Multiple myeloma: newly approved drugs forge paradigm shift toward chronic disease

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The pace of drug development for multiple myeloma was dizzying in 2015, with 5 regulatory approvals for the treatment of relapsed/refractory disease, 3 in a single month. As we stand on the brink of another paradigm shift in the management of this disease, we discuss the new classes of drugs and how they are shaping standard of care with the potential to make multiple myeloma a chronic disease.

Historic improvements

The treatment of multiple myeloma, the second most common hematologic malignancy, has improved dramatically from the rhubarb pill and infusion of orange peel administered to the first well-documented patient in 1844. The use of high-dose chemotherapy led to significant survival gains and autologous stem-cell transplantation (SCT) offers a very real chance of cure in a small proportion of eligible patients. Nonetheless, multiple myeloma remains an incurable malignancy.

In the past 2 decades, a slew of new drugs drove a paradigm shift in the treatment of multiple myeloma, that brought with it further improvements in patient outcomes, in both transplant-eligible and -ineligible patients (Figure 1).

Chief among them were immunomodulatory drugs (IMiDs) – thalidomide and its analogs. Renowned for its disastrous teratogenic effects when given as a treatment for morning sickness in the 1950s, its potential anti-cancer effects were noted at the time, but it wasn't until decades later that it was pursued further.[1]

Thalidomide was ultimately approved for the treatment of multiple myeloma in the United States in 2006, but in an attempt to improve efficacy and minimize toxicity, several analogs were synthesized. Lenalidomide also was awarded US Food and Drug Administration (FDA) approval in 2006 and pomalidomide joined them in 2013.[2-4]

The precise mechanism of action of IMiDs is somewhat unclear. They were developed primarily because of their anti-angiogenic effects, at a time when the importance of aberrant angiogenesis in cancer progression was a hot topic. However, their immunomodulatory effects were quickly recognized as a major determinant of their anticancer activity. In large part, they work by boosting the immune response through stimulation of T and natural killer (NK) cells, as well as modulating the production of a variety of immune-mediating molecules, such as cytokines. IMiDs, administered in combination with corticosteroids like dexamethasone, have been incorporated into standard of care for both newly diagnosed and relapsed/refractory disease.[5]

Another key advancement in the treatment of multiple myeloma was the development of proteasome inhibitors. This class of drug targets the 26S proteasome, the cellular machinery responsible for the degradation of regulatory proteins that need to be removed from the cell. Such proteins are tagged with ubiquitin molecules, which marks them for destruction by the proteasome.

Proteasome inhibitors prevent these proteins from being broken down and they are instead allowed to accumulate within the cell, which triggers cell death. Malignant and proliferating cells are more susceptible to proteasome inhibitors as they tend to be more dependent on proteasome activity for their survival. This is particularly true of multiple myeloma cells, which produce large amounts of abnormal immunoglobulin that needs to be cleared from the cell.

Bortezomib was the first proteasome inhibitor, receiving accelerated approval for the treatment of multiple myeloma patients who had received at least 2 prior therapies in 2003, which was subsequently translated into full regulatory approval in patients with relapsed/refractory disease and, in combination with melphalan and prednisone, in treatment-naïve patients.[6,7]

Next-generation proteasome inhibitors

Most patients will eventually relapse and become refractory to treatment with standard therapy, so the development of more effective drugs to treat patients in this setting remains a major unmet need. Remarkably, in this regard we are witnessing yet another paradigm shift in multiple myeloma, as advances in our understanding of its biology have fueled the continued discovery of an unprecedented number of new drugs (Figure 2).

Capitalizing on the success of bortezomib, 2 next-generation proteasome inhibitors are among the expanding treatment options for relapsed/refractory multiple

