Myeloma Cell Death

Subjects: Cell Biology
Contributor: Brigitte Sola

Multiple myeloma (MM) is a neoplastic disease of plasma cells, characterized by a complex array of clinical manifestations. Despite extensive efforts and progress in the care of MM patients, the disease is still fatal because of *de novo* or acquired resistance of malignant cells to standard chemotherapies. In turn, new therapies and/or combination therapies are urgently needed. Reactive oxygen species (ROS) are unstable and highly reactive chemical molecules, able to alter the main structural components of cells, such as proteins and lipids, and thus, modifying cell fates. ROS levels are tightly controlled in normal cells both for their production and degradation. In turn, an unbalance of the redox status might be exploited to induce cell death. This is indeed the case for myeloma cells even those that are resistant, opening new perspectives for refractory or relapsed MM patients.

Keywords: multiple myeloma ; ROS

1. Introduction

Multiple myeloma (MM) is a plasma cell malignancy characterized by the accumulation of clonal cells in the bone marrow and the overproduction of monoclonal immunoglobulin causing the clinical features of the disease: hypercalcemia, renal failure, anemia and bone lesions, collectively known as CRAB symptoms. Moreover, plasma cells are prone to produce large amounts of immunoglobulins, causing an endoplasmic reticulum stress, the unbalance of redox homeostasis and the production of intracellular ROS [1]. The disease progresses from benign monoclonal gammopathy of undetermined significance (MGUS) and smoldering myeloma to overt aggressive MM and ultimately plasma cell leukemia. Over the past twenty years, MM patients outcome has been improved through the use of new drugs as well as new therapeutic approaches [2][3][4][5]. For elderly patients, not eligible to autologous transplantation, the use of proteasome inhibitors (PIs), immunomodulators (IMiDs), monoclonal antibodies, histone deacetylase (HDAC) inhibitors and more recently, check-point inhibitors and their various combinations have improved substantially MM patients survival. However, most MM patients are refractory or relapse (R/R) after one or more treatment regimens and the disease is still fatal [3][5][6].

The first-in-class PI, bortezomib (BTZ) and several second-generation PIs (carfilzomib (CFZ), ixazomib) are efficient drugs, currently used for newly diagnosed patients and R/R patients alone or associated with other agents [7]. By targeting subunits of the ubiquitin/proteasome system (UPS), the major cell regulator of protein degradation, PIs cause a proteotoxic stress that activates the apoptotic function of the unfolded protein response (UPR) [8]. Indeed, after UPS inhibition, misfolded proteins accumulate in the endoplasmic reticulum (ER) generating an ER stress and activating the UPR. The survival of MM cells is highly dependent on the UPR, and inefficient or prolonged UPR activation signals apoptosis [9][10][11]. Another important mechanism of BTZ cytotoxicity in MM cells is the generation of an oxidative stress that has been long considered as a byproduct of the ER stress. The production of ROS depends on ER-resident protein disulfide isomerase (PDI) and endoplasmic reticulum oxidoreduction (ERO1) enzymes as well as nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) complexes and mitochondrial electron transport chain (ETC) [12]. The ERO1 flavoprotein consumes oxygen and generates hydrogen peroxide (H_2O_2). Under ER stress, the activity of these enzymes is increased and generates higher amounts of ROS and, in turn, an oxidative stress. Moreover, BTZ treatment induces an adaptative antioxidant response by depleting intracellular glutathione (GSH), activating CCAAT/enhancer binding protein (C/EBP)-homologous protein (CHOP) and transcription factor 4 (ATF4), two antioxidant transcription factors, and the nuclear factor-erythroid 2 p45-related factor 2 (NRF2), the key controller of detoxification genes [13].

Although BTZ and more generally PIs have achieved excellent therapeutic effects, innate resistance can be observed in drug-naive patients and acquired resistance may appear during the course of the treatment [14]. Indeed, during the progression of the disease, complex genetic alterations occur that contribute to the development of a resistant phenotype. The upregulation of the 20S proteasome subunits [15][16], the paradoxical downregulation of the 19S proteasome subunits [17], and the overexpression of efflux pumps [18] are among the main reported mechanisms of acquired resistance. However, the modulation of UPR, the alteration of apoptosis/autophagy signaling and metabolic changes contribute also

largely to PI resistance. Indeed, a high glycolytic activity and/or the rewiring of glucose metabolism through the pentose phosphate pathway (PPP) and the serine synthesis pathway (SSP), an increased mitochondrial activity and fatty acid oxidation, are associated with PIs resistance [19][20][21]. A proteomic analysis comparing naive and R/R MM patients characterized four sets of relevant proteins including proteasomal proteins, apoptosis signaling proteins, proteins regulating the inflammation response, and factors regulating the redox status [22]. Moreover, the tumor microenvironment (TME) within the bone marrow facilitates tumor cells proliferation as well as drug resistance. This is due, at least in part, to a metabolic reprogramming of mesenchymal stromal and immune cells favoring the defense against ROS [23][24].

2. Unbalancing ROS in Multiple Myeloma

The rational for manipulating the redox status of MM cells to induce their death and/or to alleviate their resistance is an old concept [25]. This is based on the observation that the oxidative metabolism in myeloma vs normal plasma cells is fundamentally different. Theoretically, either oxidant or antioxidant treatment could exacerbate an oxidative stress and in turn, cell death. Indeed, myeloma cell death is obtained either by decreasing ROS levels or by increasing them (Table 1). ROS are synthesized in MM cells at least in part by the NOX complex activity [26]. Moreover, compared to normal bone marrow plasma cells, patients with MGUS, or a smoldering myeloma, NOX2 (encoded by *CYBB*) is the only catalytic subunit expressed in MM patients along with the $p40^{phox}$ (*NCF4*) and $p22^{phox}$ (*CYBA*) regulatory subunits [27]. Although a pan-NOX inhibitor, VAS3947 has a strong anti-MM activity, it shows adverse effects when combined with BTZ [27].

The effects due to pro-oxidant strategies are more documented. Increasing the intracellular ROS level can be achieved either by their direct production or by inhibiting antioxidant defenses.

2.1. Drugs That Target Glutathione Metabolism

TP53 mutations/deletions are present in most cancers and associated with resistance to therapies. In turn, molecules acting downstream of p53, inducing the transcription of p53 targets such as $p21^{CIP}$, BAX, PUMA, and NOXA and reactivating cell death have been selected. In MM cells, *TP53* mutations/deletions are rare but increase with disease progression and associate with a bad prognosis. p53-modulating agents such as CP-31398, PRIMA-1 (p53 reactivation and induction of massive apoptosis-1), or APR-246 ($PRIMA\text{-}1^{Met}$) induce ROS-mediated apoptosis of MM regardless the *TP53* status [28][29][30][31][32]. At the molecular level, APR-246 induces ROS production by depleting GSH cell content [28][31]. Interestingly, APR-246 synergizes BSO, an irreversible inhibitor of the GSH synthesis. Another report indicated that caffeic acid phenetyl ester (CAPE), a phenolic compound, induces apoptosis through an oxidative stress caused by glutathione depletion [33].

Table 1. Drugs targeting redox metabolism in MM preclinical models.

