Targeted Oncology (2022) 17:383–405
https://doi.org/10.1007/s11523-022-00897-8

REVIEW ARTICLE

What's Old is New: The Past, Present and Future Role of Thalidomide in the Modern-Day Management of Multiple Myeloma

Bruno Almeida Costa[1] · **Tarek H. Mouhieddine**[2] · **Joshua Richter**[2]

Accepted: 6 June 2022 / Published online: 30 June 2022

Abstract

Immunomodulatory drugs (IMiDs) have become an integral part of therapy for both newly diagnosed and relapsed/refractory multiple myeloma (RRMM). IMiDs bind to cereblon, leading to the degradation of proteins involved in B-cell survival and proliferation. Thalidomide, a first-generation IMiD, has little to no myelosuppressive potential, negligible renal clearance, and long-proven anti-myeloma activity. However, thalidomide's adverse effects (e.g., somnolence, constipation, and peripheral neuropathy) and the advent of more potent therapeutic options has led to the drug being less frequently used in many countries, including the US and Canada. Newer-generation IMiDs, such as lenalidomide and pomalidomide, are utilized far more frequently. In numerous previous trials, salvage therapy with thalidomide (50–200 mg/day) plus corticosteroids (with or without selected cytotoxic or targeted agents) has been shown to be effective and well-tolerated in the RRMM setting. Hence, thalidomide-based regimens remain important alternatives for heavily pretreated patients, especially for those who have no access to novel therapies and/or are not eligible for their use (due to renal failure, high-grade myelosuppression, or significant comorbidities). Ongoing and future trials may provide further insights into the current role of thalidomide, especially by comparing thalidomide-containing regimens with protocols based on newer-generation IMiDs and by investigating thalidomide's association with novel therapies (e.g., antibody-drug conjugates, bispecific antibodies, and chimeric antigen receptor T cells).

Key Points

Thalidomide, the first immunomodulatory drug approved for multiple myeloma, has been infrequently used in the US, given its adverse effects (e.g., somnolence, constipation, and peripheral neuropathy) and the advent of more potent therapeutic options.

Numerous clinical studies have demonstrated thalidomide's effectiveness and safety in newly diagnosed and relapsed/refractory multiple myeloma, as well as its low myelotoxicity and negligible renal clearance.

Salvage regimens combining thalidomide and corticosteroids (with/without selected cytotoxic or targeted agents) remain useful in heavily pretreated patients who are ineligible for novel anti-myeloma therapies (e.g., due to poor bone marrow reserve or severe renal dysfunction).

✉ Joshua Richter
joshua.richter@mountsinai.org

[1] Department of Medicine, Mount Sinai Morningside and West, Icahn School of Medicine at Mount Sinai, New York, NY, USA

[2] Division of Hematology and Medical Oncology, Tisch Cancer Institute, Icahn School of Medicine at Mount Sinai, 1 Gustave L. Levy Place, Box 1185, New York, NY 10029, USA

1 Introduction

Multiple myeloma (MM) is a hematologic malignancy characterized by abnormal plasma cell (PC) proliferation, increased production of monoclonal protein, and end-organ damage [1, 2]. Diagnosis requires ≥ 10% clonal PCs on bone marrow (BM) examination or a biopsy-proven plasmacytoma plus at least one myeloma-defining event, such as hypercalcemia, renal dysfunction, anemia, lytic bone lesions, or a biomarker of malignancy (e.g., ≥ 60% clonal PCs within the BM, involved/uninvolved free light chain ratio ≥ 100, or more than one focal lesion on magnetic resonance imaging) [3]. In 2020, according to the World Health Organization (WHO), a total of 176,404 new patients fulfilled such criteria worldwide, making MM the second most common blood cancer after lymphoma [4]. Among affected patients, 63% were older than 65 years of age—a repercussion of the age association of MM's precursor stage, monoclonal gammopathy of undetermined significance (MGUS) [5, 6].

From the first description of MM in the literature as part of Samuel Solly's case series in 1844 [7] to the landmark trial that confirmed the safety and efficacy of the chimeric antigen receptor (CAR) T-cell idecabtagene vicleucel (idecel) in 2021 [8], remarkable advances have been made in elucidating the clinicopathological aspects and potential therapeutic targets of MM [9]. As a result, many treatment strategies are currently available. Choosing a frontline regimen depends on efficacy, local availability, risk stratification, autologous stem cell transplant (ASCT) eligibility, and patient-specific factors (e.g., performance status [PS], comorbidities and preferences) [10]. However, due to the eventual emergence of genetically heterogeneous subclones of myeloma cells, even individuals who achieved deep responses will eventually relapse and need subsequent lines of therapy [11, 12].

The list of drug classes approved for MM includes corticosteroids, alkylating agents, anthracyclines, topoisomerase II inhibitors, proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), histone deacetylase inhibitors (iHDACs), selective inhibitors of nuclear export (SINEs), monoclonal antibodies (mAbs), antibody-drug conjugates (ADCs), bispecific antibodies (BsAbs), and CAR T cells [13–16]. Moving from bench to bedside, most of those therapies were developed over the last 20 years, leading to significant prognostic implications [9, 17]. The 5-year relative survival rate among US patients, for example, increased from 28.6% in 1986–1993 to 55.6% in 2011–2017 [18, 19]. One of the pivotal discoveries within this period was the anti-myeloma activity of thalidomide, an old drug infamous for its teratogenic effects [20].

In Europe, thalidomide is still widely studied and incorporated into clinical practice, especially after the phase III CASSIOPEIA trial supported the use of bortezomib, thalidomide, and dexamethasone (VTD) plus daratumumab (Dara-VTD) as a first-line regimen for newly diagnosed MM (NDMM) [21, 22]. However, in the US and Canada, the drug has largely been replaced by newer generations of IMiDs (lenalidomide and pomalidomide)—a direct consequence of thalidomide's association with multiple adverse events (AEs), including somnolence, constipation, peripheral neuropathy (PN), and venous thromboembolism (VTE) [23]. Moreover, cereblon E3 ligase modulators (CELMoDs), such as iberdomide (CC-220) and CC-92480, are now slowly making their way into US Food and Drug Administration (FDA) approval [24]. As a result, the current role of thalidomide in both the upfront and salvage settings is less clearly defined; yet, this older agent has the advantage of providing significant anti-myeloma activity even in patients with severely compromised kidney and/or marrow function owing to its minimal renal clearance and relative lack of myelotoxicity [25].

From this perspective, the present review summarizes the available data on thalidomide's history, mechanisms and applications in MM, with a particular focus on its role in relapsed/refractory MM (RRMM). Our ultimate goal is to provide general guidance for physicians who do not currently use this drug in clinical practice, especially considering that some heavily pretreated patients may not be eligible for some of the novel targeted or immune-based therapies.

2 Historical Background

Thalidomide (α-*N*-phthalimido-glutarimide) was first introduced in 1956 by the West German pharmaceutical company Chemie Grünenthal [26]. Initially marketed as a well-tolerated sedative and antiemetic agent to reduce pregnancy-related morning sickness, thalidomide rapidly gained widespread popularity—by 1960, the drug was being sold in over 40 countries [27, 28]. Early preclinical safety evaluation using pregnant rats and mice showed no interference with embryonic development [29]; however, approval in the US was not obtained at that time, mainly due to FDA concerns about neurotoxicity [30]. Shortly afterwards, two independent clinicians (Lenz in Germany and McBride in Australia) reported the association between human prenatal exposure to thalidomide and congenital limb abnormalities, including phocomelia [31, 32]. By 1962, thalidomide had been withdrawn from most commercial markets, leaving a legacy of approximately 10,000 affected infants [30, 32]. Despite the resistance of some rodent species to thalidomide embryopathy, ensuing studies with rabbits, primates, and fish species were able to demonstrate the drug's teratogenicity [30–32]. Thalidomide's newly discovered property prompted its investigation as an antineoplastic agent during

the early 1960s. Nevertheless, two clinical studies including patients with advanced tumors of various types failed to demonstrate evidence of objective response attributable to the drug [33, 34].

In 1965, Jacob Sheskin reported thalidomide's ability to control erythema nodosum leprosum (ENL) [35]. This triggered a perspective shift on the drug from a teratogenic antiemetic to a potent anti-inflammatory and immunomodulatory agent [36]. In 1971, a WHO-coordinated, male-only clinical trial confirmed thalidomide's effectiveness in treating acute leprosy reactions [37]. However, the drug only became FDA-approved for ENL in 1998, after studies identified an immunological basis for its clinical effects [28]. The FDA subsequently supported thalidomide's experimental use in other inflammatory disorders (e.g., sarcoidosis, cutaneous lupus erythematosus, Behcet's syndrome, ankylosing spondylitis, rheumatoid arthritis, inflammatory bowel diseases, recurrent aphthous stomatitis, and chronic graft-versus-host disease), with the achievement of promising results [29, 38, 39].

Throughout the 1990s, the number of publications related to thalidomide increased exponentially, as well as the off-label uses of the drug [40, 41]. In this scenario, efforts on elucidating the teratogenic mechanisms of thalidomide eventually renewed the interest in its potential use for cancer treatment [42]. In 1994, thalidomide was shown to inhibit angiogenesis, a key process in fetal limb development [43]. Already a well-known hallmark of solid tumors, angiogenesis was also correlated to blood cancer progression by that time [44–46]. Soon, multiple preclinical and clinical studies evaluating the antineoplastic activity of thalidomide were initiated [27]. Despite varying degrees of success in solid tumors, remarkable benefits were observed in some hematologic malignancies, especially MM [27, 47]. In 2006, after mounting evidence of its efficacy, thalidomide became the first new agent in over a decade to gain FDA approval for MM. In 2008, a similar approval was obtained from the European Medicines Agency (EMA) [48, 49].

3 Mechanisms of Action

The abnormal PC proliferation inherent to MM occurs predominantly within the BM, suggesting the importance of the BM microenvironment in supporting disease activity [50]. BM angiogenesis, for example, progressively increases along the spectrum of PC disorders—from the more benign MGUS stage, throughout the smoldering phase, and up to overt MM [51]. This is secondary to the direct production of angiogenic molecules by malignant PCs, as well as their induction in BM stromal cells (BMSCs) [52, 53]. Moreover, tumor cell expression of basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF), hepatocyte growth factor (HGF), and their respective receptors creates autocrine loops of growth, survival, and migration [53–55]. Accordingly, BM microvascular density (MVD) has been shown to have a direct correlation with the PC labeling index and inverse correlation with the overall survival (OS) of MM patients [45, 56–59]. In addition, BM angiogenesis has a similar prognostic value in patients with solitary plasmacytomas [60].

In 1994, using a rabbit cornea micropocket assay, D'Amato et al. demonstrated that thalidomide inhibited bFGF-induced angiogenesis [43]. Using a model of murine cornea, his group then showed the drug's ability to suppress VEGF-induced angiogenesis [61]. Later, thalidomide was found to attenuate nitric oxide-driven angiogenesis [62, 63] and downregulate other key angiogenic genes (e.g., angiopoietin-1, insulin-like growth factor [IGF]-1, and IGF binding protein-3) [64]. Since BM neovascularization is a critical event for MM progression, thalidomide attains disease control by simultaneously targeting multiple angiogenesis pathways, ultimately decreasing the BM MVD in responders [65–67]. In contrast, anti-VEGF drugs targeting fewer angiogenesis pathways (e.g., bevacizumab, sorafenib, and vandetanib) failed to demonstrate a significant improvement in patient outcomes [65].

Besides their antiangiogenic effect, thalidomide and its analogs induce tumor cell apoptosis via activation of caspase-8, enhanced sensitivity to Fas and downregulation of cellular inhibitor of apoptosis protein-2 (cIAP-2) [68]. These agents can also suppress BMSC production of important mediators of myeloma cell proliferation, such as tumor-necrosis factor (TNF)-α and interleukin (IL)-6 [27–29]. Contrary to expectations, IL-6 blockade with siltuximab failed to improve OS or progression-free survival (PFS) in previous trials [69]. Thalidomide further hinders tumor growth via downregulation of surface adhesion molecules mediating myeloma cell interactions with the surrounding extracellular matrix and BMSCs [70, 71]. Moreover, IMiDs can potentiate T-cell proliferation, differentiation, and survival by augmenting B7-CD28 co-stimulatory signals. Apart from enhancing tumor antigen presentation by dendritic cells, thalidomide directly induces tyrosine phosphorylation of CD28, promoting activation of phosphoinositide-3-kinase (PI3K) and nuclear factor-kappa B (NF-κB) [70–73]. The resultant stimulation of interferon (IFN)-γ and IL-2 production boosts the number and function of natural killer (NK) cells, further improving the anti-myeloma immune response in IMiD-treated patients [70, 74]. Accordingly, published data on IFN use as an anti-myeloma agent demonstrated a significant, although limited, improvement in clinical outcomes [75].

Despite in vivo and in vitro demonstration of a wide range of pharmacological effects, thalidomide's primary molecular target remained uncertain until 2010, when binding to cereblon (CRBN) was identified as the key mechanism of its teratogenicity [76, 77]. Shortly afterwards, CRBN

expression was also found to be an essential requirement for the anti-myeloma activity of IMiDs [78]. CRBN serves as a substrate receptor of the Cullin-Ring ligase 4 E3 ubiquitin ligase complex ($CRL4^{CRBN}$), which recognizes substrates for ubiquitination and proteasomal degradation [79]. The binding of thalidomide to CRBN causes an allosteric modification of the $CRL4^{CRBN}$ complex, changing its substrate specificity [80]. This can lead to several downstream effects, depending on the proteins subsequently ubiquitinated [81]. Thalidomide-induced degradation of spalt-like transcription factor 4 (SALL4) and tumor protein 63 (TP63), for example, causes fetal malformations [82, 83]. Meanwhile, degradation of the zinc-finger transcription factors Ikaros (IKZF1) and Aiolos (IKZF3) exerts cytotoxic effects in myeloma cells, mainly through downregulation of IFN regulatory factor 4 (IRF4) and MYC [84, 85]. Thalidomide can also trigger the degradation of casein kinase 1α (CK1α), a pro-growth and anti-apoptotic enzyme in B-cell malignancies [86]; however, CK1α ubiquitination is substantially more extensive with lenalidomide [79]. Additionally, pomalidomide is more effective in promoting degradation of AT-rich interactive domain-containing protein 2 (ARID2), a critical protein for MYC expression [87]. Thus, substrate recognition by CRBN differs depending on the ligand structure, creating potential for sequential use of different IMiDs as a way to overcome myeloma cell resistance [79, 87]. Figures 1 and 2 illustrate the mechanisms of action of thalidomide and its analogs.

4 Therapeutic Applications in Multiple Myeloma

4.1 Use in Relapsed/Refractory Multiple Myeloma

After decades of ineffective therapies primarily based on traditional empiricism (e.g., orange peel infusions, rhubarb

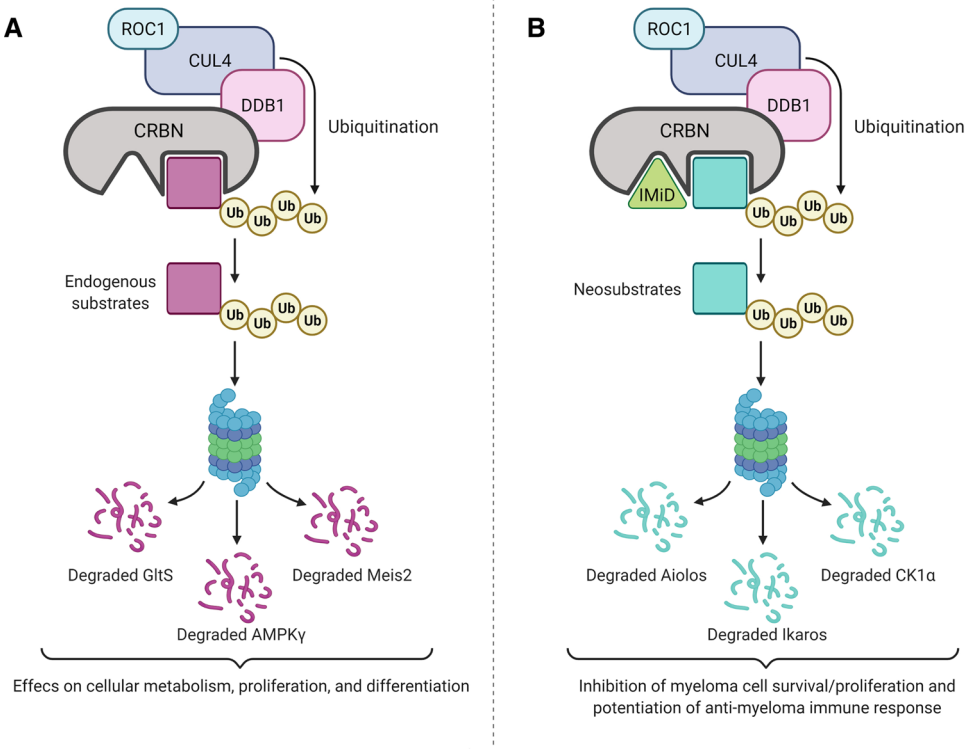

Fig. 1 CRBN interacts with DDB1, Cul4A or Cul4B, and RoC1 to form the $CRL4^{CRBN}$. CRBN functions as a receptor with a conserved tryptophan pocket in the complex, which leads to protein targeting for degradation via the ubiquitin-proteasome pathway. **a** Under normal, physiologic circumstances, binding of endogenous ligands to CRBN regulates cell metabolism, proliferation, and differentiation. Known substrates include GltS, AMPKγ, and Meis2. **b** Exposure to an IMiD leads to allosteric modification, changing the substrate specificity of CRBN and increasing degradation of Aiolos, Ikaros, and CK1α, among other proteins. Depletion of these neosubstrates leads to pleiotropic anti-myeloma effects, such as IRF4 and MYC downregulation in myeloma cells, increased IL-2 production, and enhanced immune response against the tumor. *CRBN* cereblon, *DDB1* DNA damage-binding protein-1, *Cul4* Cullin 4, *RoC1* regulator of Cullins 1, *$CRL4^{CRBN}$* Cullin-Ring ligase 4 E3 ubiquitin ligase complex, *GltS* glutamine synthase, *AMPKγ* adenosine monophosphate-activated protein kinase gamma subunit, *Meis2* Meis homeobox 2, *IMiD* immunomodulatory drug, *CK1α* casein kinase 1α, *IRF4* interferon regulatory factor 4, *IL* interleukin