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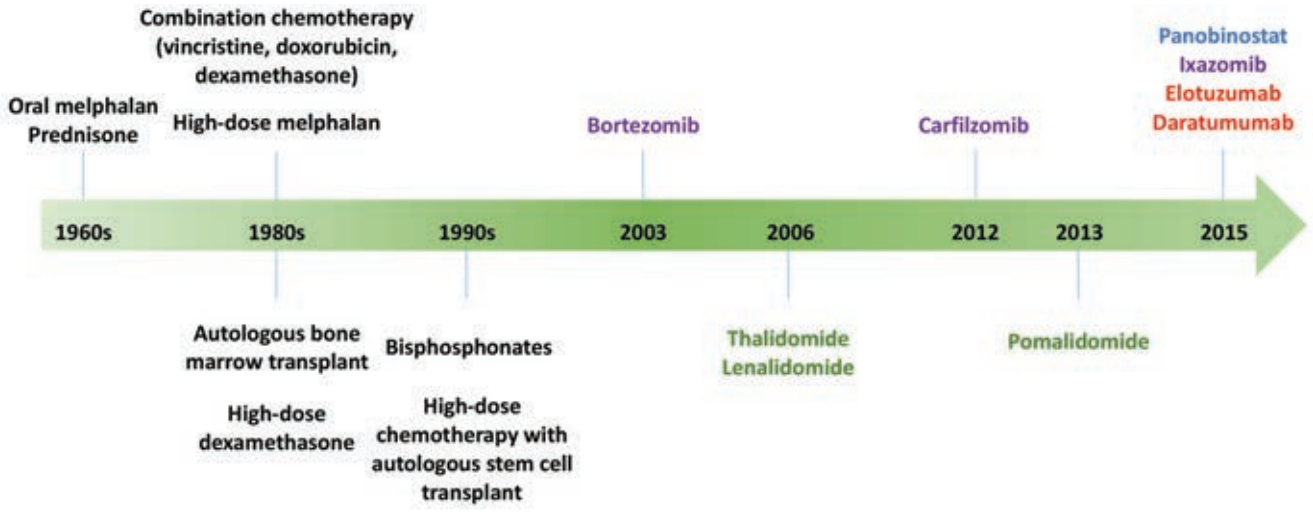

FIGURE 1 Key approvals for the treatment of multiple myeloma: a timeline of drug approvals for multiple myeloma.
■ Immunomodulatory agents ■ Proteasome inhibitors ■ Histone deacetylase inhibitors ■ Monoclonal antibodies.

myeloma. These drugs were designed to have increased potency with fewer side effects compared with bortezomib.[8]

Carfilzomib is an irreversible proteasome inhibitor that is more selective than bortezomib and invokes less neuropathy and myelosuppression, commonly observed with the former. It received accelerated approval from the FDA in 2012, based on the results of a phase 2 trial of 266 heavily pretreated patients (all but 1 with bortezomib) with relapsed/refractory multiple myeloma, in which it demonstrated an overall response rate (ORR) of 23.7%, with a median duration of response (DoR) of 7.8 months. Median progression-free survival (PFS) and overall survival (OS) were 3.7 and 15.6 months, respectively.[9]

Numerous phase 3 trials of carfilzomib are ongoing (Table), and data from several were recently published, including the ENDEAVOR trial, a pivotal head-to-head comparison of carfilzomib and bortezomib, both in combination with dexamethasone. Though data for OS is not yet mature, the carfilzomib-dexamethasone combination doubled PFS, compared with bortezomib-dexamethasone (18.7 vs 9.4 months) over a median follow-up of 11.9 months. Carfilzomib also demonstrated superiority in terms of secondary outcomes, including ORR. There was

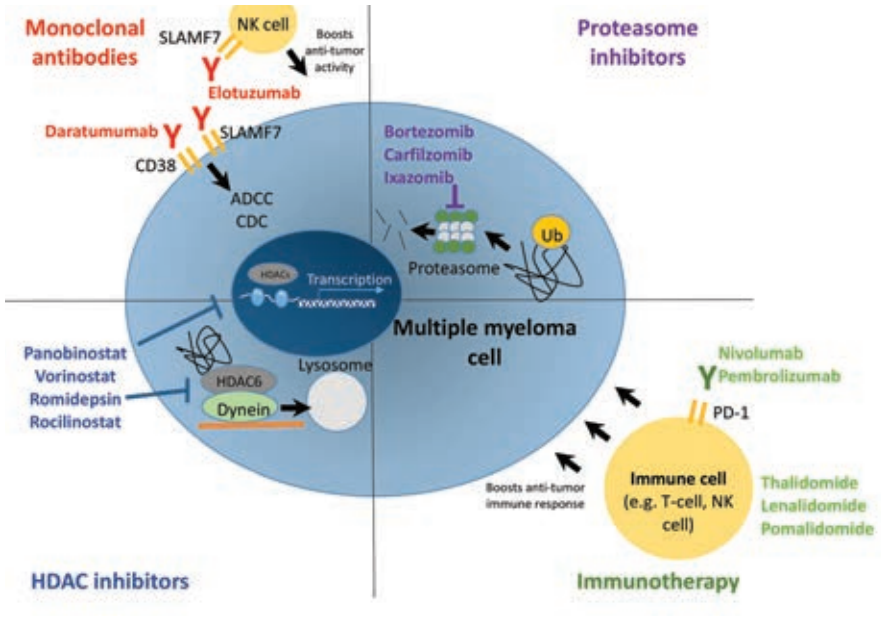

FIGURE 2 Promising new drug classes. The treatment of multiple myeloma has been revolutionized in recent years with the development of numerous different classes of targeted therapies and many more are in clinical development. The most promising recent developments include monoclonal antibodies targeting proteins that are highly expressed on the surface of multiple myeloma cells, including CD38 and SLAMF7. Proteasome inhibitors that inhibit the activity of the ubiquitin-proteasome pathway continue to evolve and show significant efficacy. Proteasome inhibitors have also demonstrated synergy with another class of exciting drugs, HDAC inhibitors that target epigenetic modifications in the cell. Finally, targeted therapies in multiple myeloma are frequently used in combination with the immunomodulatory drugs , but novel forms of immunotherapy have also become a significant focus of research, particularly PD1-targeting immune checkpoint inhibitors.