Effects on ROS Level	Drug/Combination	Effects	Preclinical Model	Reference
Decreasing	VAS3947	NOX2i [1]	HMCL	[27]
Increasing	APR-246	GSH depletion	HCML Primary cell In vivo	[30]
	CAPE	GSH	HCML	[33]
	APR-246/BSO	GSH depletion/γGCSi	In vivo	[28]
	APR-246/auranofin	GSHdepletion/TXNRD1i r	HCMLs Primary cells	[31]
	Auranofin	TXNRD1i	HCMLs	[34]
	Auranofin/ZnPP IX	TXNRD1i/HO1i	HCMLs	[35]
	PX-12	TXNi	HCMLs	[36]
	Auranofin/BTZ	TXNi/PI	HCMLs	[27]
	Lenalidomide/BTZ	TXNi/PI	HCMLs	[37]
	LCS-1	SOD1i	HCMLs Primary cells In vivo	[38]
	2-methoxyestradiol/BTZ	SOD2i/PI	HCMLs	[39]

Effects on ROS Level	Drug/Combination	Effects	Preclinical Model	Reference
	Disulfiram/BTZ	SOD1i/PI	HCMLs	[40]
	Scutellarein/BTZ	SOD2i/PI	HCMLs	[41]
	CCF642/BTZ	PDIi/PI	HCMLs In vivo	[42]
	E64FC26	PDIi	HCMLs In vivo	[43][44]
	L-asparaginase/CFZ	AA depletion/PI	HCMLs	[45]
	DPI/HK2-ASO/PER	Mitochondria complex I/HK2i/FAOi	HCMLs In vivo	[46]
	SR18292	PCG-1αi	HCMLs Primary cells	[47]

2.2. Drugs That Target Antioxidant Enzymes

MM cells display increased expression of TXN and TXNRD1 involved in the protection against oxidative stress. Moreover, antioxidant genes are overexpressed in myeloma patients, including those with a poor prognosis, and MM cell lines when compared to normal plasma cells [27]. As expected, the targeting of antioxidant enzymes could be beneficial for MM patients.

2.2.1. Thioredoxin System Inhibitors (Auranofin and Other Gold Compounds)

As described before, the thioredoxin system comprising TXN and TXNRD1 is one of the major antioxidant systems in MM cells. In turn, TXN and TXNRD1 inhibition results in ROS-induced apoptosis [48][36]. Gold compounds have a high affinity for thiol and selenol groups and auranofin is very efficient to induce MM cells death, including PI-resistant cells and those with p53 deficiency [27][48][31][34][36]. TXN inhibition activates mitophagy, the selective degradation of mitochondria by autophagy, and negatively regulates the AKT/mTOR and ERK1/2 survival signaling pathways [36]. TNXRD1 inhibition impacts the NFκB signaling pathway [34]. Importantly, auranofin combined with BTZ alleviates the chemoresistance mediated by the tumor microenvironment [27]. A bis-chelated tetrahedral gold(I) phosphine complex seems even more powerful than auranofin to induce ROS-mediated apoptosis [49]. However, TNXRD1 inhibition could be compensated by the overexpression of HO1 through the NRF2 signaling pathway [35]. HO1 pharmacological inhibition using zinc protoporphyrin IX restores BTZ sensitivity [35]. A number of drugs targeting TXN and TXNRD1 and inducing ROS, have been described in the past decade [12], but their ability to synergize with PI in MM patients remains to be established. Nevertheless, the targeting of multiple antioxidant systems could be essential for an efficient anti-MM strategy.

The IMiDs, lenalidomide and pomalidomide, are thalidomide analogs. They inhibit TXNRD1 that leads to an accumulation of cytotoxic H_2O_2 levels [37]. In contrast with auranofin and gold compounds, the cytotoxicity of IMiDs necessitates cereblon (CRBN), the substrate receptor the CUL4-RING E3 ligase complex [50]. Indeed, IMiDs/CRBN complexes are retained in the cells and change the redox status by inhibiting H_2O_2 degradation. Thus, MM cells with a low antioxidant capacity display increased sensitivity to IMiD-mediated cell death [50].

2.2.2. Superoxide Dismutase (SOD1/2) Inhibitors

Both SOD1 and SOD2 enzymes are overexpressed in MM cells and cell lines compared to normal plasma cells and mediate BTZ-resistance [27][40][39][38]. The inhibition of SOD1 with disulfiram and SOD2 with 2-methoxyestradiol induces apoptosis of both BTZ-sensitive and -resistant MM cells [40][39]. Among the various mechanisms of BTZ resistance, the 19S associated-ubiquitin receptor Rpn13 plays a major role since its inhibition restores BTZ sensitivity [51]. SOD1 is the mediator of Rpn13 signaling and in turn, SOD1 inhibition using the LCS-1 inhibitor, induces a ROS-mediated MM cell death including BTZ-resistant cells [38]. Scutellarein, a flavone extracted from a traditional Chinese medicinal herb, induces a mitochondrial-mediated apoptosis in the MM cells by activating SOD2. This leads to ROS accumulation and synergistic effects combined with BTZ [41].

2.3. Other ROS-Inducing Drugs

PDIs are ER-resident oxidoreductase enzymes that ensure the proper folding of nascent polypeptide chains by forming bonds between cysteine residues. PDIs are overexpressed in MM [43]. The inhibition of PDIs induces the accumulation of misfolded or unfolded proteins, an ER stress, and an oxidative stress. Moreover, both pathways are enhanced in

response to PIs [42][43][44]. In turn, the concomitant inhibition of PDIs and UPR further enhances the proteotoxic/ER stress and oxidative stress, and the apoptotic response.

Amino acid depletion triggered by L-asparaginase (ASNase) after hydrolysis of glutamine (glutaminolysis) sensitizes MM cells to CFZ [45]. This occurs via NRF2 upregulation, increased mitochondrial ROS generation and mitochondrial dysfunction. Deregulating the protein and amino acid synthesis programs allows PI-resistant MM cells to enter apoptosis [45].

OXPHOS genes are often overexpressed in MM cells and associated with a poor prognosis [47]. This is due to the overexpression of the transcriptional coactivator peroxisome proliferator-activated receptor gamma coactivator-1α (PGC-1α). In turn, OXPHOS genes are enriched in MM patients with high PGC-1α level and the PGC-1α inhibitor ST18292 exerts efficient antimyeloma effects trough ROS production [52].

3. Global Alteration of MM Metabolism

More generally, several metabolic pathways are altered in MM cells offering a plethora of potent targets (Figure 3) [52]. MM cells are particularly dependent on glycolysis. GLUT1/4 glucose transporters are expressed on MM cells and their activity is necessary for cell survival [53][54]. Ritonavir, a HIV protease inhibitor reversibly binds GLUT4 and induces MM cell apoptosis [55]. HK2, the first rate-limiting enzyme of the glycolysis cascade is expressed on MM cells at diagnosis and its overexpression is associated with poor prognosis [56][46]. HK2 converts glucose into G6P. The targeting of HK2 by the small molecule 3-bromopyruvate (3-BP) is efficient for killing MM cells [57]. Interestingly, the knockdown of HK2 by an antisense oligonucleotide (ASO) associated with DPI or metformin as mitochondrial complex I inhibitor, and perhexiline as β-oxidation inhibitor induces specifically tumor cell death [46]. The targeting of ENO1 that mediates the conversion 2-phospho-D-glycerate to phosphoenolpyruvate at the final step of the glycolytic pathway, also induces MM cell death. ENO1 is overexpressed in MM samples [58][59]. Other glycolytic enzymes such as phosphofructokinase (PFK), pyruvate kinase M2 (PKM2), and lactate dehydrogenase (LDHA) are also highly expressed in MM cells becoming attracting targets [56][60].

