Belantamab Mafodotin and Multiple Myeloma

Subjects: Oncology

Contributor: Cole Bergeron, Adam Kaye, Elyse Cornett

Multiple myeloma (MM) is a hematologic malignancy characterized by excessive clonal proliferation of plasma cells. The treatment of multiple myeloma presents a variety of unique challenges due to the complex molecular pathophysiology and incurable status of the disease at this time. Given that MM is the second most common blood cancer with a characteristic and unavoidable relapse/refractory state during the course of the disease, the development of new therapeutic modalities is crucial. Belantamab mafodotin (belamaf, GSK2857916) is a first-in-class therapeutic, indicated for patients who have previously attempted four other treatments, including an anti-CD38 monoclonal antibody, a proteosome inhibitor, and an immunomodulatory agent. In November 2017, the FDA designated belamaf as a breakthrough therapy for heavily pretreated patients with relapsed/refractory multiple myeloma. In August 2020, the FDA granted accelerated approval as a monotherapy for relapsed or treatment-refractory multiple myeloma. The drug was also approved in the EU for this indication in late August 2020. Of note, belamaf is associated with the following adverse events: decreased platelets, corneal disease, decreased or blurred vision, anemia, infusion-related reactions, pyrexia, and fetal risk, among others. Further studies are necessary to evaluate efficacy in comparison to other standard treatment modalities and as future drugs in this class are developed

Keywords: belantamab mafodotin ; multiple myeloma

1. Current Treatment of Multiple Myeloma

1.1. Overview

Treatment modalities have improved concomitantly with the progression in understanding of the molecular pathogenesis of MM over the past twenty years[1]. The use of corticosteroids (prednisone and dexamethasone) and alkylating agents (mainly melphalan and cyclophosphamide) as standard therapies began in the mid-1960′s. Since the 1990′s, treatment protocols have included autologous stem cell transplant (ASCT) for eligible patients [1]. Drug classes, including immunomodulatory drugs (IMiDs), proteasome inhibitors (PIs), and monoclonal antibodies (mAbs), have become the cornerstone of modern multiple myeloma therapy [1][2]. Combinations of these drug classes have become a standard of care in newly diagnosed transplant-eligible or -ineligible patients, and are utilized in triplet or quadruplet regimens relative to each patient's unique clinical profile[3].

Despite these advances, a definitive cure for this disease remains elusive; relapse is inevitable, and refractory disease requiring salvage therapy remains a considerable challenge[2][24][25][26]. This has prompted the development of new biologic agents and immunotherapy in the past decade [21][26][27][28]. The optimal sequence and combination of novel immunotherapeutic strategies remains to be determined. Current treatment options continue to evolve as we increase our understanding of multiple myeloma's complex molecular pathophysiology and resulting clinical implications (Table 1).

Table 1. Current Therapeutic Considerations for Multiple Myeloma.

Strategy	Name of the Drug	Mechanism of Action	References
Corticosteroids	**Prednisone Dexamethasone**	**Anti-inflammatory and anti-proliferative effects on myeloma cells**	[29]
Conventional Chemotherapy	**Cyclophosphamide**	**Alkylating agent**	[30]
	Doxorubicin	**Inhibits topoisomerase II; Intercalates into DNA**	[31]
	Melphalan	**Alkylating agent**	[32][33] [34][35]
	Bendamustine	**Alkylating agent**	

Strategy	Name of the Drug	Mechanism of Action	References
Immunomodulatory Drugs (IMiDs)		All: Inhibit production of TNF-a, IL-6, IL-8, VEGF; activate caspase-8	
	Thalidomide		[36]
	Lenalidomide	IL-6 inhibition; caspase-8 activation	[36]
	Pomalidomide	Inhibits Akt phosphorylation; co-stimulates CD28	[37][38]
	Avadomide (CC-122) *	Co-stimulates CD28	[39]
	Iberdomide (CC-220) *	Cereblon E3 ligase modulator	[39]
		Cereblon E3 ligase modulator	
Proteasome Inhibitors (PIs)	Bortezomib	Reversibly binds to CT-L/LMP7 subunit; binds C-L /LMP2 and T-L subunits with lower affinity	[40]
	Carfilzomib	Irreversibly binds to CT-L/LMP2 subunit; binds C-L/LMP2 and T-L subunits at high doses	[41]
	Ixazomib	Binds to beta 5 subunit of 20s proteasome	[42]
	Oprozomib *	Irreversibly binds to CT-L /LMP7 subunit	[43]
	Marizomib *	Binds CT-L/LMP7 and T-L subunits with high affinity; binds C-L/LMP2 subunit with lower affinity	[43]
	Delanzomib *	Reversibly inhibits CT-L/LMP7 and C-L /LMP2 subunits	[43]
Histone Deacetylase (HDAC) Inhibitors	Panobinostat	Pan-Histone Deacetylase Inhibitor	[44][45][46][47][48]
	Romidepsin	Histone Deacetylase Inhibitor	
	Ricolinostat	Histone Deacetylase 6 Inhibitor	
	Citarinostat *	Histone Deacetylase 6 Inhibitor	
Monoclonal Antibodies (mABs)	Daratumumab	Anti-CD38	[49][50][51][52][53] [54][55]
	Elotuzumab	Anti CS1/SLAMF7	
	Denosumab	Anti-RANKL	
	Siltuximab	Anti-IL6	
	Felzartamab (MOR202) *	Anti-CD38	
	Isatuximab	Anti-CD38	
	TAK-079 *	Anti-CD38	
Immunotherapies	Durvalumab	Anti-PDL1	[59][60][55][56][57] [58]
	Pembrolizumab	Anti-PD1	
	Nivolumab	Anti-PDL1	
	Nelfinavir	Protease Inhibitor	
	BiTE *	Anti-BCMA	
	CAR-T *	Anti-BCMA	
Novel Agents	Filanesib *	Kinesin Spindle Protein (EG5/KIF11) Inhibitor	[61][62][63][64]
	Venetoclax *	Selective Inhibitor of BCL-2	
	Selinexor	Inhibitor of XPO1-mediated nuclear export protein	
Antibody-Drug Conjugates (ADCs)	Belantamab mafodotin	Anti-BCMA	[65][66][67][68]
	Lorvotuzumab mertansine *	Anti-CD56	
	Milatuzumab doxorubicin *	Anti-CD74	
	Indatuximab ravtansine *	Anti-CD138	

* currently under clinical development for use in multiple myeloma.