ADCC, antibody-dependent cellular cytotoxicity; CDC, complement-dependent cytoxicity; HDAC, histone deacetylase; NK, natural killer; PD-1, programmed cell death-1; SLAMF7, signaling lymphocyte activation molecule 7; Ub, ubiquitin

TABLE Clinical development of select targeted therapies in multiple myeloma

Drug	Manufacturer	Select ongoing clinical trials
HDAC inhibitors		
Panobinostat (Farydak) FDA approved	Novartis	Phase 2 + bortezomib and dexamethasone in relapsed/refractory disease (PANORAMA-3; NCT02654990) Phase 2 + high-dose gemcitabine/busulfan/melphalan with ASCT in relapsed/refractory disease (NCT02506959) Phase 1 + lenalidomide, bortezomib and dexamethasone in relapsed/refractory disease (PanRVD; NCT01965353)
CUDC-907	Curis	Phase 1 (NCT01742988)
AR-42	Arno	Phase 1 + pomalidomide in relapsed disease (NCT02569320) Phase 1 in advanced/relapsed disease (NCT01129193)*
Vorinostat (Zolinza)	Merck	Phase 2 + bortezomib and dexamethasone (MUKfour; NCT01720875) Phase 1/2 + doxorubicin and dexamethasone in relapsed/refractory disease (NCT01394354) Phase 1/2 + lenalidomide and dexamethasone in patients refractory to previous lenalidomide-containing regimens (NCT01502085)* Phase 1 + lenalidomide after ASCT (NCT00729118)*
Ricolinostat (ACY-1215)	Acetylon	Phase 1/2 + pomalidomide and low-dose dexamethasone in relapsed/refractory disease (NCT01997840) Phase 1 + pomalidomide and dexamethasone in relapsed/refractory disease (NCT02189343) Phase 1/2 +/- bortezomib and dexamethasone (NCT01323751)*
Proteasome inhibitors		
Bortezomib (Velcade) FDA approved	Millennium	Phase 3 vs carfilzomib with lenalidomide in newly diagnosed disease (NCT01863550) Phase 3 + pomalidomide and low-dose dexamethasone in relapsed/refractory disease (OPTIMISMM; NCT01734928) Phase 3 + lenalidomide and busulfan in patients under 65 years old (NCT01916252) Phase 3 + melphalan for frontline transplant-eligible patients (NCT02197221) Phase 2 + lenalidomide and dexamethasone in newly diagnosed patients (NCT02441686) Phase 1 + G-CSF for stem cell mobilization (NCT02220608) Phase 1 + dinaciclib and dexamethasone in relapsed disease (NCT02668731)
Carfilzomib (Krypolis) FDA approved	Onyx	Phase 3 + lenalidomide and dexamethasone vs lenalidomide alone after stem cell transplant (NCT02659293) Phase 3 vs bortezomib + lenalidomide and dexamethasone in newly diagnosed patients (NCT01863550) Phase 2 + selinexor and dexamethasone in relapsed/refractory disease (SCORE; NCT02628704) Phase 2 in patients who have relapsed after high-dose melphalan with autologous stem cell support (CARFI; NCT02574292) Phase 2 70mg/m^2 weekly dosing in patients refractory to 27mg/m^2 dose (NCT02294357) Phase 1/2 + bendamustine and dexamethasone in newly diagnosed disease (NCT02002598) Phase 1/2 + ibrutinib in patients with relapsed/refractory disease (NCT01962792) Phase 1 + ARRY-520 in relapsed/refractory disease (NCT01372540)
Ixazomib (Ninlaro) FDA approved	Millennium	Phase 3 As maintenance therapy following ASCT (NCT02181413) Phase 3 + lenalidomide and dexamethasone in patients with newly diagnosed disease not eligible for stem cell transplant (NCT01850524) Phase 3 as maintenance therapy in patients with newly diagnosed disease not treated with stem cell transplantation (NCT02312258) Phase 2 + allo-SCT in high-risk disease (NCT02440464) Phase 2 + lenalidomide and dexamethasone post-ASCT followed by maintenance ixazomib or lenalidomide (NCT02253316) Phase 1/2 + bendamustine and dexamethasone in relapsed/refractory disease (NCT02477215)
Marizomib	Triphase	Phase 1 + pomalidomide and dexamethasone in relapsed/refractory disease (NCT02103335) Phase 1/2 in relapsed/refractory disease (NCT00461045)*
Oprozomib	Onyx	Phase 1/2 + dexamethasone and lenalidomide or cyclophosphamide in patients with newly diagnosed disease (NCT01881789)* Phase 1/2 + dexamethasone in relapsed/refractory disease (NCT01832727)* Phase 1/2 + pomalidomide and dexamethasone in relapsed/refractory disease (NCT01999335)*