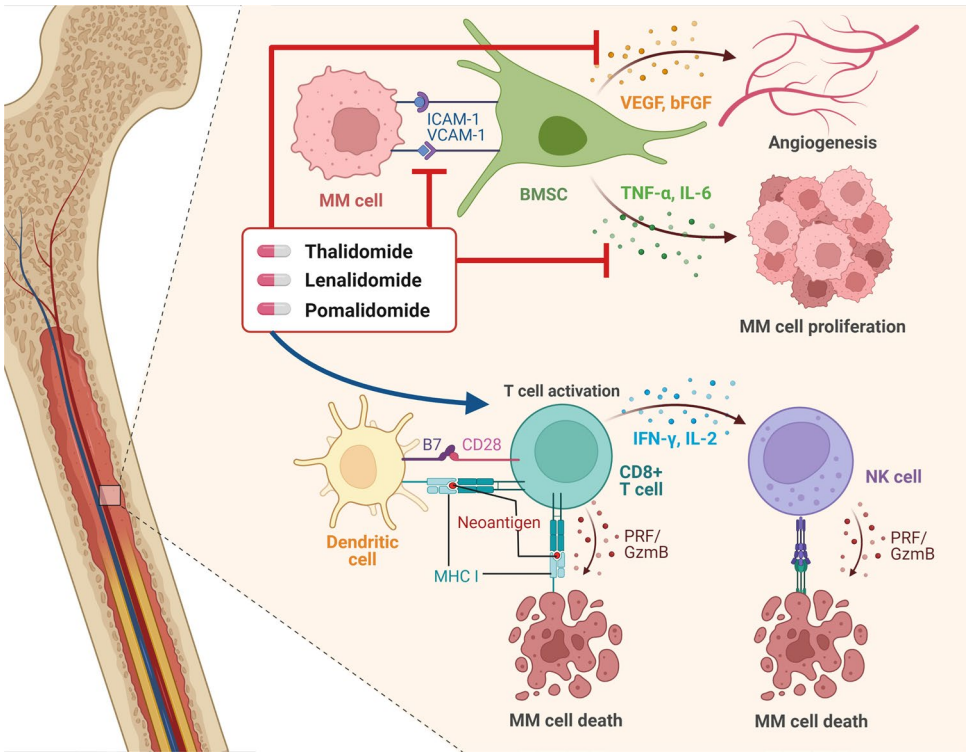

Fig. 2 IMiDs target not only the MM cell but also the BM microenvironment. By suppressing BMSC production of IL-6 and TNFα, these agents decrease MM cell proliferation. This is potentiated via downregulation of surface molecules that mediate BMSC–MM cell interactions, such as ICAM-1 and VCAM-1. Anti-angiogenesis occurs via modulation of chemotactic factors involved in endothelial cell migration, such as VEGF and bFGF. By inducing tumor antigen presentation by dendritic cells and tyrosine phosphorylation of CD28, IMiDs stimulate T-cell activation. The resultant increase in IFN-γ and IL-2 levels also enhances NK cell activity. PRF/GzmB is the main pathway of target cell apoptosis, but granzyme-independent mechanisms can also occur. *IMiDs* immunomodulatory drugs, *MM* multiple myeloma, *BM* bone marrow, *BMSC* bone marrow stem cell, *IL* interleukin, *TNF* tumor necrosis factor, *ICAM-1* intercellular adhesion molecule-1, *VCAM-1* vascular cell adhesion molecule-1, *VEGF* vascular endothelial growth factor, *bFGF* basic fibroblast growth factor, *IFN* interferon, *NK* natural killer, *PRF* perforin, *GzmB* granzyme B, *MHC I* major histocompatibility complex I

pills, and urethane), successful anti-myeloma treatment using prednisone and lower doses of melphalan (80–100 mg/m^2) was introduced in the late 1960s [88, 89]. Various dosing regimens and combinations of alkylating agents, with or without corticosteroids, were investigated during the following years [90]. In 1983, monotherapy with higher doses of melphalan (140 mg/m^2) was demonstrated to improve complete remission rates, with the drawback of profound myelosuppression [91]. In the late 1980s, Barlogie et al. suggested ASCT as a measure to hasten patient hematologic recovery after marrow-ablative chemotherapy and total body irradiation [92, 93]. In 1996, a randomized controlled trial (RCT) of 200 untreated adults under age 65 years showed that high-dose chemotherapy followed by ASCT (HDC/ASCT) could improve overall response rate (ORR), event-free survival (EFS), and OS [94]. This strategy was then established as a standard frontline treatment for transplant-eligible (TE) NDMM patients [88]. Later, further studies supported the alternative of reserving ASCT for the first disease relapse [95] and the possibility of a second peripheral blood stem cell (PBSC) infusion as part of salvage therapy in selected cases [96]. Even so, therapeutic options for RRMM remained scarce and of limited clinical benefit [97]. Some of the available salvage regimens, such as vincristine/doxorubicin/dexamethasone (VAD) and etoposide/dexamethasone/cytarabine/cisplatin (EDAP), could lead to unacceptable AEs in a patient population mainly composed of elderly adults with numerous comorbidities and cumulative toxicity from previous therapies [97, 98].

As higher BM angiogenesis favored MM progression and thalidomide possessed antiangiogenic properties, the drug emerged as an investigational therapy for compassionate use in patients with advanced disease [25]. Phase I data were first described by Singhal et al. in 1999. In that landmark study, 84 patients with RRMM received oral thalidomide monotherapy for a median of 80 days. If tolerated, an initial dose of 200 mg nightly was increased by 200 mg every 2 weeks until reaching 800 mg/day. Even though study participants had been heavily pretreated (e.g., 90% received at least one cycle of HDC/ASCT), 32% of them achieved a

≥ 25% decline in serum or urine paraprotein levels, and 10% had nearly complete or complete response (CR) [99, 100]. Of the 27 patients with a paraprotein response, 21 could have a follow-up BM examination, which showed a concurrent BM response (defined as < 5% PCs) in 81% of cases [100]. Such results stimulated multiple subsequent trials, further evaluating thalidomide's efficacy for RRMM, either as single-agent or as part of combination regimens [99]. Table 1 synthesizes data from clinical studies in which at least 25 patients received a thalidomide-based regimen for RRMM [100–157]. The ORR, defined as the percentage of patients who had at least a partial response (PR), and the PFS were reported according to International Myeloma Working Group (IMWG) uniform response criteria [158].

In a systematic review of 42 trials of single-agent thalidomide (50–800 mg/day) for RRMM, ≥ PR was seen in 479 of 1629 patients (29.4%, 95% confidence interval [CI] 27–32%). Among the 17 studies that assessed median time to response (TTR), 65% reported a period of between 1 and 2 months. The median EFS and OS were reported at 12 and 14 months, respectively. Severe AEs (grade 3–4) included somnolence (11%), constipation (16%), PN (6%), rash (3%), VTE (3%), and cardiac complications (2%) [159]. Meanwhile, a multicentric RCT coordinated by the Intergroupe Francophone du Myélome (IFM) compared the efficacy and safety of two doses of thalidomide (100 and 400 mg/day). Patients receiving 100 mg/day had significantly lower rates of most AEs, while 1-year OS was similar in both study arms after intention-to-treat (ITT) analysis [143]. The OPTIMUM trial, which compared dexamethasone against three different doses of thalidomide (100, 200, or 400 mg/day), also demonstrated that it is difficult for patients to tolerate a higher dose for the whole treatment duration—in the 400 mg/day arm, average dose intensity was 256 mg/day [144]. Noteworthy, treatment response appears to be higher if thalidomide is started after the first relapse or progression than later in the disease course [130].

Thalidomide's clinical efficacy in advanced MM and synergistic activity with dexamethasone in myeloma cell lines prompted extensive evaluation of the thalidomide/dexamethasone (TD) combination as salvage therapy [25, 160, 161]. In a systematic review of 12 trials, among 451 RRMM patients treated with TD, 209 (46%, 95% CI 42–51%) achieved at least a PR. Treatment-related toxicity was comparable with thalidomide monotherapy. Dexamethasone's median starting dose was 200 mg/day and the median target dose was 350 mg/day. While six studies reported an EFS with a weighted median value of 8 months, five studies reported an OS with a weighted median value of 27 months [161]. In 2012, Zamagni et al. investigated TD as a therapy for first relapse in 100 patients, achieving an ORR of 46%, a median PFS of 21 months, and a median OS of 43 months [142]. Subsequently, Hjorth et al. compared the efficacy of TD and bortezomib/dexamethasone (VD) in 131 patients relapsing after or refractory to initial melphalan-based treatment. Even though both study arms had a similar ORR (55% for TD, 63% for VD) and median PFS (9.0 months for TD, 7.2 for VD), rates of AEs were significantly higher in the VD arm [145].

Since thalidomide was found to lack myelosuppressive potential, the addition of conventional cytotoxic agents to salvage regimens became an attractive approach. Worldwide, many groups started to evaluate the association of TD or thalidomide/prednisolone (TP) with different alkylating agents and anthracyclines [25, 162]. A German protocol consisting of hyperfractionated intravenous cyclophosphamide (HyperCy; 300 mg/m^2 every 12 h on days 1–3), pulsed oral dexamethasone (20 mg/m^2 once daily on days 1–4, 9–12, 17–20), and escalating-dose thalidomide (100–400 mg/day) promoted CR, PR, and minor response (MR) rates of 4, 68, and 12%, respectively. However, there was high toxicity in study participants, including grade 3–4 neutropenia (86%), severe PN (16%) and VTE (8%) [111]. Later, a Spanish group evaluated the efficacy of an oral combination of thalidomide (200–800 mg/day), cyclophosphamide (50 mg/day) and pulsed dexamethasone (40 mg/day for 4 days every 3 weeks) in 71 RRMM patients. After 3 months of therapy, CR, PR and MR rates were 2%, 55% and 26%, respectively. After 6 months of therapy, most responses were maintained and the CR rate increased to 10%, although a small group of patients ($n = 6$) progressed. The replacement of HyperCy by continuous oral cyclophosphamide allowed a considerable decline in grade 3–4 neutropenia rates (from 86 to 10%) [116]. In a Korean real-world data (RWD) study, patients treated with TD plus cyclophosphamide ($n = 236$) and TP plus melphalan ($n = 140$) had a similar ORR (72 vs. 65%, $p = 0.121$). Analysis of all study subjects revealed a median PFS of 10.4 months and median OS of 28.0 months, with the drawback of a 10% rate of infections warranting intensive supportive care [152]. Due to its established role for relapsed lymphomas and better toxicity profile compared with other alkylating agents, bendamustine has also been tested in the RRMM setting [135, 149, 154, 163–166]. After phase I data showed ≥ PR in 24 of 28 patients who received TP plus bendamustine 60 mg/m^2 (B60) [135], Schey et al. and Mian et al. evaluated TD plus B60, obtaining an ORR of 41.5 and 37%, respectively [149, 154]. TD has also been tested in association with doxorubicin, doxorubicin/vincristine, cyclophosphamide/etoposide, and cisplatin/doxorubicin/cyclophosphamide/etoposide (TD-PACE), providing an ORR of 40–84% [105, 112, 124, 125]. Nowadays, these protocols are rarely indicated due to the high risk of profound cytopenias and infectious complications, with the important exception of TD-PACE [116, 167].

Similar to dexamethasone/cyclophosphamide/etoposide/cisplatin (DCEP), TD-PACE is considered a useful regimen

Table 1 Prospective trials evaluating the efficacy of thalidomide-containing regimens for relapsed/refractory multiple myeloma

Study	Regimen	T dose (mg/day)	*n*	ORR (%)	EFS/PFS	OS/MST	References
Singhal et al. (1999)	T	200–800	84	32[a]	22% at 12 months	58% at 12 months	[100]
Hus et al. (2001)	T	200–400	53	36	240 weeks[b]	250 weeks	[101]
Barlogie et al. (2001)	T	200–800	169	30	20% at 24 months	48% at 24 months	[102]
Palumbo et al. (2001)	TD	100	77	41	12 months	ND	[103]
Dimopoulos et al. (2001)	TD	200–400	44	55	4 months	13 months	[104]
Moehler et al. (2001)	TD + Cy + Eto	400	56	64	16 months	ND	[105]
Yakoub-Agha et al. (2002)	T	50–800	83	48	50% at 12 months	57% at 12 months	[106]
Tosi et al. (2002)	T	100v800	65	26	8 months[b]	ND	[107]
Neben et al. (2002)	T	100–400	83	20	45% at 12 months	86% at 12 months	[108]
Mileshkin et al. (2003)	T	200–800	75	28	23% at 12 months	56% at 12 months	[109]
Grosbois et al. (2003)	T	200–400	121	31	33% at 12 months	47% at 12 months	[110]
Kropff et al. (2003)	TD + Cy	100–400	60	72	11 months	19 months	[111]
Lee et al. (2003)	TD + PACE	50–200	236	40	ND	ND	[112]
Waage et al. (2004)	T	200–800	65	20	ND	49% at 12 months	[113]
Richardson et al. (2004)	T	200–600	30	30	6 months	ND	[114]
Offidani et al. (2004)	T vs. T + Mel	100–600	50	26 vs. 59*	45 vs. 61% at 24 months*	64 vs. 61% at 24 months	[115]
García-Sanz et al. (2004)	TD + Cy	200–800	71	57	57% at 24 months	66% at 24 months	[116]
Dimopoulos et al. (2004)	TD + Cy	400	53	60	8 months	17 months	[117]
Palumbo et al. (2004)	TD	100	120	52	17 months	60% at 36 months	[118]
Terpos et al. (2005)	TD	200	35	57	8 months	19 months	[119]
Schüt et al. (2005)	TD	400	29	62	7 months	26 months	[120]
Badros et al. (2005)	TD + G3139	100–400	33	55	12 months	17 months	[121]
Kyriakou et al. (2005)	TD + Cy	50–300	52	79	34% at 24 months	73% at 24 months	[122]
Prince et al. (2005)	T + Cel	200–800	66	42	7 months	21 months	[123]
Offidani et al. (2006)	TD + PLD	100	50	84	57% at 72 months	74% at 72 months	[124]
Hussein et al. (2006)	TD + DVd	50–400	49	75	15 months	40 months	[125]
Palumbo et al. (2006)	TD + Vel + Mel	200	26	65	6 months	ND	[126]
Palumbo et al. (2007)	TP + Vel + Mel	50	30	67	61% at 12 months	84% at 12 months	[127]
Suvannasankha et al. (2007)	TP + Cy	200	35	63	13 months	ND	[128]
Murakami et al. (2007)	TD	100–200	66	26	6 months	25 months	[129]
Maisnar et al. (2007)	T	50–100	53	30	ND	86 months	[130]
Hattori et al. (2008)	T	200–400	61	27	11% at 24 months	41% at 24 months	[131]
Morris et al. (2008)	T + Cla	50–200	30	89	10 months	16 months	[132]

Table 1 (continued)