Significant amounts of lactate are produced in MM cells confirming that the oxidative glycolysis is fully functional, but lactate is also produced by the stromal cells within the TME. Lactate enters MM cells through the MCT1 transporter and fuels OXPHOS [61]. The inhibition of MCT1 by the α-cyano-4-hydroxycinnamic acid reduces lactate incorporation and causes apoptosis [61]. Recently, phosphatase of regenerating liver 3 (PRL3), an interleukin-6-induced oncogenic phosphatase, has been shown essential for the metabolic changes of myeloma cells. PRL3 exerts pleiotropic effects. It promotes glucose uptake and glycolytic flux through the upregulation of glycolytic enzymes, and regulates the SSP leading to an increase in GSH intracellular content [59]. PRL3 is highly expressed in MM cells and correlates with poor prognosis and unfavorable outcome [62].

As much as glucose, glutamine is used as an energy provider and MM cells are addicted to glutamine [63]. Alanine/serine/cysteine-preferring transporter 2 (ASCT2), L-type amino acid transporter (LAT1), and sodium-coupled neutral amino acid transporter 1 (SNAT1) are the glutamine transporters expressed on MM cells [63]. Although ASCT2, LAT1, and SNAT1 inhibitors have been assessed on several types of tumors, to our knowledge there is no data on myeloma. Glutamine synthase (GS) is lacking in MM cells, therefore MM cells are dependent on glutamine uptake. By contrast, glutaminase 1 (GLS1) expression is increased [63]. In turn, the inhibition GLS1 that catalyzes glutamine, by benzophenanthridinone (BPI) induces MM apoptosis [64]. An increased glutamine anaplerosis toward TCA cycle is observed in malignant MM cells and this increase is even more marked in comparison with MGUS and overt myeloma [65]. Importantly and different from normal plasma cells in this regard, glycolysis and OXPHOS compensate each other as well as glycolysis and glutaminolysis [55].

Metabolic reprogramming in MM cells is also necessary for cells to adapt their TME. We have previously seen that glutamine, lactate, and probably other metabolites enter MM cells from the TME and in turn, change profoundly the cell metabolism. Furthermore, mitochondria are trafficking between MM cells and mesenchymal stromal cells through tumor-derived nanotubes [66]. The enhanced OXPHOS of MM cells could be the outcome of massive mitochondria acquisition and metabolism reprogramming. Although NOX2 could drive mitochondria transfer from stromal cells to tumor cells as shown for leukemic blasts [67], we have reported that a pan-NOX inhibitor induces MM cell death but shows adverse effect when combined with BTZ [27]. Alternatively, NOX inhibitors could be associated with drugs that have no impact on ROS production rather modifying glycolysis or glutaminolysis. Hypoxia is also a hallmark of the bone marrow niche and HIF-1α and HIF-2α that are stabilized in MM cells control glycolysis through the upregulation of genes coding for glycolytic enzymes and redox homeostasis.

The vulnerability of MM cells to fatty acid metabolism is less studied. Fatty acid synthase (FASN) is overexpressed in MM patients and the inhibition of β-oxidation as well as de novo fatty acid synthesis induces MM cell death including BTZ-resistant cells [68]. Disruption of fatty acid oxidation confers sensitivity to CFZ [69]. Moreover, PI-resistant MM cells increase lipogenesis as a mechanism of resistance [19]. Perhexiline (PER) as a β-oxidation inhibitor synergizes with HK2-antisens oligonucleotide (ASO) for inducing cell death. Cell death is even dramatically enhanced with the triple combination PER/DPI/HK2-ASO [46]. Obesity is a risk factor for MM and bone marrow-resident adipocytes sustain MM growth [70]. By analogy with leukemias, a metabolic shift from glycolysis to enhanced β-oxidation could impact on MM survival [71].

Interestingly, diet and nutrition are linked to risk factors for multiple myeloma [72][73]. Dietary factors may affect inflammation and endogenous growth factors pathways (e.g., IL6, insulin-like growth factor) thereby playing an important role in MM pathogenesis and in patients' survival [74]. Moreover, diet may also impact the risk of developing MGUS, the premalignant condition of MM [75].

The growth of MM cells within their bone marrow niche necessitates a metabolic shift that shapes the TME toward a hypoxic, acidic, and nutrients-poor milieu [76]. In turn, TME becomes unfavorable for immune cells including T cells and NK cells to exert their antitumor effects. TME displays also tumor-promoting activity by allowing the polarization of M2 macrophages and inhibiting regulatory T cells (Tregs). Several recent reviews are dedicated to this theme [77][76][78][79], we rapidly report here some important clues. The PD-1/PD-L1 pathway controls, at least in part, the maintenance of immune surveillance within the TME [80]. PD-L1 expression is increased in MM cells and associated with disease progression. Although several regulatory pathways are involved in the regulation of PD-L1 level such as JAK/STAT, PI3K/AKT, and ERK/MAPK pathways [81], it is worth noting that HIF-1α directly regulates positively *CD274* gene (encoding PD-L1) transcription [82]. The increased expression of PD-L1 increases cell resistance to cytotoxic T-cell-mediated lysis [83]. Other immune-suppressive cells such as MDSCs [84] and TAMs [85] express high levels of PD-L1. One can imagine that the presence of hypoxic niches in the bone marrow drives the stabilization of HIF-1α that favors PD-L1 expression also in these cells. Moreover, hypoxia inhibits the killing potential of NK cells favoring immune evasion [86]. As described for melanoma cells, the acidity within the TME imposed by an enhanced glycolysis could impact tumor infiltrating lymphocytes (TILs) in promoting anergy and macrophages polarization supporting tumor growth [87][88]. These immunosuppressive pathways should be considered for efficient anti-myeloma therapy.

4. Autophagy and Ferroptosis Are Forms of Death Controlled by MM Metabolism

Due to their function of immunoglobulin synthesis, MM cells are addicted to UPS and to another protein degradation pathway, macroautophagy referred to as autophagy [89]. Autophagy is the cell mechanism of self-destruction for clearing organelles and compensate proteasome deficiency to degrade ubiquitinylated proteins. SQSTM1 is the autophagy cargo receptor that bridges ubiquitinylated proteins and autophagosomes and is a critical mediator of autophagy and PI-resistance [90]. In BTZ- and CFZ-resistant cells, SQSTM1 is overexpressed through the activation of NRF2 and this affects the fatty acid oxidation and in turn the level of NADPH [69]. The simultaneous inhibition of UPS and autophagy by hydroxychloroquine induces a synergistic cytotoxicity [91]. Furthermore, *FAM46C* that encodes a non-canonical poly(A) polymerase is mutated in almost 20% of MM patients. FAM46C sustains ER biogenesis in MM cells and this activity is controlled by autophagy through an inhibitory interaction with SQSTM1 [92]. This SQSTM1/FAM46C interplay could be exploited to increase PI efficacy and alleviate PI resistance.