1.2. Anti-BCMA Compounds Under Development

In 2015, the FDA approved two mAbs, daratumumab and elotuzumab, which selectively target MM cell glycoproteins CD38 and SLAMF7, respectively[1][69]. Several novel immunotherapeutic approaches have emerged since this time. New therapies can target plasma cell-specific antigens to offer an innovative approach to treatment optimization and options for relapsed/refractory disease [21,22]. B-cell maturation antigen (BCMA), a soluble transmembrane glycoprotein

overexpressed in MM cells, represents an important target for novel therapeutics. These modalities include antibody-drug conjugates (ADCs) (belantamab mafodotin), bispecific T-cell engagers (BiTEs) (AMG 420), and CAR T-Cell Therapies[1][70].

1.2.1. Anti-BCMA Antibody-Drug Conjugates (ADCs)

Antibody-drug conjugates act as a carrier to deliver cytotoxic agents into MM cells, leading to targeted tumor cell lysis with reduced toxicity in non-targeted tissues. They are composed of a mAb, a linker connecting the drug to the antibody, and the cytoxic drug. Similar to belamaf, a first-in-class anti-BCMA ADC, there are several emerging anti-BCMA therapeutics currently under development for use in multiple myeloma.

AMG 224 is a compound consisting of an anti-BCMA IgG1 antibody conjugated via a linker (4-[N-maleimidomethyl] cyclohexane-1-carboxylate) to mertansine, an anti-tubulin inhibitor [71]. There is an ongoing phase I study of AMG 224 as monotherapy in heavily pre-treated patients with relapsed or refractory multiple myeloma (NCT02561962). Similarly, MEDI2228 is an ADC using tesirine, a pyrrolobenzodiazepine dimer, as a toxic payload to MM cells. Tesirine is a DNA cross-linking agent with site-specific conjugation to BCMA-Ab1 via a valine-alanine dipeptide linker. MEDI2228 is internalized and trafficked to the lysosome where tesirine is released, resulting in DNA damage, myeloma cell and myeloma progenitor cell death[72]. Current clinical testing is ongoing for its use in the treatment of RRMM (NCT03489525).

HDP-101 is a compound in a new class of ADCs called antibody-targeted amanitin conjugates (ATAC). Amanitin, a toxin contained in the *Amanita phalloides* death cap mushroom, selectively binds to and inhibits the RNA polymerase II subunit A with high affinity. This results in a >1000-fold decrease in transcription and protein synthesis, leading to cell apoptosis and death. Of note, HDP-101 utilizes chemically synthesized amanitin as its toxic payload conjugated to the anti-BCMA mAb via a cathepsin B protease linker[73][74]. A Phase Ia/Ib dose escalation and expansion study is expected to begin in early 2021 to evaluate the effect of HDP-101 in patients with RRMM.

Other anti-BCMA ADCs currently in phase I trials for patients with RRMM include CC-99712 (NCT04036461) and SEA-BCMA, a naked anti-BCMA mAb without conjugate (NCT03582033).

1.2.2. Anti-BCMA Bi-Specific Antibodies (BiAbs)

Bi-specific antibodies are a novel potential therapy for patients with multiple myeloma. Bi-specific T-cell engaging antibody (BiTEs) are a specific type of BiAb that transiently connect immune and tumor cells through their interaction with both CD3 on the T-cell and tumor antigens on the surface of target tumor cells. The molecules are designed with two domains, one that binds CD3 in the T-cell receptor (TCR) complex and the other that recognizes BCMA on MM cells. The binding of CD3
leads to activation of cytotoxic T-cells which release perforin and granzymes to lyse the targeted tumor cells, and interferon-γ which activates macrophages and immune cells [76][75].

Several anti-BCMA BiAbs are in ongoing clinical trials for patients with MM. These include AMG 420 (NCT03836053), AMG 701 (NCT03287908), CC-93269 (NCT03486067), Teclistamab (NCT04557098, NCT03145181, NCT04586426, NCT04108195), TNB-383B (NCT03933735), PF-06863135 (NCT03269136, NCT04649359), REGN5458 (NCT03761108) and REGN5459 (NCT04083534).

1.3. Novel Agents

Novel agents have further expanded the available therapeutic options for patients with relapsed/refractory MM. Selinexor is a first-in-class Exportin-1 (XPO-1) inhibitor, granted accelerated approval in July 2019 for patients with penta-refractory multiple myeloma. Other therapeutics in this class include Filanesib (ARRY-520) and Venetoclax (ABT-199), a kinesin spindle protein inhibitor (KSP) and selective BCL-2 inhibitor, respectively. Filanesib is the only KSP inhibitor that has shown anti-tumor activity in clinical trials. It has demonstrated clinical efficacy in heavily pretreated multiple myeloma patients and may be useful in combination with standard MM backbones, such as PIs and IMiDs [61][62]. Both Filanesib and Venetoclax are under clinical investigation for extended indications, alone and in combination regimens in patients with multiple myeloma.

Immunotherapy via adoptive cell transfer (ACT) is also a promising investigational MM treatment. Current trials are exploring the use of autologous chimeric antigen receptor (CAR)-transduced T-cells, in which host T-cells are engineered with viral vector recombinant DNA techniques. CAR T-cells are then used to initiate a targeted immune response against antigens specific to MM cells[1][26][77].