Study	Regimen	T dose (mg/day)	*n*	ORR (%)	EFS/PFS	OS/MST	References
Pineda-Roman et al. (2008)	TD + Vel	50–200	85	63	30% at 12 months	68% at 12 months	[133]
Terpos et al. (2008)	TD + Vel + Mel	100[c]	62	66	9 months	ND	[134]
Pönischet al. (2008)	TP + B60	50–200	28	86	11 months	19 months	[135]
Srikanth et al. (2008)[d]	TD + PACE	100–200	26	59	5 months	7 months	[136]
Kim et al. (2010)	TD + Vel + Cy	50	70	81	14% at 72 months	47% at 72 months	[137]
Palumbo et al. (2010)	TP + Rev + Mel	50–100	44	75	51% at 12 months	72% at 12 months	[138]
Lee et al. (2010)	PAD/TD	100	40	84	57% at 12 months	75% at 12 months	[139]
Hus et al. (2011)	TD vs. TD + Lov	100	91	32 vs. 44*	16 vs. 33 months*	39 vs. 49 months	[140]
Offidani et al. (2011)	TD + Vel + PLD	100	46	76	19 months	40 months	[141]
Zamagni et al. (2011)	TD	100–200	100	46	21 months	43 months	[142]
Yakoub-Agha et al. (2011)	T	100 vs. 400	400	14 vs. 26*	23 vs. 31 months	7 vs. 11 months	[143]
Kropff et al. (2012)	T	100 vs. 200 vs. 400	373	21 vs. 18 vs. 21	7 vs. 8 vs. 9 months	30 vs. 26 months vs. ND	[144]
Hjorth et al. (2012)	TD	50–200	67	55	9 months	23 months	[145]
Garderet et al. (2012)	TD vs. TD + Vel	200	269	72 vs. 87*	14 vs. 18 months*	65 vs. 71% at 24 months	[146]
Offidani et al. (2012)	TP + Mel + Pan	50	31	39	59% at 12 months	63% at 12 months	[147]
Geng et al. (2014)	T + CPT	100	43	21	7 months	ND	[148]
Schey et al. (2015)	TD + B60 vs. TD + B100	100	94	42 vs. 28	7 vs. 3 months	ND vs. 11 months	[149]
Mateos et al. (2016)	TD + Elo	50–200	40	38	4 months	16 months	[150]
Popat et al. (2016)	TP + Vel + Pan	50–100	42	91	16 months	ND	[151]
Kwon et al. (2016)	TD + Cy vs. TP + Mel	100	376	72 vs. 65	9 vs. 13 months	27 vs. 33 months	[152]
Leng et al. (2017)	TD vs. TD + CPT	150	71	25 vs. 38	3 vs. 7 months	ND	[153]
Mian et al. (2018)	TD + B60	50–100	26	37	22% at 18 months	40% at 18 months	[154]
Ludwig et al. (2019)	TD + Ixa	50–100	90	51	9 months	ND	[155]
Lee et al. (2019)	TD + Rev	50–200	52	52	4 months	20 months	[156]
Bergin et al. (2021)	TD + Ixa	100	39	56	14 months	ND	[157]

The daily dose of thalidomide (T dose) was administered on a continuous basis for varying periods, except where indicated. The overall response rate indicates the percentage of patients who achieved at least a 50% decline in serum and/or urine paraprotein levels, with a few exceptions. Progression-free survival and overall survival were calculated for the whole patient group (including non-responders), except where indicated

B60 bendamustine 60 mg/m^2, *B100* bendamustine 100 mg/m^2, *Cel* celecoxib, *Cla* clarithromycin, *CPT* circularly permuted TRAIL, *DVd* pegylated liposomal doxorubicin, vincristine, and decreased-frequency dexamethasone, *Eto* etoposide, *Elo* elotuzumab, *EFS* event-free survival, *G3139* Bcl-2 antisense oligodeoxynucleotide G3139, *Ixa* ixazomib, *Lov* lovastatin, *Mel* melphalan, *MST* median survival time, *n* number of patients who received a thalidomide-based regimen for relapsed/refractory multiple myeloma, *ND* not determined, *ORR* overall response rate, *OS* overall survival, *PACE* cisplatin, doxorubicin, cyclophosphamide, and etoposide, *PAD/TD* bortezomib, doxorubicin and dexamethasone followed by thalidomide and dexamethasone, *Pan* panobinostat, *PFS* progression-free survival, *Rev* Revlimid® (lenalidomide), *PLD* pegylated liposomal doxorubicin, *T* thalidomide, *TD* thalidomide and dexamethasone, *TP* thalidomide and prednisone/prednisolone, *Vel* Velcade® (bortezomib)

*Statistically significant difference between treatment groups

[a]Responders were defined by a decrease of ≥ 25% in serum or urine paraprotein levels

[b]Calculated only for patients who had evidence of objective response

[c]Administered intermittently on days 1–4 and 17–20 of a 28-day cycle, for 4–8 cycles

[d]Only included patients with extramedullary/blastoid myeloma

in early, aggressive relapses [23]. This protocol, generally administered every 4–6 weeks for 1–4 cycles, combines continuous thalidomide (50–200 mg/day) and a 4-day course of dexamethasone (40 mg/day), cisplatin (10 mg/m^2/day), doxorubicin (10 mg/m^2/day), cyclophosphamide (400 mg/m^2/day), and etoposide (40 mg/m^2/day) [112, 168]. Multiple retrospective cohort studies have reported the benefit of consolidating TD-PACE-like regimens with transplantation, highlighting the continued importance of HDC/ASCT in RRMM patients who are not eligible for, do not have access to, or did not respond to novel agents [136, 168–172]. For instance, Gerrie et al. analyzed the outcomes of 75 heavily pretreated patients at two tertiary care centers who received TD-PACE as salvage therapy. Overall, despite a reasonable ORR (49%), there was a short median PFS (5.5 months) and OS (14.0 months). However, when compared with non-transplant candidates, patients who proceeded to ASCT or achieved sufficient disease control to allow clinical trial enrollment had a non-significant trend towards improved PFS (13.4 vs. 2.9 months) and OS (20.5 vs. 7.5 months) [168].

The licensing of bortezomib as an anti-myeloma agent rapidly led to extensive investigation of its addition to thalidomide-based salvage regimens. In the MMVAR/IFM 2005-04 trial, 269 patients were randomly assigned to receive thalidomide (200 mg/day) and dexamethasone (40 mg/day) either with or without bortezomib (1.3 mg/m^2 intravenous bolus on days 1, 4, 8, and 11 for eight cycles, and then on days 1, 8, 15, and 22 for four cycles). The VTD arm achieved higher ORR (45% vs. 21%, $p = 0.001$) and median PFS (18.3 vs. 13.6 months, $p = 0.001$); however, 24-month OS rates were not significantly different (71% for VTD vs. 65% for TD; $p = 0.093$) [146]. The Total Therapy 3 trial demonstrated significantly improved CR rates and EFS, with an upfront association of bortezomib to TD-PACE (VTD-PACE) for induction prior to and consolidation after high-dose melphalan-based tandem autotransplants [173]. This prompted empirical use of VTD-PACE to rescue induction failures or for PBSC mobilization in RRMM patients [170]. In 2017, a single-center, retrospective cohort used an ITT model to evaluate the outcomes of 141 patients (median age 59.7 years) who received salvage therapy with VTD-PACE-like regimens (VTD-PACE in 67.4%). Despite a median of four previous lines of treatment, attainment of ≥ PR and ≥ very good PR (VGPR) occurred in 54.4 and 10.3% of patients, respectively. Median PFS was 3.1 months (95% CI 1.9–3.9 months), while median OS was 8.1 months (95% CI 6.2–9.9 months). However, in the subgroup who received ASCT consolidation, median OS was 15.1 months [172]. As a result, the 2022 National Comprehensive Cancer Network (NCCN) guidelines have listed both TD-PACE and VTD-PACE as salvage therapy options for patients with aggressive MM [23]. Of note, in a retrospective cohort, 32% of patients who received TD-PACE had previously been exposed to or were refractory to bortezomib. Thus, the addition of this proteasome inhibitor (PI) in the RRMM setting may not yield as significant improvements as in the NDMM setting [168]. Moreover, the cumulative neurotoxicity associated with bortezomib (particular its intravenous formulation) may be a significant dose-limiting factor in clinical practice, hindering some individuals from taking advantage of the added therapeutic benefit [174]. Approaches to optimize bortezomib tolerance include subcutaneous administration, dose reduction, and weekly scheduling [175].

In this scenario, combination regimens based on alternative PIs with a decreased neurotoxicity profile and to which fewer patients have previously been exposed (e.g., carfilzomib) could potentially improve clinical outcomes in RRMM patients [23, 168]. In 2015, a phase Ib/II study investigated the efficacy and safety of CYKLONE, a four-drug protocol administered in 28-day cycles (cyclophosphamide 300 mg/m^2 on days 1, 8, 15; carfilzomib 300 mg/m^2 on days 1, 2, 8, 9, 15, 16; thalidomide 100 mg on days 1–28; and dexamethasone 40 mg on days 1, 8, 15, 22). Among the 64 previously untreated, TE patients enrolled in the trial, 2 achieved stringent CR (sCR), 3 achieved CR, 39 achieved VGPR, and 14 achieved PR, totaling an ORR of 91%. Besides being highly efficacious, the regimen was associated with manageable toxicities (e.g., all PN was grade 1, while grade 3–4 neutropenia only occurred in 23% of cases) [176]. These results led the CYKLONE protocol to be included as a salvage therapy option in the 2022 NCCN guidelines, under the list of regimens "useful in certain circumstances for early relapses (1–3 prior therapies)" [23]. Although significant cardiotoxicity was not observed with the use of carfilzomib in the CYKLONE trial, cardiovascular AEs can be an important limitation of using this PI for treating MM patients [177].

The development of other targeted anti-myeloma agents also created interest for their combination with IMiDs as a way to overcome resistance in heavily pretreated patients [167].

In recent phase II studies, TD plus ixazomib (a novel PI with oral administration and an improved safety profile) led to an ORR of 51–56% [155, 157], while TD plus elotuzumab (an anti-SLAMF7 monoclonal antibody [mAb]) provided an ORR of 38% [150]. In the MUK-six trial, 91% of patients achieved at least a PR after receiving a salvage regimen composed of TP, bortezomib, and the iHDAC panobinostat [151]. An ongoing phase II study by the Asian Myeloma Network is investigating the efficacy of TD plus daratumumab (an anti-CD38 mAb) plus TD (Dara-TD) in RRMM. Among 36 patients included in an interim analysis, 3 achieved sCR, 3 achieved CR, 10 achieved VGPR, and 10 achieved PR, totaling an ORR of 72% [178]. Despite such encouraging results, phase III RCTs are still needed to

determine if these regimens are associated with a survival benefit in the RRMM setting.

Thalidomide doses of up to 800 mg/day were administered in early clinical trials, with some evidence of a dose–response relationship [100, 159]. Nevertheless, in a trial of thalidomide 100 versus 400 mg/day, Yakoub-Agha et al. demonstrated that the dose–response relationship of single-agent thalidomide is abrogated once corticosteroids are added [143]. In addition, doses exceeding 100 mg/day were found to cause significantly higher rates of toxicity-related symptoms (e.g., PN, constipation, somnolence), affecting health-related quality of life (HRQoL) and hindering long-term treatment continuation [143, 159, 179, 180]. Thus, in current practice, thalidomide doses of 50–200 mg/day are typically used [179]. In fact, most recent trials have employed a standard dose of 100 mg/day for RRMM patients [148, 149, 151, 152, 154, 155, 157]. Even so, 200–400 mg/day can be considered in those with good tolerance and aggressive disease that is not responding to lower doses (especially when newer therapies are unavailable, contraindicated, or cannot be tolerated) [179, 180]. A reasonable approach is to initiate therapy at 50–100 mg nightly and escalate the dose by 50 mg every 1–2 weeks as tolerated [179, 181]. The optimal duration of thalidomide-based salvage therapy has not yet been defined. In most clinical trials, RRMM patients received treatment until disease progression or AEs requiring discontinuation [180].

As previously discussed, one of the possible AEs associated with IMiDs is VTE. When administered as a single agent, thalidomide does not raise the risk of VTE compared with dexamethasone alone or melphalan/prednisone (MP). However, the risk of VTE increases from 3–4% to 10–34% when thalidomide is combined with other agents, such as high-dose dexamethasone and/or cytotoxic chemotherapy [182]. As a result, current guidelines recommend that MM patients being treated with an IMiD-containing combination regimen should receive pharmacological thromboprophylaxis (aspirin if standard risk, low-molecular-weight heparin or direct oral anticoagulants if high risk) for as long as the IMiD is being administered [1, 2, 182].

Although evidence is limited, MM patients with disease progression while taking lenalidomide may obtain clinical benefit from thalidomide. In a small Italian trial, among the 20 lenalidomide-refractory subjects who received thalidomide-based salvage therapy, 40% had a paraprotein response [183]. For patients with quadruple refractory disease (i.e., resistance to lenalidomide, pomalidomide, bortezomib, and carfilzomib), clinical trial enrollment is highly recommended if their PS allows. Additionally, some patients may still benefit from ASCT, especially if they previously had a durable response to high-dose melphalan [168, 184]. In this scenario, according to Mayo Stratification for Myeloma and Risk-Adapted Therapy guidelines, one or two cycles of VDT-PACE may be used as salvage therapy if rapid disease control is needed or as a bridge to either clinical trial enrollment or ASCT for suitable candidates [184].

4.2 Other Therapeutic Applications

Besides its role in RRMM, thalidomide is also approved for use in NDMM. During the early 2000s, VAD was long considered a standard induction therapy before ASCT [182]. However, in 2006, an Eastern Cooperative Oncology Group (ECOG)-coordinated study turned TD into the most commonly used induction regimen for TE patients worldwide [185, 186]. With the advent of PIs, the backbone of pre-ASCT induction therapy evolved into a three-drug combination of dexamethasone, a PI, and either cyclophosphamide, doxorubicin, or an IMiD [187]. While VTD became the standard induction regimen in Europe, VD plus lenalidomide (VRD), cyclophosphamide (VCD), or doxorubicin (PAD) have been more commonly used in the US [21, 23]. In phase III RCTs, PAD and VCD had similar efficacy [188], while VTD led to higher CR rates and longer PFS than VCD [189]. A meta-analysis suggested that such greater response is associated with no extra burden of toxicity [190]. Despite limited evidence suggesting a better benefit–risk profile of VRD over that of VTD [191], there is no RCT directly comparing these induction regimens [23].

Recently, the CASSIOPEIA trial reinforced thalidomide use in Europe as part of induction therapy for NDMM. In this landmark study, 1085 patients received four pre-transplant induction and two post-transplant consolidation cycles of either VTD or DaraVTD. Superiority of DaraVTD was demonstrated by the significantly increased post-consolidation sCR rates (29% vs. 20%, $p = 0.001$) and PFS at 18 months (93% vs. 85%, $p < 0.001$) [22]. The TOTAL therapy trials established TD-PACE and VTD-PACE as additional primary therapy options for transplant candidates [173, 192]; however, these regimens are generally reserved for patients with clinically aggressive disease [23, 173]. As suggested by recent phase II trials, carfilzomib/thalidomide/dexamethasone alone (CARTHADEX) or in combination with cyclophosphamide (CYKLONE) also appear to be well tolerated, rapidly effective, and well-tolerated induction regimens for TE patients [176, 193]. Importantly, as these regimens do not use bortezomib or lenalidomide, patients may still be treated with such agents if needed during consolidation, maintenance, or salvage therapy [176].

Although single-agent lenalidomide is the first-line choice for maintenance therapy after ASCT, thalidomide is an off-label alternative often used in low-resource healthcare systems [194, 195]. In 2012, an IMWG-coordinated meta-analysis found that employing thalidomide maintenance over an observation-only approach was associated with a 35% reduction in the risk for disease progression [196]. Given

the ability of bisphosphonates to hinder tumor cell proliferation and migration, induce apoptosis, block angiogenesis, and stimulate γδ T cells, these agents may synergize with IMiDs to enhance anti-myeloma effects in patients receiving maintenance [197]. Accordingly, one of the studies included in the above-cited meta-analysis was the IFM 99 02 trial, in which 597 patients were randomly assigned to receive no maintenance (arm A), pamidronate (arm B), or thalidomide/pamidronate (arm C) after double ASCT. In arm C, 65% of patients had a CR or VGPR, compared with 55% in arm A and 57% in arm B ($p = 0.03$). Meanwhile, 3-year EFS estimates were 36% in arm A, 37% in arm B, and 52% in arm C ($p < 0.009$) [198]. Later, RWD from 14 Korean university hospitals ($n = 258$) demonstrated a significantly higher 3-year PFS with thalidomide maintenance over observation (55.4 vs. 37.2%; $p = 0.005$) [195].

Despite the above data, thalidomide has not received FDA or EMA approval as maintenance therapy, since less consistent findings have been reported regarding survival benefits [199, 200]. For instance, the improved OS initially observed in the IFM 99 02 study was not maintained after long-term follow-up of patients with cytogenetics available, with an estimated 5-year OS rate of 74% in the thalidomide/pamidronate arm and 70% in both control groups ($p = 0.53$) [201]. In 2012, the Medical Research Council (MRC) Myeloma IX trial also showed a lack of survival benefit with thalidomide maintenance, although median PFS was significantly longer in the maintenance arm (23 vs. 15 months; hazard ratio [HR] 1.45, 95% CI 1.22–1.73, $p < 0.001$). In addition, subgroup analysis revealed a significantly worse OS in patients with high-risk cytogenetic abnormalities [200]. Noteworthy, approximately half of patients randomized to thalidomide maintenance had received the drug during induction, making them prone to the selection of thalidomide-resistant subclones [196, 200]. A subsequent meta-analysis with survival data from MRC Myeloma IX and four other trials demonstrated a significant effect of thalidomide maintenance therapy on OS ($p = 0.047$) [200]. Furthermore, modeling the survival benefit with effective salvage therapy removed heterogeneity between studies ($p = 0.24$) and thalidomide maintenance was shown to reduce the risk of death by 25% ($p < 0.001$) [199, 200].