Another type of cell death has been described recently for MM cells: ferroptosis [93]. Ferroptosis is an iron-dependent programmed cell death characterized by a high lipid peroxidation and accumulation of ROS that occurs mainly through intracellular GSH depletion and decreased activity of GPX4 [94]. One way to reduce GSH level is to inhibit the Xc- antiporter that allows cysteine to enter cells (Figure 3). Starheim and coworkers have reported previously that inhibiting Xc- activity induces MM cell death including BTZ-resistant cells. However, in this report the nature of cell death was not examined. GPX4 is a key regulator of ferroptosis inhibiting the formation of lipid peroxide. GPX4, highly expressed in MM cells, is targeted by FTY720 leading to MM ferroptosis [93]. It appears that autophagy and apoptosis play a role in the occurrence of ferroptosis [94]. Although such interplay has not been reported for MM cells, it opens new perspectives for combinatory therapies.

5. Conclusions

MM cells have increased ROS levels in comparison to plasma cells, their normal counterparts. This high level of ROS contributes to the initiation, promotion, and progression of MM disease, as well as, resistance to chemotherapy. Therefore, increasing ROS to highly toxic levels may provide a unique tool to kill myeloma cells. This approach seems very efficient

since ROS-inducing agents co-operate with PIs (and probably other drugs) and induce MM cell apoptosis including those that are PI-resistant. However, to our knowledge, despite preclinical evidences, no clinical trials using either drugs targeting antioxidant enzymes or depleting glutathione are currently ongoing (www.clinicaltrials.gov). One main concern is to know what are the effects of pro-oxidants on the MM cancer-stem cell (CSC). MM-CSCs is a rare subpopulation of cells that has the capacity for self-renewal and tumor initiation. CSCs are responsible for drug resistance and disease relapse [95]. Although the phenotype of MM CSC is still debated, by analogy with other hemopathies and solid tumors, CSCs likely, synthesize low levels of ROS and in turn, are little impacted by pro-oxidants. Indeed, pro-oxidants inhibit tumor cells proliferation but may have limited impact on cancer-stem cells that synthesize low ROS levels [96]. Moreover, in the perspective of an anti-myeloma immunotherapy, the complex network of immune cells, non-immune cells, and MM cells in their niche, including their redox status, should be better understood.

Interestingly, several unrelated drugs are acting by modulating the redox status. Melphalan is an alkylating agent; its toxicity is due to a redox imbalance and melphalan resistance is linked to modulation of metabolic pathways as well as oxidative stress [97][98][99]. The depletion of intracellular GSH by BSO significantly enhances melphalan activity [97][98]. The next-generation melphalan pro-drug melflufen (melphalan flufenamide ethyl ester) is an alkylating agent that has shown its high efficacy. It was recently approved by the FDA for use in combination with dexamethasone in R/R MM patients [100]. Melflufen enters cells where it is targeted by aminopeptidases resulting in its trapping in organelles and membranes allowing its accumulation. In pre-clinical models, it has been shown that it generates ROS [101]. HDAC inhibitors, which regulate gene expression by inhibiting the deacetylation of histone proteins, have been shown to exert a wide array of antitumor effects including cell cycle arrest and cell death by generating ROS [102][103].

Metabolism changes in MM cells show their vulnerability. For efficient killing of myeloma tumor cells, the design of metabolic targets and the choice of new combinations must take into account the modifications of metabolism imposed by the TME as well as the redox status of MM cells themselves.

References

1. Vené, R.; Delfino, L.; Castellani, P.; Balza, E.; Bertolotti, M.; Sitia, R.; Rubartelli, A. Redox remodeling allows and controls B-cell activation and differentiation. Antioxid. Redox Signal. 2010, 13, 1145–1155.
2. Kumar, S.K.; Dispenzieri, A.; Lacy, M.Q.; Gertz, M.A.; Buadi, F.K.; Pandey, S.; Kapoor, P.; Dingli, D.; Hayman, S.R.; Leung, N.; et al. Continued improvement in survival in multiple myeloma: Changes in early mortality and outcomes in older patients. Leukemia 2014, 28, 1122–1128.
3. Ludwig, H.; Miguel, J.S.; Dimopoulos, M.A.; Palumbo, A.; Garcia-Sanz, R.; Powles, R.; Lentzsch, S.; Ming Chen, W.; Hou, J.; Jurczyszyn, A.; et al. International Myeloma Working Group recommendations for global myeloma care. Leukemia 2014, 28, 981–992.
4. Gay, F.; Engelhardt, M.; Terpos, E.; Wäsch, R.; Giaccone, L.; Auner, H.W.; Caers, J.; Gramatzki, M.; van de Donk, N.; Oliva, S.; et al. From transplant to novel cellular therapies in multiple myeloma: European Myeloma Network guidelines and future perspectives. Haematologica 2018, 103, 197–211.
5. Dimopoulos, M.A.; Jakubowiak, A.J.; McCarthy, P.L.; Orlowski, R.Z.; Attal, M.; Bladé, J.; Goldschmidt, H.; Weisel, K.C.; Ramasamy, K.; Zweegman, S.; et al. Developments in continuous therapy and maintenance treatment approaches for patients with newly diagnosed multiple myeloma. Blood Cancer J. 2020, 10, 17.
6. Bobin, A.; Liuu, E.; Moya, N.; Gruchet, C.; Sabirou, F.; Lévy, A.; Gardeney, H.; Nsiala, L.; Cailly, L.; Guidez, S.; et al. Multiple myeloma: An overview of the current and novel therapeutic approaches in 2020. Cancers 2020, 12, 2885.
7. Ito, S. Proteasome inhibitors for the treatment of multiple myeloma. Cancers 2020, 12, 265.
8. Gandolfi, S.; Laubach, J.P.; Hideshima, T.; Chauhan, D.; Anderson, K.C.; Richardson, P.G. The proteasome and proteasome inhibitors in multiple myeloma. Cancer Metastasis Rev. 2017, 36, 561–584.
9. Obeng, E.A.; Carlson, L.M.; Gutman, D.M.; Harrington, W.J., Jr.; Lee, K.P.; Boise, L.H. Proteasome inhibitors induce a terminal unfolded protein response in multiple myeloma cells. Blood 2006, 107, 4907–4916.
10. Kawabata, S.; Gills, J.J.; Mercado-Matos, J.R.; LoPiccolo, J.; Wilson, W.; Hollander, M.C.; Dennis, P.A. Synergistic effects of nelfinavir and bortezomib on proteotoxic death of NSCLC and multiple myeloma cells. Cell Death Dis. 2012, 3, e353.
11. Mimura, N.; Fulciniti, M.; Gorgun, G.; Tai, Y.T.; Cirstea, D.; Santo, L.; Hu, Y.; Fabre, C.; Minami, J.; Ohguchi, H.; et al. Blockade of XBP1 splicing by inhibition of IRE1α is a promising therapeutic option in multiple myeloma. Blood 2012, 119, 5772–5781.

12. Lipchick, B.C.; Fink, E.E.; Nikiforov, M.A. Oxidative stress and proteasome inhibitors in multiple myeloma. Pharmacol. Res. 2016, 105, 210–215.