1.4. Hematopoietic Stem Cell Transplant Eligibility

Given the recent expansion in therapeutic options, individualized treatment for MM is ever evolving and guided by a variety of clinical parameters [24][27]. At this time, eligibility for ASCT and risk-stratification are predominant determinants of the treatment course of newly diagnosed MM[18][3]. ASCT remains the standard for first-line treatment of newly diagnosed MM; therefore, phases of management are generally defined, relative to transplant eligibility[24][78]]. Various applications of the aforementioned treatments are utilized, depending on a patient's transplant status. Transplant eligibility is primarily determined by age and existing comorbidities, since these factors predispose patients to toxicity and influence a patient's ability to endure treatment[24][79]. The majority of randomized trials limit ASCT to patients ≤ 65 years of age without significant comorbidities, although consensus regarding an age cutoff has not been established, and practice varies across institutions [79]. Contraindications for ASCT include significant cardiac or pulmonary disorders [24]. Transplant-eligible patients typically undergo 3–4 cycles of the current standard induction therapy, which is a triplet regimen consisting of bortezomib, lenalidomide, and dexamethasone (VRd). Transplant-ineligible patients undergo 8–12 cycles of VRd induction therapy [3][79][80]. Patients undergoing ASCT are treated with cytokines or chemotherapy, after which hematopoietic stem cells are mobilized into peripheral blood and harvested by apheresis[81]. The stem cells can then be used for marrow reconstitution following high-dose chemotherapy. The standard maintenance therapy for both transplant ineligible patients and eligible patients following ASCT is lenalidomide[18].

2. Belantamab Mafodotin Drug Info

In August 2020, the FDA granted accelerated approval to belantamab mafodotin-blmf (belamaf) as a monotherapy treatment for relapsed or treatment-refractory multiple myeloma. Belamaf is a first-in-class biologic for patients who have previously attempted four other treatments, including an anti-CD38 monoclonal antibody, a proteasome inhibitor, and an immunomodulatory agent[82][83]. As the first approved anti-B cell maturation antigen (BCMA), the use of belamaf may have a large impact on improving progression-free survival in patients with multiple myeloma who have limited remaining treatment options. BCMA is a cell surface receptor required for the survival of plasma cells. The expression of BCMA can be detected on all CD138+ myeloma cells, but it is not expressed in any other tissues. This receptor specificity allows belamaf to target only the malignant MM plasma cells[10][84].

Belantamab mafodotin is associated with a high incidence (≥20%) of keratopathy[85]. To mitigate such risks, an ophthalmic exam is recommended prior to and during belamaf therapy in order to assess baseline vision and possible adverse eye effects. Dosage can be reduced or held if ocular toxicity such as blurry vision, dry eyes, or corneal ulcers occurs. Belamaf should be discontinued if ocular toxicity is severe[82]. Other less common adverse effects, such as thrombocytopenia, infusion-related reactions, pyrexia, fatigue, nausea, constipation, diarrhea, arthralgia, back pain, decreased appetite, and upper respiratory infection, have been reported[86]. The most common grade 3 or 4 laboratory abnormalities (≥5%) include decreases in neutrophils, lymphocytes, platelets, and hemoglobin, along with increases in gamma-glutamyl transferase and creatinine[82].

There is a paucity of data on the use of belantamab during pregnancy and breastfeeding. Because belantamab is a large protein molecule, the amount excreted in breastmilk is postulated to be very low. However, belantamab is conjugated with mafodotin, a small-molecule toxin, which may be excreted into milk. As such, it is recommended that patients use effective contraception and avoid breastfeeding while taking the medication and for 3 months after the last dose[87].

3. Belantamab Mafodotin Mechanism of Action

3.1. Antibody Drug Conjugate (ADC)

Belantamab mafodotin (Blenrep, GSK2857916 or J6M0-MMAF) is an antibody-drug conjugate (ADC) that demonstrates a multifaceted mechanism of action based on three main components. ADCs are a new class of cancer therapeutics that confer unique pharmacologic activity via mAbs covalently conjugated to a cytotoxic agent via a specialized linker[28]. The mAb component of an ADC selectively targets tumor cells and elicits a host immune response, while simultaneously delivering a cytotoxic payload to the cell [25][86]. Belamaf consists of a humanized, afucosylated IgG1 mAb conjugated to monomethyl auristatin-F (MMAF) via a protease-resistant maleimidocaproyl linker [25][70].

3.2. Target Antigen-B-Cell Maturations Antigen (BCMA)

The high specificity of belamaf for MM cells is a hallmark feature derived from the mAb component, which targets B-Cell Maturation Antigen (BCMA). BCMA, a member of the tumor necrosis factor receptor superfamily, is a notable tumor-associated antigen of particular interest due to almost exclusive BCMA expression on mature B-cells and plasma cells.

BCMA is integral to plasma cell maturation and differentiation. BCMA is also overexpressed during the malignant transformation of plasma cells, making it an ideal pharmacologic target in the treatment of MM[21][25][70]. B-cell activating factor (BAFF) and APRIL (a proliferation-inducing ligand) are high-affinity ligands for BCMA that promote proliferation and viability of MM cells in the bone marrow. BAFF is a BCMA agonist that induces differentiation, proliferation, and antibody production [21][70]. The binding of belantamab to BCMA receptors impedes the pro-survival cytokine-signaling effects of BAFF and APRIL on malignant plasma cells[21][28].

3.3. Afucosylated Monoclonal IgG1 Antibody

Belamaf induces enhanced tumor cell lysis via natural killer cell-mediated antibody-dependent cell-mediated cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP)[28][70][86]. While naturally occurring IgG antibodies exhibit significant core-fucosylation on the N-glycan of the Fc region, the IgG1 mAb in belantamab mafodotin is afucosylated. The removal of these fucosyl groups enhances IgG1 Fc binding affinity to FcγRIIIa (CD16) on natural killer cells, which is a well-known strategy for augmenting effector cell ADCC of cancer cells [21][25].