Finally, thalidomide-based regimens can be used as initial treatment for transplant-ineligible patients [202]. In a meta-analysis of six RCTs comparing MP versus melphalan/prednisone/thalidomide (MPT), the latter regimen provided significant benefits to PFS (HR 0.68, 95% CI 0.61–0.76, $p < 0.001$) and OS (HR 0.83, 95% CI 0.73–0.94, $p = 0.004$), extending the median survival time by approximately 20% (6.6 months) [203]. MPT was then established as a standard therapy for non-transplant candidates, despite thalidomide's unfavorable toxicity profile in elderly individuals receiving the drug for prolonged periods [204]. Such treatment paradigm changed after publication of the FIRST trial, which compared MPT for 12 cycles ($n = 547$) versus lenalidomide/dexamethasone (RD) for 18 cycles ($n = 541$) versus RD until disease progression ($n = 535$). In this phase III study, continuous RD was superior to MPT in regard to PFS (HR 0.72, 95% CI 0.61–0.85, $p < 0.001$), OS (HR 0.78, 95% CI 0.64–0.96, $p = 0.02$), and all other secondary endpoints (e.g., ORR, TTR, response duration, time to treatment failure, time to second-line therapy, safety, and HRQoL) [205]. Later, the ECOG EA106 and HOVON87/NMSG18 trials showed no advantages in ORR, PFS, or OS with the use of melphalan/prednisone/lenalidomide induction followed by lenalidomide maintenance (MPR-R) over MPT induction followed by thalidomide maintenance (MPT-T); however, less toxicity was reported in the lenalidomide arm, which translated into better HRQoL [206, 207].

4.3 Role in Patients with Renal Dysfunction

Renal impairment (RI) is present in approximately 20% of MM patients at diagnosis, while 40–50% develop it throughout the disease course [208]. This complication primarily results from the nephrotoxic effects of monoclonal protein, although other factors may contribute (e.g., dehydration, hypercalcemia, hyperuricemia, use of nephrotoxic drugs, hyperviscosity, and PC infiltration) [209, 210]. Currently, the standard management of MM-induced RI combines high-dose dexamethasone with bortezomib, whose efficacy and tolerance are well-established without dose adaptation [211]. However, the addition of thalidomide to bortezomib-based combinations is a commonly used strategy for NDMM with RI, especially in Europe [208, 212]. Thalidomide is primarily metabolized via non-enzymatic hydrolysis and < 1% of unchanged drug is excreted in the urine, causing AE rates to be similar in patients with abnormal or normal kidney function. Therefore, no dose adjustment of thalidomide is needed in the setting of a low creatinine clearance (CrCl) [210, 213, 214]. In contrast, lenalidomide is eliminated predominantly via urinary excretion, such that an abnormal CrCl remarkably impacts its pharmacokinetics [215].

As listed in Table 2, many studies have evaluated the role of thalidomide in the management of MM-related kidney disease [216–223]. Kastritis et al. reported no significant difference in renal function recovery (RFR) rates among NDMM patients treated with non-thalidomide or thalidomide-based regimens (69 vs. 80%, $p = 0.453$), but median time to RFR was significantly lower in patients receiving thalidomide (2.0 vs. 0.8 months, $p = 0.005$) [217]. Tosi et al. reported an RFR rate of 55% for patients receiving TD before ASCT, with normal renal function being achieved more frequently by those with a lower degree of RI at baseline (93% if CrCl 30–50 mL/min vs. 19% if CrCl < 30 mL/min, $p < 0.001$) [218]. Morabito et al. compared bortezomib/

Table 2 Clinical studies evaluating the role of thalidomide-containing regimens on the management of myeloma-related renal impairment

Study	Setting	BRF cut-off	Regimen	T dose (mg/day)	*n*	RFR criteria	RFR rate (%)	ORR (%)	EFS/PFS	OS/MST	References
Tosi et al. (2004)	RRMM	SCr > 1.5 mg/dL	T ± D	100–400	20	SCr < 1.5 mg/dL	60	45	7 months	7 months	[216]
Kastritis et al. (2007)	NDMM	SCr ≥ 2.0 mg/dL	TD[b]	100	15	SCr < 1.5 mg/dL	80	ND	ND	ND	[217]
Tosi et al. (2010)	NDMM (TE)	CrCl ≤ 50 mL/min	TD	100–200	31	eGFR > 50 mL/min	55	74	30 months	ND	[218]
Morabito et al. (2011)	NDMM (TI)	eGFR ≤ 50 mL/min[c]	VMPT-VT	50	70	eGFR 60 mL/min	25	94	69% at 24 months	84% at 24 months	[219]
Ramasamy et al. (2011)	NDMM and RRMM	Need for dialysis	BTD	200–400	9	Dialysis independence	75	55	ND	ND	[220]
Dimopoulos et al. (2013)	NDMM	eGFR ≤ 60 mL/min	TBR	50–400	62	≥ Renal MR[c]	74	63	ND	36 months	[221]
Dimopoulos et al. (2016)	NDMM (TI)	CrCl < 50 mL/min	MPT	200	181	≥ Renal MR[c]	65	57[d]	ND	30–45% at 96 months[d]	[222]
Ramasamy et al. (2019)	NDMM	eGFR < 30 mL/min	BTD	100	13	≥ Renal PR[c]	11	77	ND	ND	[223]

Renal function cut-offs for patient inclusion are indicated for each study. The daily dose of thalidomide was administered on a continuous basis for varying periods. The overall response rate indicates the percentage of patients who achieved at least a 50% decline in serum and/or urine paraprotein levels, except where indicated. The renal function recovery rates indicate the percentage of patients who improved from baseline to most extreme post-baseline renal function values, divided by the total number of patients with baseline and post-baseline renal function data. Progression-free survival and overall survival were calculated for the whole patient group (including non-responders), except where indicated

BRF baseline renal function, *BTD* bendamustine, thalidomide, and dexamethasone *CrCl* creatinine clearance, *D* dexamethasone *EFS* event-free survival, *eGFR* estimated glomerular filtration rate, *MPT* melphalan/prednisone/thalidomide, *MR* minor response, *MST* median survival time, *n* number of patients who received a thalidomide-based regimen, *ND* not determined, *NDMM* newly diagnosed multiple myeloma, *ORR* overall response rate, *OS* overall survival, *PFS* progression-free survival, *PR* partial response, *RFR* renal function recovery, *RI* renal impairment, *RRMM* relapse/remitting multiple myeloma, *SCr* serum creatinine, *T* thalidomide, *TD* thalidomide and dexamethasone, *TBR* thalidomide-based regimen, such as TD, cyclophosphamide/thalidomide/dexamethasone (CTD), thalidomide/vincristine/doxorubicin/dexamethasone (T-VAD), or melphalan/prednisone/thalidomide (MPT), *TE* transplant-eligible, *TI* transplant-ineligible, *VMPT-VT* bortezomib/melphalan/prednisone/thalidomide followed by bortezomib/thalidomide maintenance

*Statistically significant difference between treatment groups

[a]Responders were defined by a sustained decrease of serum creatinine to < 1.5 mg/dL

[b]13 patients received a 4-week regimen of dexamethasone (40 mg/day on days 1–4 and 9–12) plus thalidomide, 1 patient received a 3-week regimen of dexamethasone (40 mg/day on days 1–4 and 9–12) plus bortezomib (1.3 mg/m^2 intravenously on days 1, 4, 8, 11), and 1 patient received the latter regimen with added thalidomide

[c]Patients with serum creatinine ≥ 2.5 mg/dL were excluded

[d]Renal minor response is defined as a sustained improvement of baseline eGFR of < 15 to 15–29 mL/min, or if baseline eGFR was 15–29 mL/min, improvement to 30–59 mL/min. Renal partial response is defined as a sustained improvement of baseline eGFR from < 15 to 30–59 mL/min. Renal complete response is defined as a sustained improvement of baseline eGFR from < 50 to ≥ 60 mL/min. The response should last for at least 2 months

[e]Calculated for patients in the moderate RI (≥ 30 to < 50 mL/min) and severe RI (< 30 mL/min) subgroups

melphalan/prednisone (VMP) versus VMP plus thalidomide followed by bortezomib/thalidomide maintenance (VMPT-VT) in renally impaired patients unfit for ASCT, reporting statistically significant improvements in ORR and PFS in those with moderate RI (estimated glomerular filtration rate [eGFR] 31–50 mL/min). Conversely, VMPT-VT had no advantage in terms of RI reversal over VMP (25.4 vs. 40.3%, $p = 0.092$) [219]. In a retrospective study comparing thalidomide- and lenalidomide-based regimens, the former were associated with a non-significant 2.36-fold increase (95% CI 0.868–6.405, $p = 0.092$) in the probability of renal PR or CR (as per IMWG criteria for the definition of renal response) [215]. Furthermore, in a secondary cohort analysis of the FIRST trial, the efficacy benefits of RD over MPT could not be demonstrated in patients with severe RI (CrCl < 30 mL/min) [216].

Nonetheless, contrasting evidence on thalidomide's advantages for renally impaired MM patients has been recently published. The OPTIMAL trial demonstrated higher rates of paraprotein response and dialysis independence among newly diagnosed individuals with a CrCl < 30 mL/min who received bortezomib/bendamustine/dexamethasone (VBD) over VTD [217]. In an RWD study, the incidence of RI in MM patients treated with thalidomide was higher than in those treated with lenalidomide [20]. However, this could be due to physician preference for thalidomide use in individuals with a low CrCl at baseline. Thus, thalidomide administration, either as part of frontline bortezomib-based combinations or as a component of second-line therapy following bortezomib refractoriness, remains a useful approach in the setting of MM-related kidney disease [206, 207]. Noteworthy, close monitoring is essential for patients undergoing dialysis, given the possibility of unexpected hyperkalemia [207].

4.4 Role in Patients with Myelotoxicity

In patients with RRMM, the association of heavy PC infiltration in the BM and numerous previous lines of therapy can often pose restrictions to the use of myelosuppressive agents [218]. While thalidomide frequently leads to dose-dependent non-hematologic adverse effects, thalidomide-induced myelotoxicity is unusual, even with doses above 400 mg/day [25]. The rates of neutropenia and thrombocytopenia may be low even when thalidomide is combined with cytotoxic chemotherapy. For instance, in a clinical trial of ThaCyDex for RRMM, 10% of patients developed grade 3–4 neutropenia, which was resolved after reducing the cyclophosphamide dosage. In the same trial, no other hematologic toxicity was attributable to the protocol.

In contrast, myelosuppression is a dose-limiting toxicity for lenalidomide- and pomalidomide-based regimens, despite the significantly lower incidence of PN with these agents [29]. In a retrospective matched-pair analysis comparing TD ($n = 183$) against RD ($n = 228$) as initial therapy for NDMM patients, TD led to significantly lower rates of neutropenia (0.6 vs. 14.0%, $p < 0.001$), thrombocytopenia (0 vs. 4.8%, $p = 0.002$), and anemia (0 vs. 4.4%, $p = 0.003$) [219]. In the HOVON87/NMSG18 trial, which included 637 untreated patients not eligible for transplant, grade 3–4 hematologic toxicity was significantly more common in the MPR-R arm (neutropenia: 64 vs. 27%; thrombocytopenia: 30% vs. 8%; anemia: 14 vs. 5%; $p < 0.001$ for all). Despite leading to higher growth factor support requirements, MPR-R use did not translate into increased infection risk [207].

Although these trials are not directly comparable, it is also interesting to note the lower rates of neutropenia and thrombocytopenia with the CYKLONE regimen (23 and 4.7%, respectively) relative to those reported with bortezomib/dexamethasone/cyclophosphamide/lenalidomide (VDCR) in the EVOLUTION study (44 and 14%, respectively) [176, 224]. In addition, a large US population-based cohort study showed a lack of survival benefit with the use of lenalidomide over thalidomide in upfront MM therapy [20]. Thus, despite not being widely used in the US, thalidomide-based regimens (e.g., TD, ThaCyDex and CYKLONE) remain useful alternatives in heavily pretreated patients with a poor BM reserve. This is particularly true for patients with age ≤ 65 years, little to no PN at baseline, and no prior thromboembolic events [116, 177]. Furthermore, thalidomide stands out as an attractive IMiD alternative when providing care for Jehovah's Witness patients with MM, since the drug's negligible myelotoxicity could translate into lower requirements for allogeneic blood product support [225].

4.5 Future Perspectives

In the POLLUX trial, the addition of daratumumab to RD (Dara-RD) was associated with significantly higher ORR and PFS in RRMM patients [226]. This led to the establishment of Dara-RD as a category 1 salvage therapy for early relapse [23]. However, common grade 3–4 AEs with the regimen included neutropenia (51.9%), thrombocytopenia (12.7%), and anemia (12.4%) [226]. In ongoing and future trials, the replacement of lenalidomide by thalidomide in daratumumab-containing regimens could potentially result in lower rates of dose-limiting cytopenias [178, 227]. Furthermore, Dara-TD could be a good option of salvage therapy for patients from resource-constrained countries, where concomitant use of two novel agents (e.g., daratumumab and lenalidomide) may lead to unaffordable healthcare costs [23, 178].

B-cell maturation antigen (BCMA)-directed therapies have substantial anti-myeloma activity but can lead to profound myelosuppression and other AEs (e.g., keratopathy

with the ADC belantamab mafodotin [belamaf], cytokine release syndrome and neurotoxicity with CAR T cells) [228, 229]. In the KarMMa trial, grade 3–4 AEs caused by ide-cell included neutropenia (89%), thrombocytopenia (52%), anemia (60%), and infections (22%) [8]. In the CARTITUDE-1 trial, grade 3–4 AEs caused by ciltacabtagene autoleucel (cilta-cel) included neutropenia (95%), thrombocytopenia (60%), anemia (68%), and infections (20%) [230]. CAR T-cell-related hematologic toxicity tends to be short-lived, with frequent recovery to grade ≤ 2 by day 30. Nevertheless, prolonged neutropenia and/or thrombocytopenia can occur in patients with inadequate BM reserve at baseline, creating the risk for life-threatening events (e.g., intracranial bleeding or sepsis) [8, 230]. Above that, some patients with a high tumor burden may lack enough BM reserve to allow autologous T-cell collection via apheresis, hindering their eligibility for CAR T-cell therapy in the first place [231]. Despite the promising preliminary results obtained with BsAbs (e.g., teclistamab, elranatamab, AMG 420, AMG 701, and REGN5458), early-phase clinical trials are still ongoing, for which many patients might not qualify [228, 229].

In the DREAMM-2 trial, the rates of grade 3–4 neutropenia, thrombocytopenia, and anemia varied according to belamaf dosing (9, 20, and 20%, respectively, in the 2.5 mg/kg cohort; 15, 33, and 40%, respectively, in the 3.4 mg/kg cohort) [232]. DREAMM-6 is an ongoing trial evaluating the safety, tolerability, and efficacy of belamaf plus RD (arm A) or VD (arm B) for RRMM patients [233, 234]. In arm B, grade 3–4 thrombocytopenia occurred in 67% of patients, leading to dose reduction in half of these patients [234]. Although preliminary data are still pending for arm A, increased rates of thrombocytopenia compared with arm B are expected, given lenalidomide's higher myelosuppressive effect [233, 235].

Investigations into other combinations of BCMA-directed agents and IMiDs are somewhat limited. In vivo studies combining CAR T cells with lenalidomide found that the latter could enhance antitumor activity and delay onset of functional exhaustion of the former [236–238]. Further preclinical data in xenograft models suggested enhanced potency of the BsAb AMG 701 with the addition of lenalidomide and pomalidomide [239, 240]. Besides boosting the anti-myeloma effects of immunotherapy, the anti-inflammatory properties of IMiDs could be potentially helpful in reducing the risk of CRS after CAR T-cell infusion. Recently, Jan et al. demonstrated the ability of lenalidomide and pomalidomide to control degradable CAR T-cell cytokine release in vivo, limiting treatment-related toxicity while maintaining antitumor activity [241]. Although only lenalidomide and pomalidomide were tested in the above-cited studies, comparable results could potentially be obtained with thalidomide, given its analogous mechanisms of action. Moreover, thalidomide's lack of renal dosing requirements or myelotoxicity could increase the inclusion of patients with severely decreased eGFR in future clinical trials, while allowing avoidance of dose delays/reductions or treatment discontinuation related to significant cytopenias. In the US, given the considerable economic burden of MM treatment to Medicare, thalidomide-based regimens can also be regarded as cost-effective alternatives to protocols containing newer-generation IMiDs or CELMoDs [242, 243]. In low- and middle-income countries, where many of the novel agents are not only costly but are still awaiting approval, thalidomide use becomes even more attractive [194, 195]. Notwithstanding, there is a persisting need for prospective trials directly evaluating thalidomide-containing regimens against novel therapies or in association with them.

5 Conclusion

Thalidomide remains a useful anti-myeloma agent in clinical practice, especially in the setting of high-grade myelosuppression and RI. Salvage regimens combining thalidomide (usually in a dose of 100 mg/day) and corticosteroids with or without selected cytotoxic or targeted agents (e.g., TD, ThaCyDex and CYKLONE) can be considered for RRMM patients who have no access to or are not eligible for novel therapies. In order to avoid severe AEs, frequent neurological monitoring and pharmacological thromboprophylaxis should be offered. By comparing thalidomide-containing regimens with protocols based on new-generation IMiDs or CELMoDs, and by investigating the association of thalidomide with novel immunotherapies (e.g., ADC, BsAbs, and CAR-T cells), ongoing and future trials may forge new ground for the revival of this old drug.

Acknowledgements Figures 1 and 2 were created with BioRender.com.

Declarations

Funding No external funding was used in the preparation of this manuscript.

Conflict of interest Bruno Costa and Tarek Mouhieddine declare that they have no conflicts of interest that might be relevant to the contents of this manuscript. Joshua Richter receives consulting fees and fees for serving on a speakers bureau from Amgen; advisory board fees and fees for serving on a speakers bureau from Celgene, Takeda, and Janssen; and advisory board fees from Sanofi, Karyopharm Therapeutics, Oncopeptides, Adaptive Biotechnologies, and Bristol-Myers Squibb.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material Not applicable.

Code availability Not applicable.