13. Nerini-Molteni, S.; Ferrarini, M.; Cozza, S.; Caligaris-Cappio, F. Redox homeostasis modulates the sensitivity of myeloma cells to bortezomib. Br. J. Haematol. 2008, 141, 494–503.

14. Pinto, V.; Bergantim, R.; Caires, H.R.; Seca, H.; Guimarães, J.E.; Vasconcelos, M.H. Multiple myeloma: Available therapies and causes of drug resistance. Cancers 2020, 12, 407.

15. Rückrich, T.; Kraus, M.; Gogel, J.; Beck, A.; Ovaa, H.; Verdoes, M.; Overkleeft, H.S.; Kalbacher, H.; Driessen, C. Characterization of the ubiquitin-proteasome system in bortezomib-adapted cells. Leukemia 2009, 23, 1098–1105.

16. Balsas, P.; Galán-Malo, P.; Marzo, I.; Naval, J. Bortezomib resistance in a myeloma cell line is associated to PSMβ5 overexpression and polyploidy. Leuk. Res. 2012, 36, 212–218.

17. Acosta-Alvear, D.; Cho, M.Y.; Wild, T.; Buchholz, T.J.; Lerner, A.G.; Simakova, O.; Hahn, J.; Korde, N.; Landgren, O.; Maric, I.; et al. Paradoxical resistance of multiple myeloma to proteasome inhibitors by decreased levels of 19S proteasomal subunits. Elife 2015, 4, e08153.

18. Besse, A.; Stolze, S.C.; Rasche, L.; Weinhold, N.; Morgan, G.J.; Kraus, M.; Bader, J.; Overkleeft, H.S.; Besse, L.; Driessen, C. Carfilzomib resistance due to ABCB1/MDR1 overexpression is overcome by nelfinavir and lopinavir in multiple myeloma. Leukemia 2017, 32, 391–401.

19. Maiso, P.; Huynh, D.; Moschetta, M.; Sacco, A.; Aljawai, Y.; Mishima, Y.; Asara, J.M.; Roccaro, A.M.; Kimmelman, A.C.; Ghobrial, I.M. Metabolic signature identifies novel targets for drug resistance in multiple myeloma. Cancer Res. 2015, 75, 2071–2082.

20. Zaal, E.A.; Wu, W.; Jansen, G.; Zweegman, S.; Cloos, J.; Berkers, C.R. Bortezomib resistance in multiple myeloma is associated with increased serine synthesis. Cancer Metab. 2017, 5, 7.

21. Besse, L.; Besse, A.; Mendez-Lopez, M. A metabolic switch in proteasome inhibitor-resistant multiple myeloma ensures higher mitochondrial metabolism, protein folding and sphingomyelin synthesis. Haematologica 2019, 104, e415–e429.

22. Soriano, G.P.; Besse, L.; Li, N.; Kraus, M.; Besse, A.; Meeuwenoord, N.; Bader, J.; Everts, B.; den Dulk, H.; Overkleeft, H.S.; et al. Proteasome inhibitor-adapted myeloma cells are largely independent from proteasome activity and show complex proteomic changes, in particular in redox and energy metabolism. Leukemia 2016, 30, 2198–2207.

23. Méndez-Ferrer, S.; Bonnet, D.; Steensma, D.P.; Hasserjian, R.P.; Ghobrial, I.M.; Gribben, J.G.; Andreeff, M.; Krause, D.S. Bone marrow niches in haematological malignancies. Nat. Rev. Cancer 2020, 20, 285–298.

24. Wu, S.; Kuang, H.; Ke, J.; Pi, M.; Yang, D.H. Metabolic reprogramming induces immune cell dysfunction in the tumor microenvironment of multiple myeloma. Front. Oncol. 2020, 10, 591342.

25. Goel, A.; Spitz, D.R.; Weiner, G.J. Manipulation of cellular redox parameters for improving therapeutic responses in B-cell lymphoma and multiple yeloma. J. Biol. Chem. 2012, 113, 419–425.

26. Bustany, S.; Bourgeais, J.; Tchakarska, G.; Body, S.; Hérault, O.; Gouilleux, F.; Sola, B. Cyclin D1 unbalances the redox status controlling cell adhesion, migration, and drug resistance in myeloma cells. Oncotarget 2016, 7, 45214–45224.

27. Caillot, M.; Zylbersztejn, F.; Maitre, E.; Bourgeais, J.; Hérault, O.; Sola, B. ROS overproduction sensitises myeloma cells to bortezomib-induced apoptosis and alleviates tumour microenvironment-mediated cell resistance. Cells 2020, 9, 2357.

28. Tessoulin, B.; Descamps, G.; Moreau, P.; Maïga, S.; Lode, L.; Godon, C.; Marionneau-Lambot, S.; Oullier, T.; Le Gouill, S.; Amiot, M.; et al. PRIMA-1Met induces myeloma cell death independent of p53 by impairing the GSH/ROS balance. Blood 2014, 124, 1626–1636.

29. Saha, M.N.; Abdi, J.; Yang, Y.; Chang, H. miRNA-29a as a tumor suppressor mediates PRIMA-1Met-induced anti-myeloma activity by targeting c-Myc. Oncotarget 2016, 7, 7149–7160.

30. Saha, M.N.; Jiang, H.; Yang, Y.; Reece, D.; Chang, H. PRIMA-1Met/APR-246 displays high antitumor activity in multiple myeloma by induction of p73 and Noxa. Mol. Cancer Ther. 2013, 12, 2331–2341.

31. Tessoulin, B.; Descamps, G.; Dousset, C.; Amiot, M.; Pellat-Deceunynck, C. Targeting oxidative stress with auranofin or Prima-1Met to circumvent p53 or Bax/Bak deficiency in myeloma cells. Front. Oncol. 2019, 9, 128.

32. Teoh, P.J.; Bi, C.; Sintosebastian, C.; Tay, L.S.; Fonseca, R.; Chng, W.J. PRIMA-1 targets the vulnerability of multiple myeloma of deregulated protein homeostasis through the perturbation of ER stress via p73 demethylation. Oncotarget 2016, 7, 61806–61819.

33. Marin Hernandez, E.; Paek, H.; Li, M.; Ban, Y.; Karaga, M.K.; Shashidharamurthy, R.; Wang, X. Caffeic acid phenethyl ester exerts apoptotic and oxidative stress on human multiple myeloma cells. Investig. New Drugs 2018, 37, 837–848.

34. Raninga, P.V.; Di Trapani, G.; Vuckovic, S.; Tonissen, K.F. Cross-talk between two antioxidants, thioredoxin reductase and heme oxygenase-1, and therapeutic implications for multiple myeloma. Redox Biol. 2016, 8, 175–185.

35. Raninga, P.V.; Di Trapani, G.; Vuckovic, S.; Tonissen, K.F. TrxR1 inhibition overcomes both hypoxia-induced and acquired bortezomib resistance in multiple myeloma through NF-κβ inhibition. Cell Cycle 2016, 15, 559–572.

36. Zheng, Z.; Fan, S.; Zheng, J.; Huang, W.; Gasparetto, C.; Chao, N.J.; Hu, J.; Kang, Y. Inhibition of thioredoxin activates mitophagy and overcomes adaptive bortezomib resistance in multiple myeloma. J. Hematol. Oncol. 2018, 11, 29.