3.4. Monomethyl Auristatin-F (MMAF) and Linker

After belamaf binds, the mAb drug complex is internalized, allowing MMAF to induce apoptosis [82]. MMAF inhibits tubulin polymerization to disrupt microtubules and arrest myeloma cells at the G2/M checkpoint[21]. Of note, the protease-resistant properties of the linker used in belamaf requires l

References

1. Abramson, H.N. B-Cell Maturation Antigen (BCMA) as a Target for New Drug Development in Relapsed and/or Refractory Multiple Myeloma. Int. J. Mol. Sci. 2020, 21, 5192, doi:10.3390/ijms21155192.
2. Mogollón, P.; Díaz-Tejedor, A.; Algarín, E.M.; Paíno, T.; Garayoa, M.; Ocio, E.M. Biological Background of Resistance to Current Standards of Care in Multiple Myeloma. Cells 2019, 8, 1432, doi:10.3390/cells8111432.
3. Rajkumar, V.S. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am. J. Hematol. 2020, 95, 548–567, doi:10.1002/ajh.25791.
4. Bird, S.; Boyd, K. Multiple myeloma: An overview of management. Palliat. Care Soc. Pract. 2019, 13, doi:10.1177/1178224219868235.
5. Albagoush, S.A.; Azevedo, A.M. Multiple Myeloma; StatPearls Publishing: Treasure Island, FL, USA, 2020; Available online: https://www.ncbi.nlm.nih.gov/books/NBK534764/ (accessed on 13 July 2020).
6. Michels, T.C.; Petersen, K.E. Multiple Myeloma: Diagnosis and Treatment. Am. Fam. Physician 2017, 95, 373–383.
7. Cowan, A.J.; Allen, C.; Barac, A.; Basaleem, H.; Bensenor, I.; Curado, M.P.; Foreman, K.; Gupta, R.; Harvey, J.; Hosgood, H.D.; et al. Global Burden of Multiple Myeloma: A Systematic Analysis for the Global Burden of Disease Study 2016. JAMA Oncol. 2018, 4, 1221–1227, doi:10.1001/jamaoncol.2018.2128.
8. Howlader, N.; Noone, A.M.; Krapcho, M.; Miller, D.; Bishop, K.; Kosary, C.L. Myeloma—Cancer Stat Facts [Internet]. SEER Cancer Statistics Review, 1975–2014. 2017. Available online: https://seer.cancer.gov/statfacts/html/mulmy.html (accessed on 10 December 2020).
9. Kumar, S.K.; Rajkumar, S.V.; Dispenzieri, A.; Lacy, M.Q.; Hayman, S.R.; Buadi, F.K.; Zeldenrust, S.R.; Dingli, D.; Russell, S.J.; Lust, J.A.; et al. Improved survival in multiple myeloma and the impact of novel therapies. Blood 2008, 111, 2516–2520, doi:10.1182/blood-2007-10-116129.
10. Trudel, S.; Lendvai, N.; Popat, R.; Voorhees, P.M.; Reeves, B.; Libby, E.N.; Richardson, P.G.; Hoos, A.; Gupta, I.; Bragulat, V.; et al. Antibody–drug conjugate, GSK2857916, in relapsed/refractory multiple myeloma: An update on safety and efficacy from dose expansion phase I study. Blood Cancer J. 2019, 9, 1–10, doi:10.1038/s41408-019-0196-6.
11. Teras, L.R.; DeSantis, C.E.; Cerhan, J.R.; Morton, L.M.; Jemal, A.; Flowers, C.R. 2016 US lymphoid malignancy statistics by World Health Organization subtypes. CA: A Cancer J. Clin. 2016, 66, 443–459, doi:10.3322/caac.21357.
12. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2020. CA Cancer J. Clin. 2020, 70, 7–30, doi:10.3322/caac.21590.
13. Siegel, R.L.; Miller, K.D.; Jemal, A. Cancer statistics, 2016. CA A Cancer J. Clin. 2016, 66, 7–30, doi:10.3322/caac.21332.
14. Castaneda, O.; Baz, R. Multiple Myeloma Genomics—A Concise Review. Acta Med Acad 2019, 48, 57–67.

15. Kuehl, W.M.; Bergsagel, P.L. Molecular pathogenesis of multiple myeloma and its premalignant precursor. J. Clin. Investig. 2012, 122, 3456–3463, doi:10.1172/jci61188.

16. Pawlyn, C.; Davies, F.E. Toward personalized treatment in multiple myeloma based on molecular characteristics. Blood 2019, 133, 660–675, doi:10.1182/blood-2018-09-825331.

17. Brioli, A.; Melchor, L.; Cavo, M.; Morgan, G.J. The impact of intra-clonal heterogeneity on the treatment of multiple myeloma. Br. J. Haematol. 2014, 165, 441–454, doi:10.1111/bjh.12805.

18. Rajkumar, V.S. Multiple myeloma: Every year a new standard? Hematol. Oncol. 2019, 37, 62–65, doi:10.1002/hon.2586.

19. Kyle, R.A.; Gertz, M.A.; Witzig, T.E.; Lust, J.A.; Lacy, M.Q.; Dispenzieri, A.; Fonseca, R.; Rajkumar, S.V.; Offord, J.R.; Larson, D.R.; et al. Review of 1027 Patients With Newly Diagnosed Multiple Myeloma. Mayo Clin. Proc. 2003, 78, 21–33, doi:10.4065/78.1.21.