References

1. van de Donk NWCJ, Pawlyn C, Yong KL. Multiple myeloma. Lancet. 2021;397(10272):410–27. https://doi.org/10.1016/S0140-6736(21)00135-5.
2. Palumbo A, Anderson K. Multiple myeloma. N Engl J Med. 2011;364(11):1046–60. https://doi.org/10.1056/NEJMra1011442.
3. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. Lancet Oncol. 2014;15(12):e538–48. https://doi.org/10.1016/S1470-2045(14)70442-5.
4. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2021;71(3):209–49. https://doi.org/10.3322/caac.21660.
5. Cowan AJ, Green DJ, Kwok M, Lee S, Coffey DG, Holmberg LA, et al. Diagnosis and management of multiple myeloma: a review. JAMA. 2022;327(5):464–77. https://doi.org/10.1001/jama.2022.0003.
6. Therneau TM, Kyle RA, Melton LJ 3rd, Larson DR, Benson JT, Colby CL, et al. Incidence of monoclonal gammopathy of undetermined significance and estimation of duration before first clinical recognition. Mayo Clin Proc. 2012;87(11):1071–9. https://doi.org/10.1016/j.mayocp.2012.06.014.
7. Solly S. Remarks on the pathology of mollities ossium; with cases. Med Chir Trans. 1844;27:435–98. https://doi.org/10.1177/095952874402700129.
8. Munshi NC, Anderson LD Jr, Shah N, Madduri D, Berdeja J, Lonial S, et al. Idecabtagene vicleucel in relapsed and refractory multiple myeloma. N Engl J Med. 2021;384(8):705–16. https://doi.org/10.1056/NEJMoa2024850.
9. Morgan GJ, Boyle EM, Davies FE. From bench to bedside: the evolution of genomics and its implications for the current and future management of multiple myeloma. Cancer J. 2021;27(3):213–21. https://doi.org/10.1097/PPO.0000000000000523.
10. Mateos MV, Ludwig H, Bazarbachi A, Beksac M, Bladé J, Boccadoro M, et al. Insights on multiple myeloma treatment strategies. Hemasphere. 2018;3(1): e163. https://doi.org/10.1097/HS9.0000000000000163.
11. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. Am J Hematol. 2020;95(5):548–67. https://doi.org/10.1002/ajh.25791.
12. Schavgoulidze A, Cazaubiel T, Perrot A, Avet-Loiseau H, Corre J. Multiple myeloma: heterogeneous in every way. Cancers (Basel). 2021;13(6):1285. https://doi.org/10.3390/cancers13061285.
13. Ackley J, Ochoa MA, Ghoshal D, Roy K, Lonial S, Boise LH. Keeping myeloma in check: the past, present and future of immunotherapy in multiple myeloma. Cancers (Basel). 2021;13(19):4787. https://doi.org/10.3390/cancers13194787.
14. Ludwig H. Myeloma research on the move. Blood Cancer J. 2021;11(9):155. https://doi.org/10.1038/s41408-021-00550-z.
15. Theodoropoulos N, Lancman G, Chari A. Targeting nuclear export proteins in multiple myeloma therapy. Target Oncol. 2020;15(6):697–708. https://doi.org/10.1007/s11523-020-00758-2.
16. Sanchez L, Dardac A, Madduri D, Richard S, Richter J. B-cell maturation antigen (BCMA) in multiple myeloma: the new frontier of targeted therapies. Ther Adv Hematol. 2021;12:2040620721989585. https://doi.org/10.1177/2040620721989585.
17. Legarda MA, Cejalvo MJ, de la Rubia J. Recent advances in the treatment of patients with multiple myeloma. Cancers (Basel). 2020;12(12):3576. https://doi.org/10.3390/cancers12123576.
18. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. SEER cancer statistics review 1973–1994. 1997. Available at: https://seer.cancer.gov/archive/csr/1973_1994/myeloma.pdf. Accessed 6 Feb 2022.
19. National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Program. Cancer stat facts: myeloma. 2021. Available at: https://seer.cancer.gov/statfacts/html/mulmy.html. Accessed 6 Feb 2022.
20. Luo J, Gagne JJ, Landon J, Avorn J, Kesselheim AS. Comparative effectiveness and safety of thalidomide and lenalidomide in patients with multiple myeloma in the United States of America: a population-based cohort study. Eur J Cancer. 2017;70:22–33. https://doi.org/10.1016/j.ejca.2016.10.018.
21. Dimopoulos MA, Moreau P, Terpos E, Mateos MV, Zweegman S, Cook G, et al. Multiple myeloma: EHA-ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2021;32(3):309–22. https://doi.org/10.1016/j.annonc.2020.11.014.
22. Moreau P, Attal M, Hulin C, Arnulf B, Belhadj K, Benboubker L, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab before and after autologous stem-cell transplantation for newly diagnosed multiple myeloma (CASSIOPEIA): a randomised, open-label, phase 3 study. Lancet. 2019;394(10192):29–38. https://doi.org/10.1016/S0140-6736(19)31240-1.
23. National Comprehensive Cancer Network (NCCN). NCCN guidelines: multiple myeloma, version 5.2022. Available at: https://www.nccn.org/professionals/physician_gls/pdf/myeloma.pdf. 2022. Accessed 15 Mar 2022.
24. Thakurta A, Pierceall WE, Amatangelo MD, Flynt E, Agarwal A. Developing next generation immunomodulatory drugs and their combinations in multiple myeloma. Oncotarget. 2021;12(15):1555–63. https://doi.org/10.18632/oncotarget.27973.
25. Harousseau JL. Thalidomide in multiple myeloma: past, present and future. Future Oncol. 2006;2(5):577–89. https://doi.org/10.2217/14796694.2.5.577.
26. Tseng S, Pak G, Washenik K, Pomeranz MK, Shupack JL. Rediscovering thalidomide: a review of its mechanism of action, side effects, and potential uses. J Am Acad Dermatol. 1996;35(6):969–79. https://doi.org/10.1016/s0190-9622(96)90122-x.
27. Ribatti D, Vacca A. Therapeutic renaissance of thalidomide in the treatment of haematological malignancies. Leukemia. 2005;19(9):1525–31. https://doi.org/10.1038/sj.leu.2403852.
28. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMiD derivatives as anticancer agents. Nat Rev Cancer. 2004;4(4):314–22. https://doi.org/10.1038/nrc1323.
29. Brent RL. Drug testing in animals for teratogenic effects. Thalidomide in the pregnant rat. J Pediatr. 1964;64:762–70. https://doi.org/10.1016/s0022-3476(64)80626-0.
30. Rehman W, Arfons LM, Lazarus HM. The rise, fall and subsequent triumph of thalidomide: lessons learned in drug development. Ther Adv Hematol. 2011;2(5):291–308. https://doi.org/10.1177/2040620711413165.

31. Ances BM. New concerns about thalidomide. Obstet Gynecol. 2002;99(1):125–8. https://doi.org/10.1016/s0029-7844(01)01662-3.
32. Vargesson N. Thalidomide-induced teratogenesis: history and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140–56. https://doi.org/10.1002/bdrc.21096.
33. Olson KB, Hall TC, Horton J, Khung CL, Hosley HF. Thalidomide (*N*-phthaloylglutamimide) in the treatment of advanced cancer. Clin Pharmacol Ther. 1965;6:292–7. https://doi.org/10.1002/cpt196563292.
34. Grabstald H, Golbey R. Clinical experiences with thalidomide in patients with cancer. Clin Pharmacol Ther. 1965;6:298–302. https://doi.org/10.1002/cpt196563298.
35. Sheskin J. Thalidomide in the treatment of lepra reactions. Clin Pharmacol Ther. 1965;6:303–6. https://doi.org/10.1002/cpt196563303.
36. Jacobson JM. Thalidomide: a remarkable comeback. Expert Opin Pharmacother. 2000;1(4):849–63. https://doi.org/10.1517/14656566.1.4.849.
37. Iyer CG, Languillon J, Ramanujam K, Tarabini-Castellani G, De las Aguas JT, Bechelli LM, et al. WHO co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. Bull World Health Organ. 1971;45(6):719–32.
38. Lenardo TM, Calabrese LH. The role of thalidomide in the treatment of rheumatic disease. J Clin Rheumatol. 2000;6(1):19–26. https://doi.org/10.1097/00124743-200002000-00003.
39. Wines NY, Cooper AJ, Wines MP. Thalidomide in dermatology. Australas J Dermatol. 2002;43(4):229–40. https://doi.org/10.1046/j.1440-0960.2002.00608.x.
40. Kim JH, Scialli AR. Thalidomide: the tragedy of birth defects and the effective treatment of disease. Toxicol Sci. 2011;122(1):1–6. https://doi.org/10.1093/toxsci/kfr088.
41. Matthews SJ, McCoy C. Thalidomide: a review of approved and investigational uses. Clin Ther. 2003;25(2):342–95. https://doi.org/10.1016/s0149-2918(03)80085-1.
42. Calabrese L, Resztak K. Thalidomide revisited: pharmacology and clinical applications. Expert Opin Investig Drugs. 1998;7(12):2043–60. https://doi.org/10.1517/13543784.7.12.2043.
43. D'Amato RJ, Loughnan MS, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA. 1994;91(9):4082–5. https://doi.org/10.1073/pnas.91.9.4082.
44. Folkman J. Angiogenesis in cancer, vascular, rheumatoid and other disease. Nat Med. 1995;1(1):27–31. https://doi.org/10.1038/nm0195-27.
45. Vacca A, Ribatti D, Roncali L, Ranieri G, Serio G, Silvestris F, et al. Bone marrow angiogenesis and progression in multiple myeloma. Br J Haematol. 1994;87(3):503–8. https://doi.org/10.1111/j.1365-2141.1994.tb08304.x.
46. Vacca A, Ribatti D, Roncali L, Dammacco F. Angiogenesis in B cell lymphoproliferative diseases. Biological and clinical studies. Leuk Lymphoma. 1995;20(1–2):27–38. https://doi.org/10.3109/10428199509054750.
47. Amare GG, Meharie BG, Belayneh YM. A drug repositioning success: the repositioned therapeutic applications and mechanisms of action of thalidomide. J Oncol Pharm Pract. 2021;27(3):673–8. https://doi.org/10.1177/1078155220975825.
48. Palumbo A, Palladino C. Venous and arterial thrombotic risks with thalidomide: evidence and practical guidance. Ther Adv Drug Saf. 2012;3(5):255–66. https://doi.org/10.1177/2042098612452291.
49. Kazandjian D, Landgren O. A look backward and forward in the regulatory and treatment history of multiple myeloma: approval of novel-novel agents, new drug development, and longer patient survival. Semin Oncol. 2016;43(6):682–9. https://doi.org/10.1053/j.seminoncol.2016.10.008.
50. Kawano Y, Moschetta M, Manier S, Glavey S, Görgün GT, Roccaro AM, et al. Targeting the bone marrow microenvironment in multiple myeloma. Immunol Rev. 2015;263(1):160–72. https://doi.org/10.1111/imr.12233.
51. Rajkumar SV, Mesa RA, Fonseca R, Schroeder G, Plevak MF, Dispenzieri A, et al. Bone marrow angiogenesis in 400 patients with monoclonal gammopathy of undetermined significance, multiple myeloma, and primary amyloidosis. Clin Cancer Res. 2002;8(7):2210–6.
52. Rajkumar SV, Witzig TE. A review of angiogenesis and antiangiogenic therapy with thalidomide in multiple myeloma. Cancer Treat Rev. 2000;26(5):351–62. https://doi.org/10.1053/ctrv.2000.0188.
53. Jakob C, Sterz J, Zavrski I, Heider U, Kleeberg L, Fleissner C, et al. Angiogenesis in multiple myeloma. Eur J Cancer. 2006;42(11):1581–90. https://doi.org/10.1016/j.ejca.2006.02.017.
54. Moser-Katz T, Joseph NS, Dhodapkar MV, Lee KP, Boise LH. Game of bones: how myeloma manipulates its microenvironment. Front Oncol. 2021;10: 625199. https://doi.org/10.3389/fonc.2020.625199.
55. Podar K, Anderson KC. The pathophysiologic role of VEGF in hematologic malignancies: therapeutic implications. Blood. 2005;105(4):1383–95. https://doi.org/10.1182/blood-2004-07-2909.
56. Rajkumar SV, Leong T, Roche PC, Fonseca R, Dispenzieri A, Lacy MQ, et al. Prognostic value of bone marrow angiogenesis in multiple myeloma. Clin Cancer Res. 2000;6(8):3111–6.
57. Sezer O, Niemöller K, Eucker J, Jakob C, Kaufmann O, Zavrski I, et al. Bone marrow microvessel density is a prognostic factor for survival in patients with multiple myeloma. Ann Hematol. 2000;79(10):574–7. https://doi.org/10.1007/s002770000236.
58. Lee N, Lee H, Moon SY, Sohn JY, Hwang SM, Yoon OJ, et al. Adverse prognostic impact of bone marrow microvessel density in multiple myeloma. Ann Lab Med. 2015;35(6):563–9. https://doi.org/10.3343/alm.2015.35.6.563.
59. Kumar S, Gertz MA, Dispenzieri A, Lacy MQ, Wellik LA, Fonseca R, et al. Prognostic value of bone marrow angiogenesis in patients with multiple myeloma undergoing high-dose therapy. Bone Marrow Transplant. 2004;34(3):235–9. https://doi.org/10.1038/sj.bmt.1704555.
60. Kumar S, Fonseca R, Dispenzieri A, Lacy MQ, Lust JA, Wellik L, et al. Prognostic value of angiogenesis in solitary bone plasmacytoma. Blood. 2003;101(5):1715–7. https://doi.org/10.1182/blood-2002-08-2441.
61. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolites in a mouse corneal model of neovascularization. Exp Eye Res. 1997;64(6):971–8. https://doi.org/10.1006/exer.1997.0292.
62. Tamilarasan KP, Kolluru GK, Rajaram M, Indhumathy M, Saranya R, Chatterjee S. Thalidomide attenuates nitric oxide mediated angiogenesis by blocking migration of endothelial cells. BMC Cell Biol. 2006;7:17. https://doi.org/10.1186/1471-2121-7-17.
63. Majumder S, Rajaram M, Muley A, Reddy HS, Tamilarasan KP, Kolluru GK, et al. Thalidomide attenuates nitric oxide-driven angiogenesis by interacting with soluble guanylyl cyclase. Br J Pharmacol. 2009;158(7):1720–34. https://doi.org/10.1111/j.1476-5381.2009.00446.x.
64. Vacca A, Scavelli C, Montefusco V, Di Pietro G, Neri A, Mattioli M, et al. Thalidomide downregulates angiogenic genes in bone marrow endothelial cells of patients with active multiple myeloma. J Clin Oncol. 2005;23(23):5334–46. https://doi.org/10.1200/JCO.2005.03.723.

