FDA-approved molecules studied in clinical trials for treatment of MM: marizomib (NPI-0052), oprozomib (ONX0912) and delanzomib (CEP-18770). Marizomib has been investigated both in monotherapy in RRMM (NCT00461045) and in marizomib-pomalidomide-dexamethasone combination therapy (NCT02103335, NCT05050305). It is hypothesized that marizomib is active in case of central nervous involvement (CNS). In contrast to the currently approved PIs, it has been demonstrated that marizomib crosses the blood-brain barrier [197]. Thus, the phase 2 NCT05050305 recruited RRMM patients with CNS involvement. No results have been published yet. Oprozomib trials have been initiated in transplant-ineligible NDMM in combination with melphalan-prednisone (NCT02072863 – OPZ006); lenalidomide-dexamethasone or cyclophosphamide-dexamethasone (NCT01881789 – OPZ003). Due to adverse events, these trials have been terminated [198]. Delanzomib has been also tested in phase 1/2 RRMM trials in monotherapy (NCT01023880) and in a delanzomib-lenalidomide-dexamethasone triplet (NCT01348919). Due to inferior efficacy results (median time to progression of 2.5 months), delanzomib trials were terminated [199]. Since proteasomes are composed of multiple structural subunits, generation of more targeted, site-specific PIs, such as NC-005, NC-001, and LU-102 and their coadministration with the classical inhibitor molecules may resensitize bortezomib-, carfilzomib- or ixazomib-resistant MM cells. Preclinical studies already demonstrated their efficacy, clinical trials are required to confirm the results [200]. Targeting molecules upstream the 20S proteasome could be another option to overcome PI-resistance. Deubiquitinating enzymes or ubiquitin receptors are such targetable molecules that are targeted by WP1130, EOAI3402153, capzimin, O-phenanthroline, or thilutin; however, there are no ongoing clinical trials on those substances yet.

9. Discussion

PI-including combination therapy is currently advised to be initiated as soon as MM criteria are met. Although current data show that starting therapy in the SMM phase has a significant benefit in long-term outcomes, treatment initiation of SMM remains a question of debate. Further studies are needed to assess benefit-to-risk profile of early treatment initiation in high-risk SMM. Since the efficacy and safety profile of FDA-approved proteasome inhibitors have been established, current research questions include which combination regimens are best, how many cycles should be used for induction, consolidation, and/or maintenance. There is also debate about optimal dosing, such as once-weekly versus twice-weekly administration of bortezomib or carfilzomib. More research is needed to address this issue. Another pertinent question is which endpoints are best to follow in these clinical trials, such as minimal residual disease (MRD)-status, overall response rate (ORR), progression-free survival (PFS) or overall survival (OS). Regarding transition from one PI to another, data are conflicting. In the phase 1/2 NCT02206425 trial, switching from bortezomib or carfilzomib to ixazomib in bortezomib- and/or carfilzomib-resistant patients failed to demonstrate efficacy [201]. The phase 4 TOURMALINE-MM6 (NCT03173092), however, achieved an increase in ORR from 60% to 79% when switching bortezomib to ixazomib. Another phase 1/2 trial (NCT01365559) showed that replacement of bortezomib in bortezomib-resistant patients to carfilzomib may lead to durable responses [202]. An important aspect revealed by clinical trials was that transition from parenteral bortezomib to oral ixazomib is safe and may even improve outcomes. NRd is an all-oral alternative both for NDMM and RRMM, currently approved for RRMM only. Since all three (V, K or N) FDA-approved PIs show significant results in NDMM, a possible approach for clinicians in the future may be to adapt treatment decisions based on the patient comorbidities. In case of the presence of peripheral neuropathy, carfilzomib and ixazomib may be a feasible alternative. In case of high-risk of cardiac and cardiovascular events, clinicians should evaluate the benefit-risk ratio of administering carfilzomib while bortezomib and ixazomib may be a safer option in this patient population. We don't have enough data to compare the three PIs in the case of renal impairment. When it comes to CNS involvement, current FDA-approved PIs may not be as effective as marizomib, a novel generation PI that crosses the blood-brain barrier. Further studies on efficacy of marizomib are required. PI monotherapy with carfilzomib or ixazomib as maintenance therapy is recommended only in case of absolute contraindication to lenalidomide. Otherwise, lenalidomide alone, KR, NR or Dara-R doublets would be safe options for maintenance. Future studies are required to establish which doublet is the best. VRd or KR is currently recommended maintenance therapy for high-risk MM, optimal duration remains to be determined, most trials used a fixed duration of 1, 2 or 3 years but an MRD-driven approach also seems promising. In conclusion, there is a significant gap in current knowledge, so the question of which PI + immunotherapy combination is best cannot be answered. Novel-generation PI (carfilzomib, ixazomib, marizomib) trials with novel generation IMiDs (such as mezigdomide), anti-CD38 antibodies (isatuximab, mezagitamab), anti-SLAMF7 antibodies (elotuzumab), ADCs (balantamab mafodotin), bispecific antibodies (teclistamab, talquetamab) and CAR T-cell therapies (idecabtagene vicleucel, ciltacabtagene autoleucel) should also be initiated.

Practice bullet points

- Bortezomib-based regimens remain the cornerstone of induction therapies in patients who are eligible for ASCT; bortezomib combinations (VRD or Dara-VMP) are also used extensively as first line therapies in transplant ineligible patients.
- Since all three (V, K or N) FDA-approved PIs show significant results in RRMM, a possible approach for clinicians is to adapt treatment decisions based on the patient comorbidities and previous therapies. In case of previous use of bortezomib, carfilzomib combinations can be used; in the presence of peripheral neuropathy, carfilzomib and ixazomib may be a feasible alternative to bortezomib. In case of high-risk of cardiac and cardiovascular events, clinicians should evaluate the benefit-risk ratio of administering carfilzomib while bortezomib and ixazomib may be a safer option in this patient population.

- For lenalidomide refractory patients, combinations of carfilzomib with anti-CD38 monoclonal antibodies offer the best results to-date.
- For both lenalidomide and anti-CD38 refractory patients, the combinations of bortezomib with selinexor or pomalidomide and dexamethasone or Kd are the best approved regimens.

Future considerations and research agenda

- Novel-generation PI (carfilzomib, ixazomib, marizomib) trials with novel generation IMiDs (such as mezigdomide), anti-CD38 antibodies (isatuximab, mezagitamab), anti-SLAMF7 antibodies (elotuzumab), ADCs (balantamab mafodotin), bispecific antibodies (teclistamab, talquetamab) and CAR T-cell therapies (idecabtagene vicleucel, ciltacabtagene autoleucel) should be initiated.
- Prospective studies are needed to assess optimal timing of HSCT.
- Larger-scale studies should be conducted to determine which immune therapy is the most effective and safe to begin with in combination with Pis, if feasible.

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

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Declaration of Competing Interest

No potential conflict of interest is reported.

Data availability

Not applicable.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.blre.2023.101100.

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