20. Eslick, R.; Talaulikar, D. Multiple myeloma: From diagnosis to treatment. Aust. Fam. Physician 2013, 42, 684–688.

21. Diercks, D.B.; Shumaik, G.M.; Harrigan, R.A.; Brady, W.J.; Chan, T.C. Electrocardiographic manifestations: Electrolyte abnormalities. J. Emerg. Med. 2004, 27, 153–160, doi:10.1016/j.jemermed.2004.04.006.

22. Rajkumar, V.S.; Kumar, S.K. Multiple Myeloma: Diagnosis and Treatment. Mayo Clin. Proc. 2016, 91, 101–119, doi:10.1016/j.mayocp.2015.11.007.

23. Kristinsson, S.Y.; Minter, A.R.; Korde, N.; Tan, E.; Landgren, O. Bone disease in multiple myeloma and precursor disease: Novel diagnostic approaches and implications on clinical management. Expert Rev. Mol. Diagn. 2011, 11, 593–603, doi:10.1586/erm.11.44.

24. Rajkumar, S.V.; Rajkumar, V.; Kyle, R.A.; Van Duin, M.; Sonneveld, P.; Mateos, M.-V.; Gay, F.; Anderson, K.C. Multiple myeloma. Nat. Rev. Dis. Prim. 2017, 3, 17046, doi:10.1038/nrdp.2017.46.

25. Shah, N.; Chari, A.; Scott, E.; Mezzi, K.; Usmani, S.Z. B-cell maturation antigen (BCMA) in multiple myeloma: Rationale for targeting and current therapeutic approaches. Leukemia 2020, 34, 985–1005, doi:10.1038/s41375-020-0734-z.

26. D'Agostino, M.; Raje, N.S. Anti-BCMA CAR T-cell therapy in multiple myeloma: Can we do better? Leukemia 2019, 34, 21–34, doi:10.1038/s41375-019-0669-4.

27. Bazarbachi, A.H.; Al Hamed, R.; Malard, F.; Harousseau, J.-L.; Mohty, M. Relapsed refractory multiple myeloma: A comprehensive overview. Leukemia 2019, 33, 2343–2357, doi:10.1038/s41375-019-0561-2.

28. Tai, Y.-T.; Anderson, K.C. B cell maturation antigen (BCMA)-based immunotherapy for multiple myeloma. Expert Opin. Biol. Ther. 2019, 19, 1143–1156, doi:10.1080/14712598.2019.1641196.

29. Burwick, N.; Sharma, S. Glucocorticoids in multiple myeloma: Past, present, and future. Ann. Hematol. 2019, 98, 19–28, doi:10.1007/s00277-018-3465-8.

30. Swan, D.; Gurney, M.; Krawczyk, J.; Ryan, A.E.; O'Dwyer, M. Beyond DNA Damage: Exploring the Immunomodulatory Effects of Cyclophosphamide in Multiple Myeloma. Hemasphere 2020, 4, e350.

31. Gabizon, A.A.; Patil, Y.; La-Beck, N.M. New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy. Drug Resist. Updat. 2016, 29, 90–106, doi:10.1016/j.drup.2016.10.003.

32. Kuczma, M.; Ding, Z.-C.; Zhou, G. Immunostimulatory Effects of Melphalan and Usefulness in Adoptive Cell Therapy with Antitumor CD4+ T Cells. Crit. Rev. Immunol. 2016, 36, 179–191, doi:10.1615/critrevimmunol.2016017507.

33. Esma, F.; Salvini, M.; Troia, R.; Boccadoro, M.; LaRocca, A.; Pautasso, C. Melphalan hydrochloride for the treatment of multiple myeloma. Expert Opin. Pharmacother. 2017, 18, 1127–1136, doi:10.1080/14656566.2017.1349102.

34. Palumbo, A.; Offidani, M.; Patriarca, F.; Petrucci, M.T.; Cavo, M. Bendamustine for the treatment of multiple myeloma in first-line and relapsed–refractory settings: A review of clinical trial data. Leuk. Lymphoma 2014, 56, 559–567, doi:10.3109/10428194.2014.915545.

35. Offidani, M.; Corvatta, L.; Maracci, L.; Liberati, A.M.; Ballanti, S.; Attolico, I.; Caraffa, P.; Alesiani, F.; Di Toritto, T.C.; Gentili, S.; et al. Efficacy and tolerability of bendamustine, bortezomib and dexamethasone in patients with relapsed-refractory multiple myeloma: A phase II study. Blood Cancer J. 2013, 3, e162, doi:10.1038/bcj.2013.58.

36. Latif, T.; Chauhan, N.; Khan, R.; Morán, A.; Usmani, S.Z. Thalidomide and its analogues in the treatment of Multiple Myeloma. Exp. Hematol. Oncol. 2012, 1, 27, doi:10.1186/2162-3619-1-27.

37. San-Miguel, J.; Weisel, K.; Moreau, P.; Lacy, M.; Song, K.; Delforge, M.; Karlin, L.; Goldschmidt, H.; Banos, A.; Oriol, A.; et al. Pomalidomide plus low-dose dexamethasone versus high-dose dexamethasone alone for patients with relapsed and refractory multiple myeloma (MM-003): A randomised, open-label, phase 3 trial. Lancet Oncol. 2013, 14, 1055–1066, doi:10.1016/s1470-2045(13)70380-2.

38. Moreau, P.; Weisel, K.C.; Song, K.W.; Gibson, C.J.; Saunders, O.; Sternas, L.A.; Hong, K.; Zaki, M.H.; Dimopoulos, M.A. Relationship of response and survival in patients with relapsed and refractory multiple myeloma treated with pomalidomide plus low-dose dexamethasone in the MM-003 trial randomized phase III trial (NIMBUS). Leuk. Lymphoma 2016, 57, 2839–2847, doi:10.1080/10428194.2016.1180685.

39. Ito, T.; Handa, H. Cereblon as a primary target of IMiDs. Jpn. J. Clin. Hematol. 2019, 60, 1013–1019, doi:10.11406/rinketsu.60.1013.