65. Ria R, Melaccio A, Racanelli V, Vacca A. Anti-VEGF drugs in the treatment of multiple myeloma patients. J Clin Med. 2020;9(6):1765. https://doi.org/10.3390/jcm9061765.
66. Ribatti D, Vacca A. New insights in anti-angiogenesis in multiple myeloma. Int J Mol Sci. 2018;19(7):2031. https://doi.org/10.3390/ijms19072031.
67. Kumar S, Witzig TE, Dispenzieri A, Lacy MQ, Wellik LE, Fonseca R, et al. Effect of thalidomide therapy on bone marrow angiogenesis in multiple myeloma. Leukemia. 2004;18(3):624–7. https://doi.org/10.1038/sj.leu.2403285.
68. Mitsiades N, Mitsiades CS, Poulaki V, Chauhan D, Richardson PG, Hideshima T, et al. Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: therapeutic implications. Blood. 2002;99(12):4525–30. https://doi.org/10.1182/blood.v99.12.4525.
69. Al-Hujaily EM, Oldham RA, Hari P, Medin JA. Development of novel immunotherapies for multiple myeloma. Int J Mol Sci. 2016;17(9):1506. https://doi.org/10.3390/ijms17091506.
70. Quach H, Ritchie D, Stewart AK, Neeson P, Harrison S, Smyth MJ, et al. Mechanism of action of immunomodulatory drugs (IMiDS) in multiple myeloma. Leukemia. 2010;24(1):22–32. https://doi.org/10.1038/leu.2009.236.
71. D'Souza C, Prince HM, Neeson PJ. Understanding the role of T-cells in the antimyeloma effect of immunomodulatory drugs. Front Immunol. 2021;12: 632399. https://doi.org/10.3389/fimmu.2021.632399.
72. Haslett PA, Corral LG, Albert M, Kaplan G. Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med. 1998;187(11):1885–92. https://doi.org/10.1084/jem.187.11.1885.
73. LeBlanc R, Hideshima T, Catley LP, Shringarpure R, Burger R, Mitsiades N, et al. Immunomodulatory drug costimulates T cells via the B7-CD28 pathway. Blood. 2004;103(5):1787–90. https://doi.org/10.1182/blood-2003-02-0361.
74. Davies FE, Raje N, Hideshima T, Lentzsch S, Young G, Tai YT, et al. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. Blood. 2001;98(1):210–6. https://doi.org/10.1182/blood.v98.1.210.
75. Fritz E, Ludwig H. Interferon-alpha treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. Ann Oncol. 2000;11(11):1427–36. https://doi.org/10.1023/a:1026548226770.
76. Ito T, Handa H. Cereblon and its downstream substrates as molecular targets of immunomodulatory drugs. Int J Hematol. 2016;104(3):293–9. https://doi.org/10.1007/s12185-016-2073-4.
77. Ito T, Ando H, Suzuki T, Ogura T, Hotta K, Imamura Y, et al. Identification of a primary target of thalidomide teratogenicity. Science. 2010;327(5971):1345–50. https://doi.org/10.1126/science.1177319.
78. Zhu YX, Braggio E, Shi CX, Bruins LA, Schmidt JE, Van Wier S, et al. Cereblon expression is required for the antimyeloma activity of lenalidomide and pomalidomide. Blood. 2011;118(18):4771–9. https://doi.org/10.1182/blood-2011-05-356063.
79. Sato T, Ito T, Handa H. Cereblon-based small-molecule compounds to control neural stem cell proliferation in regenerative medicine. Front Cell Dev Biol. 2021;9: 629326. https://doi.org/10.3389/fcell.2021.629326.
80. Kowalski TW, Gomes JDA, Garcia GBC, Fraga LR, Paixao-Cortes VR, Recamonde-Mendoza M, et al. CRL4-cereblon complex in thalidomide embryopathy: a translational investigation. Sci Rep. 2020;10(1):851. https://doi.org/10.1038/s41598-020-57512-x.
81. Shi Q, Chen L. Cereblon: a protein crucial to the multiple functions of immunomodulatory drugs as well as cell metabolism and disease generation. J Immunol Res. 2017;2017:9130608. https://doi.org/10.1155/2017/9130608.
82. Asatsuma-Okumura T, Ito T, Handa H. Molecular mechanisms of the teratogenic effects of thalidomide. Pharmaceuticals (Basel). 2020;13(5):95. https://doi.org/10.3390/ph13050095.
83. Gao S, Wang S, Fan R, Hu J. Recent advances in the molecular mechanism of thalidomide teratogenicity. Biomed Pharmacother. 2020;127: 110114. https://doi.org/10.1016/j.biopha.2020.110114.
84. Stewart AK. Medicine. How thalidomide works against cancer. Science. 2014;343(6168):256–7. https://doi.org/10.1126/science.1249543.
85. Nooka AK, Lonial S. Mechanism of action and novel IMiD-based compounds and combinations in multiple myeloma. Cancer J. 2019;25(1):19–31. https://doi.org/10.1097/PPO.0000000000000354.
86. Krönke J, Fink EC, Hollenbach PW, MacBeth KJ, Hurst SN, Udeshi ND, et al. Lenalidomide induces ubiquitination and degradation of CK1α in del(5q) MDS. Nature. 2015;523(7559):183–8. https://doi.org/10.1038/nature14610.
87. Yamamoto J, Suwa T, Murase Y, Tateno S, Mizutome H, Asatsuma-Okumura T, et al. ARID2 is a pomalidomide-dependent CRL4CRBN substrate in multiple myeloma cells. Nat Chem Biol. 2020;16(11):1208–17. https://doi.org/10.1038/s41589-020-0645-3.
88. Kyle RA, Rajkumar SV. Multiple myeloma. Blood. 2008;111(6):2962–72. https://doi.org/10.1182/blood-2007-10-078022.
89. Ribatti D. A historical perspective on milestones in multiple myeloma research. Eur J Haematol. 2018;100(3):221–8. https://doi.org/10.1111/ejh.13003.
90. Kyle RA. Five decades of therapy for multiple myeloma: a paradigm for therapeutic models. Leukemia. 2005;19(6):910–2. https://doi.org/10.1038/sj.leu.2403728.
91. McElwain TJ, Powles RL. High-dose intravenous melphalan for plasma-cell leukaemia and myeloma. Lancet. 1983;2(8354):822–4. https://doi.org/10.1016/s0140-6736(83)90739-0.
92. Barlogie B, Hall R, Zander A, Dicke K, Alexanian R. High-dose melphalan with autologous bone marrow transplantation for multiple myeloma. Blood. 1986;67(5):1298–301.
93. Barlogie B, Alexanian R, Dicke KA, Zagars G, Spitzer G, Jagannath S, et al. High-dose chemoradiotherapy and autologous bone marrow transplantation for resistant multiple myeloma. Blood. 1987;70(3):869–72.
94. Attal M, Harousseau JL, Stoppa AM, Sotto JJ, Fuzibet JG, Rossi JF, et al. A prospective, randomized trial of autologous bone marrow transplantation and chemotherapy in multiple myeloma. Intergroupe Français du Myélome. N Engl J Med. 1996;335(2):91–7. https://doi.org/10.1056/NEJM199607113350204.
95. Attal M, Harousseau JL, Facon T, Guilhot F, Doyen C, Fuzibet JG, et al. Single versus double autologous stem-cell transplantation for multiple myeloma. N Engl J Med. 2003;349(26):2495–502. https://doi.org/10.1056/NEJMoa032290.
96. Fermand JP, Ravaud P, Chevret S, Divine M, Leblond V, Belanger C, et al. High-dose therapy and autologous peripheral blood stem cell transplantation in multiple myeloma: up-front or rescue treatment? Results of a multicenter sequential randomized clinical trial. Blood. 1998;92(9):3131–6.
97. Barlogie B, Smith L, Alexanian R. Effective treatment of advanced multiple myeloma refractory to alkylating agents. N Engl J Med. 1984;310(21):1353–6. https://doi.org/10.1056/NEJM198405243102104.
98. Barlogie B, Velasquez WS, Alexanian R, Cabanillas F. Etoposide, dexamethasone, cytarabine, and cisplatin in vincristine, doxorubicin, and dexamethasone-refractory myeloma. J Clin

Oncol. 1989;7(10):1514–7. https://doi.org/10.1200/JCO.1989.7.10.1514.
99. Latif T, Chauhan N, Khan R, Moran A, Usmani SZ. Thalidomide and its analogues in the treatment of multiple myeloma. Exp Hematol Oncol. 2012;1(1):27. https://doi.org/10.1186/2162-3619-1-27.
100. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med. 1999;341(21):1565–71. https://doi.org/10.1056/NEJM199911183412102.
101. Hus M, Dmoszynska A, Soroka-Wojtaszko M, Jawniak D, Legiec W, Ciepnuch H, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. Haematologica. 2001;86(4):404–8.
102. Barlogie B, Desikan R, Eddlemon P, Spencer T, Zeldis J, Munshi N, et al. Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: identification of prognostic factors in a phase 2 study of 169 patients. Blood. 2001;98(2):492–4. https://doi.org/10.1182/blood.v98.2.492.
103. Palumbo A, Giaccone L, Bertola A, Pregno P, Bringhen S, Rus C, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica. 2001;86(4):399–403.
104. Dimopoulos MA, Zervas K, Kouvatseas G, Galani E, Grigoraki V, Kiamouris C, et al. Thalidomide and dexamethasone combination for refractory multiple myeloma. Ann Oncol. 2001;12(7):991–5. https://doi.org/10.1023/a:1011132808904.
105. Moehler TM, Neben K, Benner A, Egerer G, Krasniqi F, Ho AD, et al. Salvage therapy for multiple myeloma with thalidomide and CED chemotherapy. Blood. 2001;98(13):3846–8. https://doi.org/10.1182/blood.v98.13.3846.
106. Yakoub-Agha I, Attal M, Dumontet C, Delannoy V, Moreau P, Berthou C, et al. Thalidomide in patients with advanced multiple myeloma: a study of 83 patients—report of the Intergroupe Francophone du Myélome (IFM). Hematol J. 2002;3(4):185–92. https://doi.org/10.1038/sj.thj.6200175.
107. Tosi P, Zamagni E, Cellini C, Ronconi S, Patriarca F, Ballerini F, et al. Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma. Haematologica. 2002;87(4):408–14.
108. Neben K, Moehler T, Benner A, Kraemer A, Egerer G, Ho AD, et al. Dose-dependent effect of thalidomide on overall survival in relapsed multiple myeloma. Clin Cancer Res. 2002;8(11):3377–82.
109. Mileshkin L, Biagi JJ, Mitchell P, Underhill C, Grigg A, Bell R, et al. Multicenter phase 2 trial of thalidomide in relapsed/refractory multiple myeloma: adverse prognostic impact of advanced age. Blood. 2003;102(1):69–77. https://doi.org/10.1182/blood-2002-09-2846.
110. Grosbois B, Bellissant E, Moreau P, Attal M, Voillat L, Muret P, et al. Treatment of advanced multiple myeloma (MM) with thalidomide (THAL). Long term follow-up in a prospective study of 121 patients. Eur J Intern Med. 2003;4:226. https://doi.org/10.1016/S0953-6205(03)91244-1.
111. Kropff MH, Lang N, Bisping G, Dominé N, Innig G, Hentrich M, et al. Hyperfractionated cyclophosphamide in combination with pulsed dexamethasone and thalidomide (HyperCDT) in primary refractory or relapsed multiple myeloma. Br J Haematol. 2003;122(4):607–16. https://doi.org/10.1046/j.1365-2141.2003.04473.x.
112. Lee CK, Barlogie B, Munshi N, Zangari M, Fassas A, Jacobson J, et al. DTPACE: an effective, novel combination chemotherapy with thalidomide for previously treated patients with myeloma. J Clin Oncol. 2003;21(14):2732–9. https://doi.org/10.1200/JCO.2003.01.055.
113. Waage A, Gimsing P, Juliusson G, Turesson I, Gulbrandsen N, Eriksson T, et al. Early response predicts thalidomide efficiency in patients with advanced multiple myeloma. Br J Haematol. 2004;125(2):149–55. https://doi.org/10.1111/j.1365-2141.2004.04879.x.
114. Richardson P, Schlossman R, Jagannath S, Alsina M, Desikan R, Blood E, et al. Thalidomide for patients with relapsed multiple myeloma after high-dose chemotherapy and stem cell transplantation: results of an open-label multicenter phase 2 study of efficacy, toxicity, and biological activity. Mayo Clin Proc. 2004;79(7):875–82. https://doi.org/10.4065/79.7.875.
115. Offidani M, Corvatta L, Marconi M, Olivieri A, Catarini M, Mele A, et al. Thalidomide plus oral melphalan compared with thalidomide alone for advanced multiple myeloma. Hematol J. 2004;5(4):312–7. https://doi.org/10.1038/sj.thj.6200401.
116. García-Sanz R, González-Porras JR, Hernández JM, Polo-Zarzuela M, Sureda A, Barrenetxea C, et al. The oral combination of thalidomide, cyclophosphamide and dexamethasone (ThaCyDex) is effective in relapsed/refractory multiple myeloma. Leukemia. 2004;18(4):856–63. https://doi.org/10.1038/sj.leu.2403322.
117. Dimopoulos MA, Hamilos G, Zomas A, Gika D, Efstathiou E, Grigoraki V, et al. Pulsed cyclophosphamide, thalidomide and dexamethasone: an oral regimen for previously treated patients with multiple myeloma. Hematol J. 2004;5(2):112–7. https://doi.org/10.1038/sj.thj.6200326.
118. Palumbo A, Bertola A, Falco P, Rosato R, Cavallo F, Giaccone L, et al. Efficacy of low-dose thalidomide and dexamethasone as first salvage regimen in multiple myeloma. Hematol J. 2004;5(4):318–24. https://doi.org/10.1038/sj.thj.6200403.
119. Terpos E, Mihou D, Szydlo R, Tsimirika K, Karkantaris C, Politou M, et al. The combination of intermediate doses of thalidomide with dexamethasone is an effective treatment for patients with refractory/relapsed multiple myeloma and normalizes abnormal bone remodeling, through the reduction of sRANKL/osteoprotegerin ratio. Leukemia. 2005;19(11):1969–76. https://doi.org/10.1038/sj.leu.2403890.
120. Schütt P, Ebeling P, Buttkereit U, Brandhorst D, Opalka B, Poser M, et al. Thalidomide in combination with dexamethasone for pretreated patients with multiple myeloma: serum level of soluble interleukin-2 receptor as a predictive factor for response rate and for survival. Ann Hematol. 2005;84(9):594–600. https://doi.org/10.1007/s00277-005-1007-7.
121. Badros AZ, Goloubeva O, Rapoport AP, Ratterree B, Gahres N, Meisenberg B, et al. Phase II study of G3139, a Bcl-2 antisense oligonucleotide, in combination with dexamethasone and thalidomide in relapsed multiple myeloma patients. J Clin Oncol. 2005;23(18):4089–99. https://doi.org/10.1200/JCO.2005.14.381.
122. Kyriakou C, Thomson K, D'Sa S, Flory A, Hanslip J, Goldstone AH, et al. Low-dose thalidomide in combination with oral weekly cyclophosphamide and pulsed dexamethasone is a well tolerated and effective regimen in patients with relapsed and refractory multiple myeloma. Br J Haematol. 2005;129(6):763–70. https://doi.org/10.1111/j.1365-2141.2005.05521.x.
123. Prince HM, Mileshkin L, Roberts A, Ganju V, Underhill C, Catalano J, et al. A multicenter phase II trial of thalidomide and celecoxib for patients with relapsed and refractory multiple myeloma. Clin Cancer Res. 2005;11(15):5504–14. https://doi.org/10.1158/1078-0432.CCR-05-0213.
124. Offidani M, Corvatta L, Marconi M, Visani G, Alesiani F, Brunori M, et al. Low-dose thalidomide with pegylated liposomal doxorubicin and high-dose dexamethasone for relapsed/refractory multiple myeloma: a prospective, multicenter, phase II study. Haematologica. 2006;91(1):133–6.
125. Hussein MA, Baz R, Srkalovic G, Agrawal N, Suppiah R, Hsi E, et al. Phase 2 study of pegylated liposomal doxorubicin, vincristine, decreased-frequency dexamethasone, and thalidomide