37. Sebastian, S.; Zhu, Y.X.; Braggio, E.; Shi, C.X.; Panchabhai, S.C.; Van Wier, S.A.; Ahmann, G.J.; Chesi, M.; Bergsagel, P.L.; Stewart, A.K.; et al. Multiple myeloma cells' capacity to decompose H2O2 determines lenalidomide sensitivity. Blood 2017, 129, 991–1007.

38. Du, T.; Song, Y.; Ray, A.; Chauhan, D.; Anderson, K.C. Proteomic analysis identifies mechanism(s) of overcoming bortezomib resistance via targeting ubiquitin receptor Rpn13. Leukemia 2021, 35, 550–561.

39. Song, I.S.; Kim, H.K.; Lee, S.R.; Jeong, S.H.; Kim, N.; Ko, K.S.; Rhee, B.D.; Han, J. Mitochondrial modulation decreases the bortezomib-resistance in multiple myeloma cells. Int. J. Cancer 2013, 133, 1357–1367.

40. Salem, K.; McCormick, M.L.; Wendlandt, E.; Zhan, F.; Goel, A. Copper–zinc superoxide dismutase-mediated redox regulation of bortezomib resistance in multiple myeloma. Redox Biol. 2015, 4, 23–33.

41. Shi, L.; Wu, Y.; Liang, D.; Feng, L. Scutellarein selectively targets multiple myeloma cells by increasing mitochondrial superoxide production and activating intrinsic apoptosis pathway. Biomed. Pharmacol. 2019, 109, 2109–2118.

42. Vatolin, S.; Phillips, J.G.; Jha, B.K.; Govindgari, S.; Hu, J.; Grabowski, D.; Parker, Y.; Lindner, D.J.; Zhong, F.; Distelhorst, C.W.; et al. Novel protein disulfide isomerase inhibitor with anticancer activity in multiple myeloma. Cancer Res. 2016, 76, 3340–3350.

43. Robinson, R.M.; Reyes, L.; Duncan, R.M.; Bian, H.; Reitz, A.B.; Manevich, Y.; McClure, J.J.; Champion, M.M.; Chou, C.J.; Sharik, M.E.; et al. Inhibitors of the protein disulfide isomerase family for the treatment of multiple myeloma. Leukemia 2019, 33, 1011–1022.

44. Robinson, R.M.; Reyes, L.; Duncan, R.M.; Bian, H.; Strobel, E.D.; Hyman, S.L.; Reitz, A.B.; Dolloff, N.G. Tuning isoform selectivity and bortezomib sensitivity with a new class of alkenyl indene PDI inhibitor. Eur. J. Med. Chem. 2020, 186, 111906.

45. Soncini, D.; Minetto, P.; Martinuzzi, C.; Becherini, P.; Fenu, V.; Guolo, F.; Todoerti, K.; Calice, G.; Contini, P.; Miglino, M.; et al. Amino acid depletion triggered by L-asparaginase sensitizes MM cells to carfilzomib by inducing mitochondria ROS-mediated cell death. Blood Adv. 2020, 4, 4312–4326.

46. Xu, S.; Zhou, T.; Doh, H.M.; Trinh, K.R.; Catapang, A.; Lee, J.T.; Braas, D.; Bayley, N.A.; Yamada, R.E.; Vasuthasawat, A.; et al. An HK2 antisense oligonucleotide induces synthetic lethality in HK1−HK2+ multiple myeloma. Cancer Res. 2019, 79, 2748–2760.

47. Xiang, Y.; Fang, B.; Liu, Y.; Yan, S.; Cao, D.; Mei, H.; Wang, Q.; Hu, Y.; Guo, T. SR18292 exerts potent antitumor effects in multiple myeloma via inhibition of oxidative phosphorylation. Life Sci. 2020, 256, 117971.

48. Raninga, P.V.; Di Trapani, G.; Vuckovic, S.; Bhatia, M.; Tonissen, K.F. Inhibition of thioredoxin 1 leads to apoptosis in drug-resistant multiple myeloma. Oncotarget 2015, 6, 15410–15424.

49. Sze, J.H.; Raninga, P.V.; Nakamura, K.; Casey, M.; Khanna, K.K.; Berners-Price, S.J.; Di Trapani, G.; Tonissen, K.F. Anticancer activity of a Gold(I) phosphine thioredoxin reductase inhibitor in multiple myeloma. Redox Biol. 2020, 28, 101310.

50. Mountjoy, L.; Sebastian, S.; Jain, T.; Hilal, T.; Gonzalez-Velez, M.; Girardo, M.; Ahmann, G.; Larsen, J.; Bergsagel, L.; Fonseca, R. Prediction of immunomodulatory drugs (IMiDs) sensitivity in myeloma via determination of baseline anti-oxidative stress capacity. Leukemia 2020, 34, 3060–3063.

51. Ray, A.; Song, Y.; Chauhan, D.; Anderson, K.C. Blockade of ubiquitin receptor Rpn13 in plasmacytoid dendritic cells triggers anti-myeloma immunity. Blood Cancer J. 2019, 9, 64.

52. Rizzieri, D.; Paul, B.; Kang, Y. Metabolic alterations and the potential for targeting metabolic pathways in the treatment of multiple myeloma. J. Cancer Metastasis Treat. 2019, 5, 26.

53. McBrayer, S.K.; Cheng, J.C.; Singhal, S.; Krett, N.L.; Rosen, S.T.; Shanmugam, M. Multiple myeloma exhibits novel dependence on GLUT4, GLUT8, and GLUT11: Implications for glucose transporter-directed therapy. Blood 2012, 119, 4686–4697.

54. Matsumoto, T.; Jimi, S.; Migita, K.; Takamatsu, Y.; Hara, S. Inhibition of glucose transporter 1 induces apoptosis and sensitizes multiple myeloma cells to conventional chemotherapeutic agents. Leuk. Res. 2016, 41, 103–110.

55. Dalva-Aydemir, S.; Bajpai, R.; Martinez, M.; Adekola, K.U.A.; Kandela, I.; Wei, C.; Singhal, S.; Koblinski, J.E.; Raje, N.S.; Rosen, S.T.; et al. Targeting the metabolic plasticity of multiple myeloma with FDA-approved ritonavir and metformin. Clin. Cancer Res. 2015, 21, 1161–1171.

56. Caillot, M.; Bourgeais, J.; Dakik, H.; Costé, É.; Mazure, N.M.; Lelièvre, É.; Coqueret, O.; Hérault, O.; Mazurier, F.; Sola, B. Cyclin D1 targets hexokinase 2 to control aerobic glycolysis in myeloma cells. Oncogenesis 2020, 9, 1–13.

57. Niedzwiecka, K.; Dylag, M.; Augustyniak, D.; Majkowska-Skrobek, G.; Cal-Bakowska, M.; Ko, Y.H.; Pedersen, P.L.; Goffeau, A.; Ułaszewski, S. Glutathione may have implications in the design of 3-bromopyruvate treatment protocols for both fungal and algal infections as well as multiple myeloma. Oncotarget 2017, 7, 65614–65626.