40. Accardi, F.; Toscani, D.; Bolzoni, M.; Palma, B.D.; Aversa, F.; Giuliani, N. Mechanism of Action of Bortezomib and the New Proteasome Inhibitors on Myeloma Cells and the Bone Microenvironment: Impact on Myeloma-Induced Alterations of Bone Remodeling. BioMed Res. Int. 2015, 2015, 1–13, doi:10.1155/2015/172458.

41. Groen, K.; Van De Donk, N.W.C.J.; Stege, C.; Zweegman, S.; Nijhof, I. Carfilzomib for relapsed and refractory multiple myeloma. Cancer Manag. Res. 2019, 11, 2663–2675, doi:10.2147/cmar.s150653.

42. Raedler, L.A. Ninlaro (Ixazomib): First Oral Proteasome Inhibitor Approved for the Treatment of Patients with Re-lapsed or Refractory Multiple Myeloma. Am. Health Drug Benefits 2016, 9, 102–105.

43. Narayanan, S.; Cai, C.-Y.; Assaraf, Y.G.; Guo, H.-Q.; Cui, Q.; Wei, L.; Huang, J.-J.; Ashby, C.R.; Chen, Z.-S. Targeting the ubiquitin-proteasome pathway to overcome anti-cancer drug resistance. Drug Resist. Updat. 2020, 48, 100663, doi:10.1016/j.drup.2019.100663.

44. Eleutherakis-Papaiakovou, E.; Kanellias, N.; Kastritis, E.; Gavriatopoulou, M.; Terpos, E.; Dimopoulos, M.A. Efficacy of Panobinostat for the Treatment of Multiple Myeloma. J. Oncol. 2020, 2020, 1–11, doi:10.1155/2020/7131802.

45. Bringhen, S.; De Wit, E.; Dimopoulos, M.-A. New Agents in Multiple Myeloma: An Examination of Safety Profiles. Clin. Lymphoma Myeloma Leuk. 2017, 17, 391–407.e5, doi:10.1016/j.clml.2017.05.003.

46. Yee, A.J.; Bensinger, W.I.; Supko, J.G.; Voorhees, P.M.; Berdeja, J.G.; Richardson, P.G.; Libby, E.N.; Wallace, E.E.; Birrer, N.E.; Burke, J.N.; et al. Ricolinostat plus lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: A multicentre phase 1b trial. Lancet Oncol. 2016, 17, 1569–1578, doi:10.1016/s1470-2045(16)30375-8.

47. Vogl, D.T.; Raje, N.; Jagannath, S.; Richardson, P.; Hari, P.; Orlowski, R.; Supko, J.G.; Tamang, D.; Yang, M.; Jones, S.S.; et al. Ricolinostat, the First Selective Histone Deacetylase 6 Inhibitor, in Combination with Bortezomib and Dexamethasone for Relapsed or Refractory Multiple Myeloma. Clin. Cancer Res. 2017, 23, 3307–3315, doi:10.1158/1078-0432.ccr-16-2526.

48. Pulya, S.; Amin, S.A.; Adhikari, N.; Biswas, S.; Jha, T.; Ghosh, B. HDAC6 as privileged target in drug discovery: A perspective. Pharmacol. Res. 2020, 105274, doi:10.1016/j.phrs.2020.105274.

49. Nooka, A.K.; Kaufman, J.L.; Hofmeister, C.C.; Joseph, N.S.; Heffner, T.L.; Gupta, V.A.; Sullivan, H.C.; Neish, A.S.; Dhodapkar, M.V.; Lonial, S. Daratumumab in multiple myeloma. Cancer 2019, 125, 2364–2382, doi:10.1002/cncr.32065.

50. Lonial, S.; Vij, R.; Harousseau, J.-L.; Facon, T.; Moreau, P.; Mazumder, A.; Kaufman, J.L.; Leleu, X.; Tsao, L.C.; Westland, C.; et al. Elotuzumab in Combination With Lenalidomide and Low-Dose Dexamethasone in Relapsed or Refractory Multiple Myeloma. J. Clin. Oncol. 2012, 30, 1953–1959, doi:10.1200/jco.2011.37.2649.

51. Richardson, P.G.; Jagannath, S.; Moreau, P.; Jakubowiak, A.J.; Raab, M.S.; Facon, T.; Vij, R.; White, D.; Reece, D.E.; Benboubker, L.; et al. Elotuzumab in combination with lenalidomide and dexamethasone in patients with relapsed multiple myeloma: Final phase 2 results from the randomised, open-label, phase 1b–2 dose-escalation study. Lancet Haematol. 2015, 2, e516–e527, doi:10.1016/s2352-3026(15)00197-0.

52. Yee, A.J.; Raje, N.S. Denosumab for the treatment of bone disease in solid tumors and multiple myeloma. Future Oncol. 2018, 14, 195–203, doi:10.2217/fon-2017-0403.

53. Varga, C.; Laubach, J.P.; Anderson, K.C.; Richardson, P.G. Investigational agents in immunotherapy: A new horizon for the treatment of multiple myeloma. Br. J. Haematol. 2018, 181, 433–446, doi:10.1111/bjh.15116.

54. Moreno, L.; Perez, C.; Zabaleta, A.; Manrique, I.; Alignani, D.; Ajona, D.; Blanco, L.; Lasa, M.; Maiso, P.; Rodriguez, I.; et al. The Mechanism of Action of the Anti-CD38 Monoclonal Antibody Isatuximab in Multiple Myeloma. Clin. Cancer Res. 2019, 25, 3176–3187, doi:10.1158/1078-0432.ccr-18-1597.

55. Van De Donk, N.W.; Usmani, S.Z. CD38 Antibodies in Multiple Myeloma: Mechanisms of Action and Modes of Resistance. Front. Immunol. 2018, 9, 2134, doi:10.3389/fimmu.2018.02134.