in newly diagnosed and relapsed-refractory multiple myeloma. Mayo Clin Proc. 2006;81(7):889–95. https://doi.org/10.4065/81.7.889.
126. Palumbo A, Avonto I, Bruno B, Falcone A, Scalzulli PR, Ambrosini MT, et al. Intermediate-dose melphalan (100 mg/m2)/bortezomib/thalidomide/dexamethasone and stem cell support in patients with refractory or relapsed myeloma. Clin Lymphoma Myeloma. 2006;6(6):475–7. https://doi.org/10.3816/CLM.2006.n.028.
127. Palumbo A, Ambrosini MT, Benevolo G, Pregno P, Pescosta N, Callea V, et al. Bortezomib, melphalan, prednisone, and thalidomide for relapsed multiple myeloma. Blood. 2007;109(7):2767–72. https://doi.org/10.1182/blood-2006-08-042275.
128. Suvannasankha A, Fausel C, Juliar BE, Yiannoutsos CT, Fisher WB, Ansari RH, et al. Final report of toxicity and efficacy of a phase II study of oral cyclophosphamide, thalidomide, and prednisone for patients with relapsed or refractory multiple myeloma: a Hoosier Oncology Group Trial, HEM01-21. Oncologist. 2007;12(1):99–106. https://doi.org/10.1634/theoncologist.12-1-99.
129. Murakami H, Handa H, Abe M, et al. Low-dose thalidomide plus low-dose dexamethasone therapy in patients with refractory multiple myeloma. Eur J Haematol. 2007;79(3):234–9. https://doi.org/10.1111/j.1600-0609.2007.00908.x.
130. Maisnar V, Radocha J, Büchler T, Bláha V, Malý J, Hájek R. Monotherapy with low-dose thalidomide for relapsed or refractory multiple myeloma: better response rate with earlier treatment. Eur J Haematol. 2007;79(4):305–9. https://doi.org/10.1111/j.1600-0609.2007.00930.x.
131. Hattori Y, Okamoto S, Shimada N, Kakimoto T, Morita K, Tanigawara Y, et al. Single-institute phase 2 study of thalidomide treatment for refractory or relapsed multiple myeloma: prognostic factors and unique toxicity profile. Cancer Sci. 2008;99(6):1243–50. https://doi.org/10.1111/j.1349-7006.2008.00792.x.
132. Morris TC, Kettle PJ, Drake M, Jones FC, Hull DR, Boyd K, et al. Clarithromycin with low dose dexamethasone and thalidomide is effective therapy in relapsed/refractory myeloma. Br J Haematol. 2008;143(3):349–54. https://doi.org/10.1111/j.1365-2141.2008.07360.x.
133. Pineda-Roman M, Zangari M, van Rhee F, Anaissie E, Szymonifka J, Hoering A, et al. VTD combination therapy with bortezomib-thalidomide-dexamethasone is highly effective in advanced and refractory multiple myeloma. Leukemia. 2008;22(7):1419–27. https://doi.org/10.1038/leu.2008.99.
134. Terpos E, Kastritis E, Roussou M, Heath D, Christoulas D, Anagnostopoulos N, et al. The combination of bortezomib, melphalan, dexamethasone and intermittent thalidomide is an effective regimen for relapsed/refractory myeloma and is associated with improvement of abnormal bone metabolism and angiogenesis. Leukemia. 2008;22(12):2247–56. https://doi.org/10.1038/leu.2008.235.
135. Pönisch W, Rozanski M, Goldschmidt H, Hoffmann FA, Boldt T, Schwarzer A, et al. Combined bendamustine, prednisolone and thalidomide for refractory or relapsed multiple myeloma after autologous stem-cell transplantation or conventional chemotherapy: results of a Phase I clinical trial. Br J Haematol. 2008;143(2):191–200. https://doi.org/10.1111/j.1365-2141.2008.07076.x.
136. Srikanth M, Davies FE, Wu P, Jenner MW, Ethell ME, Potter MN, et al. Survival and outcome of blastoid variant myeloma following treatment with the novel thalidomide containing regime DT-PACE. Eur J Haematol. 2008;81(6):432–6. https://doi.org/10.1111/j.1600-0609.2008.01131.x.
137. Kim YK, Sohn SK, Lee JH, Yang DH, Moon JH, Ahn JS, et al. Clinical efficacy of a bortezomib, cyclophosphamide, thalidomide, and dexamethasone (Vel-CTD) regimen in patients with relapsed or refractory multiple myeloma: a phase II study. Ann Hematol. 2010;89(5):475–82. https://doi.org/10.1007/s00277-009-0856-x.
138. Palumbo A, Larocca A, Falco P, Sanpaolo G, Falcone AP, Federico V, et al. Lenalidomide, melphalan, prednisone and thalidomide (RMPT) for relapsed/refractory multiple myeloma. Leukemia. 2010;24(5):1037–42. https://doi.org/10.1038/leu.2010.58.
139. Lee SS, Suh C, Kim BS, Chung J, Joo YD, Ryoo HM, et al. Bortezomib, doxorubicin, and dexamethasone combination therapy followed by thalidomide and dexamethasone consolidation as a salvage treatment for relapsed or refractory multiple myeloma: analysis of efficacy and safety. Ann Hematol. 2010;89(9):905–12. https://doi.org/10.1007/s00277-010-0943-z.
140. Hus M, Grzasko N, Szostek M, Pluta A, Helbig G, Woszczyk D, et al. Thalidomide, dexamethasone and lovastatin with autologous stem cell transplantation as a salvage immunomodulatory therapy in patients with relapsed and refractory multiple myeloma. Ann Hematol. 2011;90(10):1161–6. https://doi.org/10.1007/s00277-011-1276-2.
141. Offidani M, Corvatta L, Polloni C, Gentili S, Mele A, Rizzi R, et al. Thalidomide, dexamethasone, Doxil and Velcade (ThaDD-V) followed by consolidation/maintenance therapy in patients with relapsed-refractory multiple myeloma. Ann Hematol. 2011;90(12):1449–56. https://doi.org/10.1007/s00277-011-1217-0.
142. Zamagni E, Petrucci A, Tosi P, Tacchetti P, Perrone G, Brioli A, et al. Long-term results of thalidomide and dexamethasone (thal-dex) as therapy of first relapse in multiple myeloma. Ann Hematol. 2012;91(3):419–26. https://doi.org/10.1007/s00277-011-1320-2.
143. Yakoub-Agha I, Mary JY, Hulin C, Doyen C, Marit G, Benboubker L, et al. Low-dose vs. high-dose thalidomide for advanced multiple myeloma: a prospective trial from the Intergroupe Francophone du Myélome. Eur J Haematol. 2012;88(3):249–59. https://doi.org/10.1111/j.1600-0609.2011.01729.x.
144. Kropff M, Baylon HG, Hillengass J, Robak T, Hajek R, Liebisch P, et al. Thalidomide versus dexamethasone for the treatment of relapsed and/or refractory multiple myeloma: results from OPTIMUM, a randomized trial. Haematologica. 2012;97(5):784–91. https://doi.org/10.3324/haematol.2011.044271.
145. Hjorth M, Hjertner Ø, Knudsen LM, Gulbrandsen N, Holmberg E, Pedersen PT, et al. Thalidomide and dexamethasone vs. bortezomib and dexamethasone for melphalan refractory myeloma: a randomized study. Eur J Haematol. 2012;88(6):485–96. https://doi.org/10.1111/j.1600-0609.2012.01775.x.
146. Garderet L, Iacobelli S, Moreau P, Dib M, Lafon I, Niederwieser D, et al. Superiority of the triple combination of bortezomib-thalidomide-dexamethasone over the dual combination of thalidomide-dexamethasone in patients with multiple myeloma progressing or relapsing after autologous transplantation: the MMVAR/IFM 2005–04 randomized phase III trial from the chronic leukemia working party of the European Group for blood and marrow transplantation. J Clin Oncol. 2012;30(20):2475–82. https://doi.org/10.1200/JCO.2011.37.4918.
147. Offidani M, Polloni C, Cavallo F, Liberati AM, Ballanti S, Pulini S, et al. Phase II study of melphalan, thalidomide and prednisone combined with oral panobinostat in patients with relapsed/refractory multiple myeloma. Leuk Lymphoma. 2012;53(9):1722–7. https://doi.org/10.3109/10428194.2012.664844.
148. Geng C, Hou J, Zhao Y, Ke X, Wang Z, Qiu L, et al. A multicenter, open-label phase II study of recombinant CPT (Circularly Permuted TRAIL) plus thalidomide in patients with relapsed and refractory multiple myeloma. Am J Hematol. 2014;89(11):1037–42. https://doi.org/10.1002/ajh.23822.

149. Schey S, Brown SR, Tillotson AL, Yong K, Williams C, Davies F, et al. Bendamustine, thalidomide and dexamethasone combination therapy for relapsed/refractory myeloma patients: results of the MUKone randomized dose selection trial. Br J Haematol. 2015;170(3):336–48. https://doi.org/10.1111/bjh.13435.
150. Mateos MV, Granell M, Oriol A, Martinez-Lopez J, Blade J, Hernandez MT, et al. Elotuzumab in combination with thalidomide and low-dose dexamethasone: a phase 2 single-arm safety study in patients with relapsed/refractory multiple myeloma. Br J Haematol. 2016;175(3):448–56. https://doi.org/10.1111/bjh.14263.
151. Popat R, Brown SR, Flanagan L, Hall A, Gregory W, Kishore B, et al. Bortezomib, thalidomide, dexamethasone, and panobinostat for patients with relapsed multiple myeloma (MUK-six): a multicentre, open-label, phase 1/2 trial. Lancet Haematol. 2016;3(12):e572–80. https://doi.org/10.1016/S2352-3026(16)30165-X.
152. Kwon J, Min CK, Kim K, Han JJ, Moon JH, Kang HJ, et al. Efficacy and toxicity of the combination chemotherapy of thalidomide, alkylating agent, and steroid for relapsed/refractory myeloma patients: a report from the Korean Multiple Myeloma Working Party (KMMWP) retrospective study. Cancer Med. 2017;6(1):100–8. https://doi.org/10.1002/cam4.970.
153. Leng Y, Hou J, Jin J, Zhang M, Ke X, Jiang B, et al. Circularly permuted TRAIL plus thalidomide and dexamethasone versus thalidomide and dexamethasone for relapsed/refractory multiple myeloma: a phase 2 study. Cancer Chemother Pharmacol. 2017;79(6):1141–9. https://doi.org/10.1007/s00280-017-3310-0.
154. Mian M, Pescosta N, Badiali S, Cappelletto PC, Marcheselli L, Luminari S, et al. Phase II trial to investigate efficacy and safety of bendamustine, dexamethasone and thalidomide in relapsed or refractory multiple myeloma patients after treatment with lenalidomide and bortezomib. Br J Haematol. 2019;185(5):944–7. https://doi.org/10.1111/bjh.15645.
155. Ludwig H, Poenisch W, Knop S, Egle A, Schreder M, Lechner D, et al. Ixazomib–thalidomide–dexamethasone for induction therapy followed by ixazomib maintenance treatment in patients with relapsed/refractory multiple myeloma. Br J Cancer. 2019;121(9):751–7. https://doi.org/10.1038/s41416-019-0581-8.
156. Lee HC, Shah JJ, Feng L, Morphey A, Johnson RJ, Wesson ET, et al. A phase I/II trial of the combination of lenalidomide, thalidomide and dexamethasone in relapsed and/or refractory multiple myeloma. Am J Hematol. 2019;94(12):E319–22. https://doi.org/10.1002/ajh.25633.
157. Bergin K, Yuen F, Wallington-Beddoe C, Kalff A, Sirdesai S, Reynolds J, et al. A phase II trial of continuous ixazomib, thalidomide and dexamethasone for relapsed and/or refractory multiple myeloma: the Australasian Myeloma Research Consortium (AMaRC) 16–02 trial. Br J Haematol. 2021;194(3):580–6. https://doi.org/10.1111/bjh.17504.
158. Rajkumar SV, Harousseau JL, Durie B, Anderson KC, Dimopoulos M, Kyle R, et al. Consensus recommendations for the uniform reporting of clinical trials: report of the International Myeloma Workshop Consensus Panel 1. Blood. 2011;117(18):4691–5. https://doi.org/10.1182/blood-2010-10-299487.
159. Glasmacher A, Hahn C, Hoffmann F, Naumann R, Goldschmidt H, von Lilienfeld-Toal M, et al. A systematic review of phase-II trials of thalidomide monotherapy in patients with relapsed or refractory multiple myeloma. Br J Haematol. 2006;132(5):584–93. https://doi.org/10.1111/j.1365-2141.2005.05914.x.
160. Hideshima T, Chauhan D, Shima Y, Raje N, Davies FE, Tai YT, et al. Thalidomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood. 2000;96(9):2943–50.
161. von Lilienfeld-Toal M, Hahn-Ast C, Furkert K, Hoffmann F, Naumann R, Bargou R, et al. A systematic review of phase II trials of thalidomide/dexamethasone combination therapy in patients with relapsed or refractory multiple myeloma. Eur J Haematol. 2008;81(4):247–52. https://doi.org/10.1111/j.1600-0609.2008.01121.x.
162. Lee JH, Kim SH. Treatment of relapsed and refractory multiple myeloma. Blood Res. 2020;55(S1):S43–53. https://doi.org/10.5045/br.2020.S008.
163. Bogeljić Patekar M, Milunović V, Mišura Jakobac K, Perica D, Mandac Rogulj I, Kursar M, et al. Bendamustine: an old drug in the new era for patients with non-Hodgkin lymphomas and chronic lymphocytic leukemia. Acta Clin Croat. 2018;57(3):542–53. https://doi.org/10.20471/acc.2018.57.03.18.
164. Kumar SK, Krishnan A, LaPlant B, Laumann K, Roy V, Zimmerman T, et al. Bendamustine, lenalidomide, and dexamethasone (BRD) is highly effective with durable responses in relapsed multiple myeloma. Am J Hematol. 2015;90(12):1106–10. https://doi.org/10.1002/ajh.24181.
165. Mey UJ, Brugger W, Schwarb H, Pederiva S, Schwarzer A, Dechow T, et al. Bendamustine, lenalidomide and dexamethasone (BRd) has high activity as 2nd -line therapy for relapsed and refractory multiple myeloma—a phase II trial. Br J Haematol. 2017;176(5):770–82. https://doi.org/10.1111/bjh.14481.
166. Dhakal B, D'Souza A, Hamadani M, Arce-Lara C, Schroeder K, Chhabra S, et al. Phase I/II trial of bendamustine, ixazomib, and dexamethasone in relapsed/refractory multiple myeloma. Blood Cancer J. 2019;9(8):56. https://doi.org/10.1038/s41408-019-0219-3.
167. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood. 2001;98(5):1614–5. https://doi.org/10.1182/blood.v98.5.1614.
168. Gerrie AS, Mikhael JR, Cheng L, Jiang H, Kukreti V, Panzarella T, et al. D(T)PACE as salvage therapy for aggressive or refractory multiple myeloma. Br J Haematol. 2013;161(6):802–10. https://doi.org/10.1111/bjh.12325.
169. Buda G, Orciuolo E, Galimberti S, Ghio F, Petrini M. VDT-PACE as salvage therapy for heavily pretreated MM patients. Blood. 2013;122(21):5377. https://doi.org/10.1182/blood.V122.21.5377.5377.
170. Beyer K, Rosner S, Woo KM, Devlin SM, Landau H, Hassoun H, et al. Analysis of VDT-PACE utilization in multiple myeloma patients treated at MSKCC for relapsed disease or cytoreduction and stem cell mobilization after initial induction therapy. Blood. 2014;124(21):3459. https://doi.org/10.1182/blood.V124.21.3459.3459.
171. Ainley L, Chavda SJ, Counsell N, Cheesman S, Newrick F, Horder J, et al. DT-PACE/ESHAP chemotherapy regimens as salvage therapy for multiple myeloma prior to autologous stem cell transplantation. Br J Haematol. 2021;192(3):e73–7. https://doi.org/10.1111/bjh.17248.
172. Lakshman A, Singh PP, Rajkumar SV, Dispenzieri A, Lacy MQ, Gertz MA, et al. Efficacy of VDT PACE-like regimens in treatment of relapsed/refractory multiple myeloma. Am J Hematol. 2018;93(2):179–86. https://doi.org/10.1002/ajh.24954.
173. Pineda-Roman M, Zangari M, Haessler J, Anaissie E, Tricot G, van Rhee F, et al. Sustained complete remissions in multiple myeloma linked to bortezomib in total therapy 3: comparison with total therapy 2. Br J Haematol. 2008;140(6):625–34. https://doi.org/10.1111/j.1365-2141.2007.06921.x.
174. Koeppen S. Treatment of multiple myeloma: thalidomide-, bortezomib-, and lenalidomide-induced peripheral neuropathy. Oncol Res Treat. 2014;37(9):506–13. https://doi.org/10.1159/000365534.