58. Ray, A.; Song, Y.; Du, T.; Chauhan, D.; Anderson, K.C. Preclinical validation of alpha-enolase (ENO1) as a novel immunometabolic target in multiple myeloma. Oncogene 2020, 39, 2786–2796.

59. Abdollahi, P.; Vandsemb, E.N.; Elsaadi, S.; Røst, L.M.; Yang, R.; Hjort, M.A.; Andreassen, T.; Misund, K.; Slørdahl, T.S.; Rø, T.B.; et al. Phosphatase of regenerating liver-3 regulates cancer cell metabolism in multiple myeloma. FASEB J. 2021, 35, e21344.

60. He, Y.; Wang, Y.; Liu, H.; Xu, X.; He, S.; Tang, J.; Huang, Y.; Miao, X.; Wu, Y.; Wang, Q.; et al. Pyruvate kinase isoform M2 (PKM2) participates in multiple myeloma cell proliferation, adhesion and chemoresistance. Leuk. Res. 2015, 39, 1428–1436.

61. Fujiwara, S.; Wada, N.; Kawano, Y.; Okuno, Y.; Kikukawa, Y.; Endo, S.; Nishimura, N.; Ueno, N.; Mitsuya, H.; Hata, H. Lactate, a putative survival factor for myeloma cells, is incorporated by myeloma cells through monocarboxylate transporters 1. Exp. Hematol. Oncol. 2015, 4, 12.

62. Chong, P.S.Y.; Zhou, J.; Lim, J.S.L.; Hee, Y.T.; Chooi, J.Y.; Chung, T.H.; Tan, Z.T.; Zeng, Q.; Waller, D.D.; Sebag, M.; et al. IL6 promotes a STAT3-PRL3 feedforward loop via SHP2 repression in multiple myeloma. Cancer Res. 2019, 79, 4679–4688.

63. Bolzoni, M.; Chiu, M.; Accardi, F.; Vescovini, R.; Airoldi, I.; Storti, P.; Todoerti, K.; Agnelli, L.; Missale, G.; Andreoli, R.; et al. Dependence on glutamine uptake and glutamine addiction characterize myeloma cells: A new attractive target. Blood 2016, 128, 667–679.

64. Effenberger, M.; Bommert, K.S.; Kunz, V.; Kruk, J.; Leich, E.; Rudelius, M.; Bargou, R.; Bommert, K. Glutaminase inhibition in multiple myeloma induces apoptosis via MYC degradation. Oncotarget 2017, 8, 85858–85867.

65. Gonsalves, W.I.; Jang, J.S.; Jessen, E.; Hitosugi, T.; Evans, L.A.; Jevremovic, D.; Pettersson, X.M.; Bush, A.G.; Gransee, J.; Anderson, E.I.; et al. In vivo assessment of glutamine anaplerosis into the TCA cycle in human pre-malignant and malignant clonal plasma cells. Cancer Metab. 2020, 8, 29.

66. Marlein, C.R.; Piddock, R.E.; Mistry, J.J.; Zaitseva, L.; Hellmich, C.; Horton, R.H.; Zhou, Z.; Auger, M.J.; Bowles, K.M.; Rushworth, S.A. CD38-driven mitochondrial trafficking promotes bioenergetic plasticity in multiple myeloma. Cancer Res. 2019, 79, 2285–2297.

67. Marlein, C.R.; Zaitseva, L.; Piddock, R.E.; Robinson, S.D.; Edwards, D.R.; Shafat, M.S.; Zhou, Z.; Lawes, M.; Bowles, K.M.; Rushworth, S.A. NADPH oxidase-2 derived superoxide drives mitochondrial transfer from bone marrow stromal cells to leukemic blasts. Blood 2017, 130, 1649–1660.

68. Tirado-Vélez, J.M.; Joumady, I.; Sáez-Benito, A.; Cózar-Castellano, I.; Perdomo, G. Inhibition of fatty acid metabolism reduces human myeloma cells proliferation. PLoS ONE 2012, 7, e46484.

69. Riz, I.; Hawley, T.S.; Marsal, J.W.; Hawley, R.G. Noncanonical SQSTM1/p62-Nrf2 pathway activation mediates proteasome inhibitor resistance in multiple myeloma cells via redox, metabolic and translational reprogramming. Oncotarget 2016, 7, 66360–66385.

70. Trotter, T.N.; Gibson, J.T.; Sherpa, T.L.; Gowda, P.S.; Peker, D.; Yang, Y. Adipocyte-lineage cells support growth and dissemination of multiple myeloma in bone. Am. J. Pathol. 2016, 186, 3054–3063.

71. Masarwi, M.; DeSchiffart, A.; Ham, J.; Reagan, M.R. Multiple myeloma and fatty acid metabolism. JBMR Plus 2019, 3, e10173.

72. Brown, L.M.; Gridley, G.; Pottern, L.M.; Baris, D.; Swanso, C.A.; Silverman, D.T.; Hayes, R.B.; Greenberg, R.S.; Swanson, G.M.; Schoenberg, J.B.; et al. Diet and nutrition as risk factors for multiple myeloma among blacks and whites in the United States. Cancer Causes Control 2001, 12, 117–125.

73. Hosgood, H.D., 3rd; Baris, D.; Zahm, S.H.; Zheng, T.; Cross, A.J. Diet and risk of multiple myeloma in Connecticut women. Cancer Causes Control 2007, 18, 1065–1076.

74. Lee, D.H.; Fung, T.T.; Tabung, F.K.; Marinac, C.R.; Devore, E.E.; Rosner, B.A.; Ghobrial, I.M.; Colditz, G.A.; Giovannucci, E.L.; Birmann, B.M. Prediagnosis dietary pattern and survival in patients with multiple myeloma. Int. J. Cancer 2020, 147, 1823–1830.

75. Thordardottir, M.; Lindqvist, E.K.; Lund, S.H.; Costello, R.; Burton, D.; Steingrimsdottir, L.; Korde, N.; Mailankody, S.; Eiriksdottir, G.; Launer, L.J.; et al. Dietary intake is associated with risk of multiple myeloma and its precursor disease. PLoS ONE 2018, 13, e0206047.

76. Janker, L.; Mayer, R.L.; Bileck, A.; Kreutz, D.; Mader, J.C.; Utpatel, K.; Heudobler, D.; Agis, H.; Gerner, C.; Slany, A. Metabolic, anti-apoptotic and immune evasion strategies of primary human myeloma cells indicate adaptations to hypoxia. Mol. Cell Proteom. 2019, 18, 936–953.

77. Suzuki, K.; Nishiwaki, K.; Yano, S. Treatment strategies considering micro-environment and clonal evolution in multiple myeloma. Cancers 2021, 13, 215.

78. Uckun, F.M. Overcoming the immunosuppressive tumor microenvironment in multiple myeloma. Cancers 2021, 13, 2018.

79. Díaz-Tejedor, A.; Lorenzo-Mohamed, M.; Puig, N.; García-Sanz, R.; Mateos, M.V.; Garayoa, M.; Paíno, T. Immune system alterations in multiple myeloma: Molecular mechanisms and therapeutic strategies to reverse immunosuppression. Cancers 2021, 13, 1353.

80. Tamura, H.; Ishibashi, M.; Sunakawa-Kii, M.; Inokuchi, K. PD-L1-PD-1 pathway in the pathophysiology of multiple myeloma. Cancers 2020, 12, 924.