56. Jelinek, T.; Paiva, B.; Hajek, R. Update on PD-1/PD-L1 Inhibitors in Multiple Myeloma. Front. Immunol. 2018, 9, 2431, doi:10.3389/fimmu.2018.02431.

57. Boussi, L.; Niesvizky, R. Advances in immunotherapy in multiple myeloma. Curr. Opin. Oncol. 2017, 29, 460–466.

58. Topp, M.S.; Duell, J.; Zugmaier, G.; Attal, M.; Moreau, P.; Langer, C.; Krönke, J.; Facon, T.; Salnikov, A.V.; Lesley, R.; et al. Anti–B-Cell Maturation Antigen BiTE Molecule AMG 420 Induces Responses in Multiple Myeloma. J. Clin. Oncol. 2020, 38, 775–783, doi:10.1200/jco.19.02657.

59. Cohen, A.D.; Raje, N.; Fowler, J.A.; Mezzi, K.; Scott, E.C.; Dhodapkar, M.V. How to Train Your T Cells: Overcoming Immune Dysfunction in Multiple Myeloma. Clin. Cancer Res. 2020, 26, 1541–1554, doi:10.1158/1078-0432.ccr-19-2111.

60. Lin, Q.; Zhao, J.; Song, Y.; Liu, D. Recent updates on CAR T clinical trials for multiple myeloma. Mol. Cancer 2019, 18, 1–11, doi:10.1186/s12943-019-1092-1.

61. Khoury, H.J.; Garcia-Manero, G.; Borthakur, G.; Kadia, T.; Foudray, M.C.; Arellano, M.; Langston, A.; Bethelmie-Bryan, B.; Rush, S.; Litwiler, K.; et al. A phase 1 dose-escalation study of ARRY-520, a kinesin spindle protein in-hibitor, in patients with advanced myeloid leukemias: ARRY-520 in Advanced Leukemias. Cancer 2012, 118, 3556–3564.

62. Shah, J.J.; Kaufman, J.L.; Zonder, J.A.; Cohen, A.D.; Bensinger, W.I.; Hilder, B.W.; Rush, S.A.; Walher, D.H.; Tunquist, B.J.; Litwiler, K.S.; et al. A Phase 1 and 2 study of Filanesib alone and in combination with low-dose dexame-thasone in relapsed/refractory multiple myeloma: Filanesib ± Dex in Multiple Myeloma. Cancer 2017, 123, 4617–4630.

63. Vaxman, I.; Sidiqi, M.H.; Gertz, M.A. Venetoclax for the treatment of multiple myeloma. Expert Rev. Hematol. 2018, 11, 915–920, doi:10.1080/17474086.2018.1548931.

64. Podar, K.; Shah, J.; Chari, A.; Richardson, P.G.; Jagannath, S. Selinexor for the treatment of multiple myeloma. Expert Opin. Pharmacother. 2020, 21, 399–408, doi:10.1080/14656566.2019.1707184.

65. Lonial, S.; Lee, H.C.; Badros, A.; Trudel, S.; Nooka, A.K.; Chari, A.; Abdallah, A.-O.; Callander, N.; Lendvai, N.; Sborov, D.; et al. Belantamab mafodotin for relapsed or refractory multiple myeloma (DREAMM-2): A two-arm, randomised, open-label, phase 2 study. Lancet Oncol. 2020, 21, 207–221, doi:10.1016/s1470-2045(19)30788-0.

66. Farooq, A.V.; Degli Esposti, S.; Popat, R.; Thulasi, P.; Lonial, S.; Nooka, A.K.; Jakubowiak, A.; Sborov, D.; Zaugg, B.E.; Badros, A.Z.; et al. Corneal Epithelial Findings in Patients with Multiple Myeloma Treated with Antibody–Drug Conjugate Belantamab Mafodotin in the Pivotal, Randomized, DREAMM-2 Study. Ophthalmol. Ther. 2020, 9, 889–911, doi:10.1007/s40123-020-00280-8.

67. Ailawadhi, S.; Kelly, K.R.; Vescio, R.A.; Jagannath, S.; Wolf, J.; Gharibo, M.; Sher, T.; Bojanini, L.; Kirby, M.; Chanan-Khan, A. A Phase I Study to Assess the Safety and Pharmacokinetics of Single-agent Lorvotuzumab Mertansine (IMGN901) in Patients with Relapsed and/or Refractory CD–56-positive Multiple Myeloma. Clin. Lymphoma Myeloma Leuk. 2019, 19, 29–34, doi:10.1016/j.clml.2018.08.018.

68. Iftikhar, A.; Hassan, H.; Iftikhar, N.; Mushtaq, A.; Sohail, A.; Rosko, N.; Chakraborty, R.; Razzaq, F.; Sandeep, S.; Valent, J.; et al. Investigational Monoclonal Antibodies in the Treatment of Multiple Myeloma: A Systematic Review of Agents under Clinical Development. Antibodies 2019, 8, 34, doi:10.3390/antib8020034.

69. Bonello, F.; Mina, R.; Boccadoro, M.; Gay, F. Therapeutic Monoclonal Antibodies and Antibody Products: Current Practices and Development in Multiple Myeloma. Cancers 2019, 12, 15, doi:10.3390/cancers12010015.

70. Gavriatopoulou, M.; Ntanasis-Stathopoulos, I.; Dimopoulos, M.A.; Terpos, E. Anti-BCMA antibodies in the future management of multiple myeloma. Expert Rev. Anticancer. Ther. 2019, 19, 319–326, doi:10.1080/14737140.2019.1586539.

71. O'Donnell, E.K.; Raje, N.S. New monoclonal antibodies on the horizon in multiple myeloma. Ther. Adv. Hematol. 2016, 8, 41–53, doi:10.1177/2040620716682490.