175. Mohan M, Matin A, Davies FE. Update on the optimal use of bortezomib in the treatment of multiple myeloma. Cancer Manag Res. 2017;9:51–63. https://doi.org/10.2147/CMAR.S105163.
176. Mikhael JR, Reeder CB, Libby EN, Costa LJ, Bergsagel PL, Buadi F, et al. Phase Ib/II trial of CYKLONE (cyclophosphamide, carfilzomib, thalidomide and dexamethasone) for newly diagnosed myeloma. Br J Haematol. 2015;169(2):219–27. https://doi.org/10.1111/bjh.13296.
177. Waxman AJ, Clasen S, Hwang WT, Garfall A, Vogl DT, Carver J, et al. Carfilzomib-associated cardiovascular adverse events: a systematic review and meta-analysis. JAMA Oncol. 2018;4(3):e174519. https://doi.org/10.1001/jamaoncol.2017.4519.
178. Chng W, Lin C, Li X, Nagarajan C, Yoon S, Durie BGM. Phase 2 study of daratumumab in combination with thalidomide and dexamethasone in Asian patients with relapsed/refractory myeloma (RRMM)—interim analysis of a trial by the Asian Myeloma Network (AMN). Blood. 2020;136(Suppl 1):21. https://doi.org/10.1182/blood-2020-139092.
179. Chanan-Khan A. Immunomodulating drugs for the treatment of cancer. 1st ed. Philadelphia: Lippincott Williams & Wilkins: Wolters Kluwer; 2011.
180. Sonneveld P, De Wit E, Moreau P. How have evolutions in strategies for the treatment of relapsed/refractory multiple myeloma translated into improved outcomes for patients? Crit Rev Oncol Hematol. 2017;112:153–70. https://doi.org/10.1016/j.critrevonc.2017.02.007.
181. Thompson JL, Hansen LA. Thalidomide dosing in patients with relapsed or refractory multiple myeloma. Ann Pharmacother. 2003;37(4):571–6. https://doi.org/10.1345/aph.1A155.
182. Palumbo A, Rajkumar SV, Dimopoulos MA, Richardson PG, San Miguel J, Barlogie B, et al. Prevention of thalidomide- and lenalidomide-associated thrombosis in myeloma. Leukemia. 2008;22(2):414–23. https://doi.org/10.1038/sj.leu.2405062.
183. Guglielmelli T, Petrucci MT, Saglio G, Palumbo A. Thalidomide after lenalidomide: a possible treatment regimen in relapsed refractory multiple myeloma patients. Br J Haematol. 2011;152(1):108–10. https://doi.org/10.1111/j.1365-2141.2010.08416.x.
184. Dingli D, Ailawadhi S, Bergsagel PL, Buadi FK, Dispenzieri A, Fonseca R, et al. Therapy for relapsed multiple myeloma: guidelines from the mayo stratification for myeloma and risk-adapted therapy. Mayo Clin Proc. 2017;92(4):578–98. https://doi.org/10.1016/j.mayocp.2017.01.003.
185. Palumbo A, Cerrato C. Diagnosis and therapy of multiple myeloma. Korean J Intern Med. 2013;28(3):263–73. https://doi.org/10.3904/kjim.2013.28.3.263.
186. Rajkumar SV, Blood E, Vesole D, Fonseca R, Greipp PR. Eastern Cooperative Oncology Group. Phase III clinical trial of thalidomide plus dexamethasone compared with dexamethasone alone in newly diagnosed multiple myeloma: a clinical trial coordinated by the Eastern Cooperative Oncology Group. J Clin Oncol. 2006;24(3):431–6. https://doi.org/10.1200/JCO.2005.03.0221.
187. Paul B, Lipe B, Ocio EM, Usmani SZ. Induction therapy for newly diagnosed multiple myeloma. Am Soc Clin Oncol Educ Book. 2019;39:e176–86. https://doi.org/10.1200/EDBK_238527.
188. Mai EK, Bertsch U, Dürig J, Kunz C, Haenel M, Blau IW, et al. Phase III trial of bortezomib, cyclophosphamide and dexamethasone (VCD) versus bortezomib, doxorubicin and dexamethasone (PAd) in newly diagnosed myeloma. Leukemia. 2015;29(8):1721–9. https://doi.org/10.1038/leu.2015.80.
189. Moreau P, Hulin C, Macro M, Caillot D, Chaleteix C, Roussel M, et al. VTD is superior to VCD prior to intensive therapy in multiple myeloma: results of the prospective IFM2013-04 trial. Blood. 2016;127(21):2569–74. https://doi.org/10.1182/blood-2016-01-693580.
190. Leiba M, Kedmi M, Duek A, Freidman T, Weiss M, Leiba R, et al. Bortezomib-cyclophosphamide-dexamethasone (VCD) versus bortezomib-thalidomide-dexamethasone (VTD) -based regimens as induction therapies in newly diagnosed transplant eligible patients with multiple myeloma: a meta-analysis. Br J Haematol. 2014;166(5):702–10. https://doi.org/10.1111/bjh.12946.
191. Rosinol L, Hebraud B, Oriol A, Colin AL, Tamayo RR, Hulin C, et al. Integrated analysis of bortezomib–lenalidomide–dexamethasone vs bortezomib–thalidomide–dexamethasone in transplant-eligible newly diagnosed myeloma. Clin Lymphoma Myeloma Leuk. 2019;19(Suppl 10):1–2.
192. Zangari M, van Rhee F, Anaissie E, Pineda-Roman M, Haessler J, Crowley J, et al. Eight-year median survival in multiple myeloma after total therapy 2: roles of thalidomide and consolidation chemotherapy in the context of total therapy 1. Br J Haematol. 2008;141(4):433–44. https://doi.org/10.1111/j.1365-2141.2008.06982.x.
193. Wester R, van der Holt B, Asselbergs E, Zweegman S, Kersten MJ, Vellenga E, et al. Phase II study of carfilzomib, thalidomide, and low-dose dexamethasone as induction and consolidation in newly diagnosed, transplant eligible patients with multiple myeloma; the Carthadex trial. Haematologica. 2019;104(11):2265–73. https://doi.org/10.3324/haematol.2018.205476.
194. Paumgartten FJR. The tale of lenalidomide clinical superiority over thalidomide and regulatory and cost-effectiveness issues. Cien Saude Colet. 2019;24(10):3783–92. https://doi.org/10.1590/1413-812320182410.28522017.
195. Lee HS, Min CK, Lee JJ, Kim K, Kim SJ, Yoon DH, et al. The clinical impact of thalidomide maintenance after autologous stem cell transplantation in patients with newly diagnosed multiple myeloma in real clinical practice of Korea. Ann Hematol. 2016;95(6):911–9. https://doi.org/10.1007/s00277-016-2660-8.
196. Ludwig H, Durie BG, McCarthy P, Palumbo A, San Miguel J, Barlogie B, et al. IMWG consensus on maintenance therapy in multiple myeloma. Blood. 2012;119(13):3003–15. https://doi.org/10.1182/blood-2011-11-374249.
197. Berenson JR. Antitumor effects of bisphosphonates: from the laboratory to the clinic. Curr Opin Support Palliat Care. 2011;5(3):233–40. https://doi.org/10.1097/SPC.0b013e328349dc17.
198. Attal M, Harousseau JL, Leyvraz S, Doyen C, Hulin C, Benboubker L, et al. Maintenance therapy with thalidomide improves survival in patients with multiple myeloma. Blood. 2006;108(10):3289–94. https://doi.org/10.1182/blood-2006-05-022962.
199. Dimopoulos MA, Jakubowiak AJ, McCarthy PL, Orlowski RZ, Attal M, Bladé J, et al. Developments in continuous therapy and maintenance treatment approaches for patients with newly diagnosed multiple myeloma. Blood Cancer J. 2020;10(2):17. https://doi.org/10.1038/s41408-020-0273-x.
200. Morgan GJ, Gregory WM, Davies FE, Bell SE, Szubert AJ, Brown JM, et al. The role of maintenance thalidomide therapy in multiple myeloma: MRC Myeloma IX results and meta-analysis. Blood. 2012;119(1):7–15. https://doi.org/10.1182/blood-2011-06-357038.
201. Barlogie B, Attal M, Crowley J, van Rhee F, Szymonifka J, Moreau P, et al. Long-term follow-up of autotransplantation trials for multiple myeloma: update of protocols conducted by the intergroupe francophone du myelome, southwest oncology group, and university of arkansas for medical sciences. J Clin Oncol. 2010;28(7):1209–14. https://doi.org/10.1200/JCO.2009.25.6081.
202. Ramasamy K, Dhanasiri S, Thom H, Buchanan V, Robinson S, D'Souza VK, et al. Relative efficacy of treatment options in transplant-ineligible newly diagnosed multiple myeloma: results

from a systematic literature review and network meta-analysis. Leuk Lymphoma. 2020;61(3):668–79. https://doi.org/10.1080/10428194.2019.1683736.
203. Fayers PM, Palumbo A, Hulin C, Waage A, Wijermans P, Beksaç M, et al. Thalidomide for previously untreated elderly patients with multiple myeloma: meta-analysis of 1685 individual patient data from 6 randomized clinical trials. Blood. 2011;118(5):1239–47. https://doi.org/10.1182/blood-2011-03-341669.
204. Kaweme NM, Changwe GJ, Zhou F. Approaches and challenges in the management of multiple myeloma in the very old: future treatment prospects. Front Med (Lausanne). 2021;8: 612696. https://doi.org/10.3389/fmed.2021.612696.
205. Benboubker L, Dimopoulos MA, Dispenzieri A, Catalano J, Belch AR, Cavo M, et al. Lenalidomide and dexamethasone in transplant-ineligible patients with myeloma. N Engl J Med. 2014;371(10):906–17. https://doi.org/10.1056/NEJMoa1402551.
206. Stewart AK, Jacobus S, Fonseca R, Weiss M, Callander NS, Chanan-Khan AA, et al. Melphalan, prednisone, and thalidomide vs melphalan, prednisone, and lenalidomide (ECOG E1A06) in untreated multiple myeloma. Blood. 2015;126(11):1294–301. https://doi.org/10.1182/blood-2014-12-613927.
207. Zweegman S, van der Holt B, Mellqvist UH, Salomo M, Bos GM, Levin MD, et al. Melphalan, prednisone, and lenalidomide versus melphalan, prednisone, and thalidomide in untreated multiple myeloma. Blood. 2016;127(9):1109–16. https://doi.org/10.1182/blood-2015-11-679415.
208. Gavriatopoulou M, Terpos E, Kastritis E, Dimopoulos MA. Current treatments for renal failure due to multiple myeloma. Expert Opin Pharmacother. 2016;17(16):2165–77. https://doi.org/10.1080/14656566.2016.1236915.
209. Chu P. Managing multiple myeloma patients with renal failure. Hong Kong J Nephrol. 2013;15(2):62–7. https://doi.org/10.1016/j.hkjn.2013.09.001.
210. Bozic B, Rutner J, Zheng C, Ruckser R, Selimi F, Racz K, et al. Advances in the treatment of relapsed and refractory multiple myeloma in patients with renal insufficiency: novel agents, immunotherapies and beyond. Cancers (Basel). 2021;13(20):5036. https://doi.org/10.3390/cancers13205036.
211. Bridoux F, Leung N, Belmouaz M, Royal V, Ronco P, Nasr SH, et al. Management of acute kidney injury in symptomatic multiple myeloma. Kidney Int. 2021;99(3):570–80. https://doi.org/10.1016/j.kint.2020.11.010.
212. Gavriatopoulou M, Terpos E, Dimopoulos MA. IMiDs for myeloma induced renal impairment. Oncotarget. 2018;9(84):35476–7. https://doi.org/10.18632/oncotarget.26270.
213. Wanchoo R, Abudayyeh A, Doshi M, Edeani A, Glezerman IG, Monga D, et al. Renal toxicities of novel agents used for treatment of multiple myeloma. Clin J Am Soc Nephrol. 2017;12(1):176–89. https://doi.org/10.2215/CJN.06100616.
214. Palumbo A, Facon T, Sonneveld P, Bladè J, Offidani M, Gay F, et al. Thalidomide for treatment of multiple myeloma: 10 years later. Blood. 2008;111(8):3968–77. https://doi.org/10.1182/blood-2007-10-117457.
215. Chen N, Lau H, Kong L, Kumar G, Zeldis JB, Knight R, et al. Pharmacokinetics of lenalidomide in subjects with various degrees of renal impairment and in subjects on hemodialysis. J Clin Pharmacol. 2007;47(12):1466–75. https://doi.org/10.1177/0091270007309563.
216. Tosi P, Zamagni E, Cellini C, Cangini D, Tacchetti P, Tura S, et al. Thalidomide alone or in combination with dexamethasone in patients with advanced, relapsed or refractory multiple myeloma and renal failure. Eur J Haematol. 2004;73(2):98–103. https://doi.org/10.1111/j.1600-0609.2004.00272.x.
217. Kastritis E, Anagnostopoulos A, Roussou M, Gika D, Matsouka C, Barmparousi D, et al. Reversibility of renal failure in newly diagnosed multiple myeloma patients treated with high dose dexamethasone-containing regimens and the impact of novel agents. Haematologica. 2007;92(4):546–9. https://doi.org/10.3324/haematol.10759.
218. Tosi P, Zamagni E, Tacchetti P, Ceccolini M, Perrone G, Brioli A, et al. Thalidomide-dexamethasone as induction therapy before autologous stem cell transplantation in patients with newly diagnosed multiple myeloma and renal insufficiency. Biol Blood Marrow Transplant. 2010;16(8):1115–21. https://doi.org/10.1016/j.bbmt.2010.02.020.
219. Morabito F, Gentile M, Mazzone C, Rossi D, Di Raimondo F, Bringhen S, et al. Safety and efficacy of bortezomib–melphalan–prednisone–thalidomide followed by bortezomib-thalidomide maintenance (VMPT-VT) versus bortezomib–melphalan–prednisone (VMP) in untreated multiple myeloma patients with renal impairment. Blood. 2011;118(22):5759–66. https://doi.org/10.1182/blood-2011-05-353995.
220. Ramasamy K, Hazel B, Mahmood S, Corderoy S, Schey S. Bendamustine in combination with thalidomide and dexamethasone is an effective therapy for myeloma patients with end stage renal disease. Br J Haematol. 2011;155(5):632–4. https://doi.org/10.1111/j.1365-2141.2011.08754.x.
221. Dimopoulos MA, Roussou M, Gkotzamanidou M, Nikitas N, Psimenou E, Mparmparoussi D, et al. The role of novel agents on the reversibility of renal impairment in newly diagnosed symptomatic patients with multiple myeloma. Leukemia. 2013;27(2):423–9. https://doi.org/10.1038/leu.2012.182.
222. Dimopoulos MA, Cheung MC, Roussel M. Impact of renal impairment on outcomes with lenalidomide and dexamethasone treatment in the FIRST trial, a randomized, open-label phase 3 trial in transplant-ineligible patients with multiple myeloma. Haematologica. 2016;101(3):363–70. https://doi.org/10.3324/haematol.2015.133629.
223. Ramasamy K, Drayson MT, Iqbal G, Stalker V, Akhtar S, Dunn J, et al. Optimal—a study of bortezomib, bendamustine and dexamethasone (BBD) vs thalidomide, bendamustine and dexamethasone (BTD) in patients with renal failure defined as an Egfr below 30 Mls/Min. Blood. 2019;134(Suppl 1):3135. https://doi.org/10.1182/blood-2019-128157.
224. Kumar S, Flinn I, Richardson PG, Hari P, Callander N, Noga SJ, et al. Randomized, multicenter, phase 2 study (EVOLUTION) of combinations of bortezomib, dexamethasone, cyclophosphamide, and lenalidomide in previously untreated multiple myeloma. Blood. 2012;119(19):4375–82. https://doi.org/10.1182/blood-2011-11-395749.
225. Schmitt S, Mailaender V, Egerer G, Leo A, Becker S, Reinhardt P, et al. Successful autologous peripheral blood stem cell transplantation in a Jehovah's Witness with multiple myeloma: review of literature and recommendations for high-dose chemotherapy without support of allogeneic blood products. Int J Hematol. 2008;87(3):289–97. https://doi.org/10.1007/s12185-008-0055-x.
226. Dimopoulos MA, Oriol A, Nahi H, San-Miguel J, Bahlis NJ, Usmani SZ, et al. Daratumumab, lenalidomide, and dexamethasone for multiple myeloma. N Engl J Med. 2016;375(14):1319–31. https://doi.org/10.1056/NEJMoa1607751.
227. Xia R, Cheng Y, Han X, Wei Y, Wei X. Ikaros proteins in tumor: current perspectives and new developments. Front Mol Biosci. 2021;8: 788440. https://doi.org/10.3389/fmolb.2021.788440.
228. Swan D, Routledge D, Harrison S. The evolving status of immunotherapies in multiple myeloma: the future role of bispecific antibodies. Br J Haematol. 2022;196(3):488–506. https://doi.org/10.1111/bjh.17805.
229. Hernández-Rivas JÁ, Ríos-Tamayo R, Encinas C, Alonso R, Lahuerta JJ. The changing landscape of relapsed and/or refractory multiple myeloma (MM): fundamentals and controversies. Biomark Res. 2022;10(1):1. https://doi.org/10.1186/s40364-021-00344-2.

230. Berdeja JG, Madduri D, Usmani SZ, Jakubowiak A, Agha M, Cohen AD, et al. Ciltacabtagene autoleucel, a B-cell maturation antigen-directed chimeric antigen receptor T-cell therapy in patients with relapsed or refractory multiple myeloma (CARTITUDE-1): a phase 1b/2 open-label study. Lancet. 2021;398(10297):314–24. https://doi.org/10.1016/S0140-6736(21)00933-8.
231. Hayden PJ, Roddie C, Bader P, Basak GW, Bonig H, Bonini C, et al. Management of adults and children receiving CAR T-cell therapy: 2021 best practice recommendations of the European Society for Blood and Marrow Transplantation (EBMT) and the Joint Accreditation Committee of ISCT and EBMT (JACIE) and the European Haematology Association (EHA). Ann Oncol. 2022;33(3):259–75. https://doi.org/10.1016/j.annonc.2021.12.003.
232. Lonial S, Lee HC, Badros A, Trudel S, Nooka AK, Chari A, 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(2):207–21. https://doi.org/10.1016/S1470-2045(19)30788-0.
233. Becnel MR, Lee HC. The role of belantamab mafodotin for patients with relapsed and/or refractory multiple myeloma. Ther Adv Hematol. 2020;11:2040620720979813. https://doi.org/10.1177/2040620720979813.
234. Popat R, Nooka A, Stockerl-Goldstein K, Abonour R, Ramaekers R, Khot A, et al. DREAMM-6: safety, tolerability and clinical activity of belantamab mafodotin (Belamaf) in combination with bortezomib/dexamethasone (BorDex) in relapsed/refractory multiple myeloma (RRMM). Blood. 2020;136(Suppl 1):19–20. https://doi.org/10.1182/blood-2020-139332.
235. Reece D, Kouroukis CT, Leblanc R, Sebag M, Song K, Ashkenas J. Practical approaches to the use of lenalidomide in multiple myeloma: a Canadian consensus. Adv Hematol. 2012;2012:621958. https://doi.org/10.1155/2012/621958.
236. Works M, Soni N, Hauskins C, Sierra C, Baturevych A, Jones JC, et al. Anti-B-cell maturation antigen chimeric antigen receptor T cell function against multiple myeloma is enhanced in the presence of lenalidomide. Mol Cancer Ther. 2019;18(12):2246–57. https://doi.org/10.1158/1535-7163.MCT-18-1146.
237. Wang X, Walter M, Urak R, Weng L, Huynh C, Lim L, et al. Lenalidomide enhances the function of CS1 chimeric antigen receptor-redirected T cells against multiple myeloma. Clin Cancer Res. 2018;24(1):106–19. https://doi.org/10.1158/1078-0432.CCR-17-0344.
238. Teoh PJ, Chng WJ. CAR T-cell therapy in multiple myeloma: more room for improvement. Blood Cancer J. 2021;11(4):84. https://doi.org/10.1038/s41408-021-00469-5.
239. Cho SF, Lin L, Xing L, Li Y, Wen K, Yu T, et al. The immunomodulatory drugs lenalidomide and pomalidomide enhance the potency of AMG 701 in multiple myeloma preclinical models. Blood Adv. 2020;4(17):4195–207. https://doi.org/10.1182/bloodadvances.2020002524.
240. Louvet C, Nadeem O, Smith EL. Finding the optimal partner to pair with bispecific antibody therapy for multiple myeloma. Blood Cancer Discov. 2021;2(4):297–9. https://doi.org/10.1158/2643-3230.BCD-21-0073.
241. Jan M, Scarfò I, Larson RC, Walker A, Schmidts A, Guirguis AA, et al. Reversible ON- and OFF-switch chimeric antigen receptors controlled by lenalidomide. Sci Transl Med. 2021;13(575):eabb6295. https://doi.org/10.1126/scitranslmed.abb6295.
242. Bhattacharya K, Bentley JP, Ramachandran S, Chang Y, Banahan BF 3rd, Shah R, et al. Phase-specific and lifetime costs of multiple myeloma among older adults in the US. JAMA Netw Open. 2021;4(7): e2116357. https://doi.org/10.1001/jamanetworkopen.2021.16357.
243. Blommestein HM, Franken MG, van Beurden-Tan CHY, Blijlevens NMA, Huijgens PC, Sonneveld P, et al. Cost-effectiveness of novel treatment sequences for transplant-ineligible patients with multiple myeloma. JAMA Netw Open. 2021;4(3): e213497. https://doi.org/10.1001/jamanetworkopen.2021.3497.