81. Tremblay-Lemay, R.; Rastgoo, N.; Chang, H. Modulating PD-L1 expression in multiple myeloma: An alternative strategy to target the PD-1/PD-L1 pathway. J. Hematol. Oncol. 2018, 11, 46.

82. Ryu, D.; Kim, S.J.; Hong, Y.; Jo, A.; Kim, N.; Kim, H.J.; Lee, H.O.; Kim, K.; Park, W.Y. Alterations in the transcriptional programs of myeloma cells and the microenvironment during extramedullary progression affect proliferation and immune evasion. Clin. Cancer Res. 2020, 26, 935–944.

83. Barsoum, I.B.; Smallwood, C.A.; Siemens, D.R.; Graham, C.H. A Mechanism of hypoxia-mediated escape from adaptive immunity in cancer cells. Cancer Res. 2014, 74, 665–674.

84. Görgün, G.T.; Whitehill, G.; Anderson, J.L.; Hideshima, T.; Maguire, C.; Laubach, J.; Raje, N.; Munshi, N.C.; Richardson, P.G.; Anderson, K.C. Tumor-promoting immune-suppressive myeloid-derived suppressor cells in the multiple myeloma microenvironment in humans. Blood 2013, 121, 2975–2987.

85. de Beule, N.; de Veirman, K.; Maes, K.; de Bruyne, E.; Menu, E.; Breckpot, K.; de Raeve, H.; van Rampelbergh, R.; van Ginderachter, J.A.; Schots, R.; et al. Tumour-associated macrophage-mediated survival of myeloma cells through STAT3 activation. J. Pathol. 2017, 241, 534–546.

86. Sarkar, S.; Germeraad, W.T.V.; Rouschop, K.M.A.; Steeghs, E.M.P.; van Gelder, M.; Bos, G.M.J.; Wieten, L. Hypoxia induced impairment of NK cell cytotoxicity against multiple myeloma can be overcome by IL-2 activation of the NK cells. PLoS ONE 2013, 8, e64835.

87. Calcinotto, A.; Filipazzi, P.; Grioni, M.; Iero, M.; de Milito, A.; Ricupito, A.; Cova, A.; Canese, R.; Jachetti, E.; Rossetti, M.; et al. Modulation of microenvironment acidity reverses anergy in human and murine tumor-infiltrating T lymphocytes. Cancer Res. 2012, 72, 2746–2756.

88. Bohn, T.; Rapp, S.; Luther, N.; Klein, M.; Bruehl, T.J.; Kojima, N.; Aranda Lopez, P.; Hahlbrock, J.; Muth, S.; Endo, S.; et al. Tumor immunoevasion via acidosis-dependent induction of regulatory tumor-associated macrophages. Nat. Immunol. 2018, 19, 1319–1329.

89. Anderson, K.C. Progress and paradigms in multiple myeloma. Clin. Cancer Res. 2016, 22, 5419–5427.

90. Milan, E.; Fabbri, M.; Cenci, S. Autophagy in plasma cell ontogeny and malignancy. J. Clin. Immunol. 2016, 36 (Suppl. 1), 18–24.

91. Di Lernia, G.; Leone, P.; Solimando, A.G.; Buonavoglia, A.; Saltarella, I.; Ria, R.; Ditonno, P.; Silvestris, N.; Crudele, L.; Vacca, A.; et al. Bortezomib treatment modulates autophagy in multiple myeloma. J. Clin. Med. 2020, 9, 552.

92. Fucci, C.; Resnati, M.; Riva, E.; Perini, T.; Ruggieri, E.; Orfanelli, U.; Paradiso, F.; Cremasco, F.; Raimondi, A.; Pasqualetto, E.; et al. The interaction of the tumor suppressor FAM46C with p62 and FNDC3 proteins integrates protein and secretory homeostasis. Cell Rep. 2020, 32, 108162.

93. Zhong, Y.; Tian, F.; Ma, H.; Wang, H.; Yang, W.; Liu, Z.; Liao, A. FTY720 induces ferroptosis and autophagy via PP2A/AMPK pathway in multiple myeloma cells. Life Sci. 2020, 260, 118077.

94. Li, J.; Cao, F.; Yin, H.L.; Huang, Z.J.; Lin, Z.T.; Mao, N.; Sun, B.; Wang, G. Ferroptosis: Past, present and future. Cell Death Dis. 2020, 11, 88.

95. Gao, M.; Kong, Y.; Yang, G.; Gao, L.; Shi, J. Multiple myeloma cancer stem cells. Oncotarget 2016, 7, 35466–35477.

96. Galadari, S.; Rahman, A.; Pallichankandy, S.; Thayyullathil, F. Reactive oxygen species and cancer paradox: To promote or to suppress? Free Radic. Biol. Med. 2017, 104, 144–164.

97. Tagde, A.; Singh, H.; Kang, M.H.; Reynolds, C.P. The glutathione synthesis inhibitor buthionine sulfoximine synergistically enhanced melphalan activity against preclinical models of multiple myeloma. Blood Cancer J. 2014, 4, e229.
98. Gourzones, C.; Bellanger, C.; Lamure, S.; Gadacha, O.; Garcia De Paco, E.; Vincent, L.; Cartron, G.; Klein, B.; Moreaux, J. Antioxidant defenses confer resistance to high dose melphalan in multiple myeloma cells. Cancers 2019, 11, 439.
99. Zub, K.A.; Mittelstedt Leal de Sousa, M.; Sarno, A.; Sharma, A.; Demirovic, A.; Rao, S.; Young, C.; Aas, P.A.; Ericsson, I.; Sundan, A.; et al. Modulation of cell metabolic pathways and oxidative stress signaling contribute to acquired melphalan resistance in multiple myeloma cells. PLoS ONE 2015, 10, e0119857.
100. Richardson, P.G.; Oriol, A.; Larocca, A.; Bladé, J.; Cavo, M.; Rodriguez-Otero, P.; Leleu, X.; Nadeem, O.; Hiemenz, J.W.; Hassoun, H.; et al. HORIZON (OP-106) investigators. Melflufen and dexamethasone in heavily pretreated relapsed and refractory multiple myeloma. J. Clin. Oncol. 2021, 39, 757–767.
101. Chauhan, D.; Ray, A.; Viktorsson, K.; Spira, J.; Paba-Prada, C.; Munshi, N.; Richardson, P.; Lewensohn, R.; Anderson, K.C. In vitro and in vivo antitumor activity of a novel alkylating agent, melphalan-flufenamide, against multiple myeloma cells. Clin. Cancer Res. 2013, 19, 3019–3031.
102. Hu, Y.; Lu, W.; Chen, G.; Zhang, H.; Jia, Y.; Wei, Y.; Yang, H.; Zhang, W.; Fiskus, W.; Bhalla, K.; et al. Overcoming resistance to histone deacetylase inhibitors in human leukemia with the redox modulating compound β-phenylethyl isothiocyanate. Blood 2010, 116, 2732–2741.
103. Imai, Y.; Hirano, M.; Kobayashi, M.; Futami, M.; Tojo, A. HDAC inhibitors exert anti-myeloma effects through multiple modes of action. Cancers 2019, 11, 475.