72. Kinneer, K.; Flynn, M.; Thomas, S.B.; Meekin, J.; Varkey, R.; Xiao, X.; Zhong, H.; Breen, S.; Hynes, P.G.; Fleming, R.; et al. Preclinical assessment of an antibody–PBD conjugate that targets BCMA on multiple myeloma and myeloma progenitor cells. Leukemia 2019, 33, 766–771, doi:10.1038/s41375-018-0278-7.

73. Matinkhoo, K.; Pryyma, A.; Todorovic, M.; Patrick, B.; Perrin, D.M. Synthesis of the Death-Cap Mushroom Toxin α-Amanitin. J. Am. Chem. Soc. 2018, 140, 6513–6517, doi:10.1021/jacs.7b12698.

74. Pahl, A.; Lutz, C.; Hechler, T. Amanitins and their development as a payload for antibody-drug conjugates. Drug Discov. Today Technol. 2018, 30, 85–89, doi:10.1016/j.ddtec.2018.08.005.

75. Zou, J.; Chen, D.; Zong, Y.; Ye, S.; Tang, J.; Meng, H.; An, G.; Zhang, X.; Yang, L. Immunotherapy based on bispecific T-cell engager with hIgG 1 Fc sequence as a new therapeutic strategy in multiple myeloma. Cancer Sci. 2015, 106, 512–521, doi:10.1111/cas.12631.

76. Chan, W.K.; Kang, S.; Youssef, Y.; Glankler, E.N.; Barrett, E.R.; Carter, A.M.; Ahmed, E.H.; Prasad, A.; Chen, L.; Zhang, J.; et al. A CS1-NKG2D Bispecific Antibody Collectively Activates Cytolytic Immune Cells against Multiple Myeloma. Cancer Immunol. Res. 2018, 6, 776–787, doi:10.1158/2326-6066.cir-17-0649.

77. Terpos, E.; Ntanasis-Stathopoulos, I. International Myeloma Society Multiple Myeloma: Clinical Updates From the American Society of Hematology Annual Meeting 2018. Clin. Lymphoma Myeloma Leuk. 2019, 19, e324–e336, doi:10.1016/j.clml.2019.03.008.

78. Mikhael, J.R.; Dingli, D.; Roy, V.; Reeder, C.B.; Buadi, F.K.; Hayman, S.R.; Dispenzieri, A.; Fonseca, R.; Sher, T.; Kyle, R.A.; et al. Management of Newly Diagnosed Symptomatic Multiple Myeloma: Updated Mayo Stratification of Myeloma and Risk-Adapted Therapy (mSMART) Consensus Guidelines 2013. Mayo Clin. Proc. 2013, 88, 360–376.

79. Al Hamed, R.; Bazarbachi, A.H.; Malard, F.; Harousseau, J.-L.; Mohty, M. Current status of autologous stem cell transplantation for multiple myeloma. Blood Cancer J. 2019, 9, 1–10, doi:10.1038/s41408-019-0205-9.

80. Durie, B.G.M.; Hoering, A.; Abidi, M.H.; Rajkumar, S.V.; Epstein, J.; Kahanic, S.P.; Thakuri, M.; Reu, F.; Reynolds, C.M.; Sexton, R.; et al. Bortezomib with lenalidomide and dexamethasone versus lenalidomide and dexamethasone alone in patients with newly diagnosed myeloma without intent for immediate autologous stem-cell transplant (SWOG S0777): A randomised, open-label, phase 3 trial. Lancet 2017, 389, 519–527, doi:10.1016/s0140-6736(16)31594-x.

81. Arora, S.; Majhail, N.S.; Liu, H. Hematopoietic Progenitor Cell Mobilization for Autologous Stem Cell Transplantation in Multiple Myeloma in Contemporary Era. Clin. Lymphoma Myeloma Leuk. 2019, 19, 200–205, doi:10.1016/j.clml.2018.12.010.

82. BLENREP-Belantamab Injection, Powder, Lyophilized, for Solution: Highlights of Prescribing Information. Updated 8/2020. GlaxoSmithKline LLC. Available online: https://dailymed.nlm.nih.gov/dailymed/fda/fdaDrugXsl.cfm?setid=16a160a4-3ec0-4ddf-99ce-05912dd3382d&type=display (accessed on 21 October 2020.).

83. FDA Approves GSK’s BLENREP (Belantamab Mafodotin-Blmf) for the Treatment of Patients with Relapsed or Refractory Multiple Myeloma. GSK. Published 6 August 2020. Available online: https://www.gsk.com/en-gb/media/press-releases/fda-approves-gsk-s-blenrep-belantamab-mafodotin-blmf-for-the-treatment-of-patients-with-relapsed-or-refractory-multiple-myeloma/ (accessed on 6 August 2020).

84. O’Connor, B.P.; Raman, V.S.; Erickson, L.D.; Cook, W.J.; Weaver, L.K.; Ahonen, C.; Lin, L.-L.; Mantchev, G.T.; Bram, R.J.; Noelle, R.J. BCMA Is Essential for the Survival of Long-lived Bone Marrow Plasma Cells. J. Exp. Med. 2004, 199, 91–98, doi:10.1084/jem.20031330.

85. Anti-BCMA Therapy Endorsed, despite Eye Toxicity. Cancer Discov. 2020, 10, OF2, doi:10.1158/2159-8290.cd-nb2020-074.

86. McMillan, A.; Warcel, D.; Popat, R. Antibody-drug conjugates for multiple myeloma. Expert Opin. Biol. Ther. 2020, 1-13, 1–13, doi:10.1080/14712598.2020.1802422.

87. Drugs and Lactation Database (LactMed) [Internet]. Bethesda (MD): National Library of Medicine (US). Belantamab Mafodotin. 2006. Available online: https://www.ncbi.nlm.nih.gov/books/NBK561136/ (accessed on 17 August 2020).