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TABLE /continued

Drug	Manufacturer	Select ongoing clinical trials
Monoclonal antibodies		
Elotuzumab (Empliciti)	Bristol-Myers Squibb	Phase 3 + bortezomib, lenalidomide and dexamethasone as induction and consolidation therapy and + lenalidomide as maintenance therapy in newly diagnosed disease (NCT02495922) Phase 3 + lenalidomide and dexamethasone in relapsed/refractory disease (ELOQUENT-2; NCT01239797)* Phase 3 + lenalidomide and dexamethasone in previously untreated patients (ELO1; NCT01891643)* Phase 2 + pomalidomide and low-dose dexamethasone in relapsed/refractory disease (NCT02654132) Phase 2 administered over approximately 60 minutes + lenalidomide and dexamethasone in newly diagnosed or relapsed/refractory disease (NCT02159365) Phase 2 + lenalidomide +/- dexamethasone in high-risk smoldering disease (NCT02279394) Phase 2 + bortezomib, lenalidomide and dexamethasone in newly diagnosed disease (NCT02375555) Phase 1 + ASCT and lenalidomide maintenance therapy (NCT02655458)
Daratumumab (Darzalex)	Janssen	Phase 3 + lenalidomide and dexamethasone in previously untreated disease (NCT02252172) Phase 3 in transplant eligible patients with previously untreated disease (Cassiopeia; NCT02541383) Phase 3 + bortezomib, melphalan and prednisone in patients with previously untreated disease (NCT02195479) Phase 2 + dexamethasone in relapsed/refractory disease (NCT02626481) Phase 2 Three dose schedules in smoldering disease (NCT02316106) Phase 1 + various backbone regimens (NCT01998971)
SAR650984	Sanofi	Phase 1 + carfilzomib in relapsed/refractory disease (NCT02332850) Phase 1 + lenalidomide and dexamethasone in relapsed/refractory disease (NCT01749969) Phase 1 in relapsed/refractory disease (NCT02514668) Phase 1 + bortezomib, cyclophosphamide, and dexamethasone in newly diagnosed disease (NCT02513186) Phase 1 + pomalidomide and dexamethasone in relapsed/refractory disease (PomdeSAR; NCT02283775)
MOR-202	MorphoSys	Phase 1/2 in relapsed/refractory disease (NCT01421186)
Indatuximab ravtansine (BT-062)	Biotest	Phase 1/2 + lenalidomide/pomalidomide and dexamethasone in relapsed/refractory disease (NCT01638936)* Phase 1/2 as monotherapy in relapsed/refractory disease (NCT01001442)*
Immune checkpoint inhibitors		
Nivolumab (Opdivo)	Bristol-Myers Squibb	Phase 1/2 + ipilimumab after ASCT in high-risk and recurrent disease (NCT02681302) Phase 1 +/- ipilimumab or lirilumab in relapsed/refractory disease (NCT01592370) Phase 1 in patients with relapsed disease after stem cell transplant (NCT01822509)
Pembrolizumab (Keytruda)	Merck	Phase 3 +/- pomalidomide and low-dose dexamethasone in relapsed/refractory disease (KEYNOTE-183; NCT02576977) Phase 2 in residual disease (NCT02636010) Phase 2 during lymphopenic state after high-dose chemotherapy and ASCT (NCT02331368) Phase 1/2 + pomalidomide in relapsed/refractory disease (NCT02289222) Phase 1 + lenalidomide and dexamethasone (KEYNOTE-023; NCT02036502) Phase 1 + dinaciclib (KEYNOTE-155; NCT02684617)
Atezolizumab (MPDL3280A)	Roche	Phase 1 +/- lenalidomide in patients with relapsed/refractory disease post-ASCT (NCT02431208) Phase 1 as monotherapy in patients with locally advanced or metastatic disease (NCT013755842)
Ipilimumab (Yervoy)	Bristol-Myers Squibb	Phase 1/2 + nivolumab in patients at high risk of recurrence after ASCT (NCT02681302) Phase 1 in patients with relapsed disease after allo-SCT (NCT01822509)

HDAC, histone deacetylase; ASCT, autologous stem cell transplant; allo-SCT, allogeneic stem cell transplant

*Trial is ongoing, but not actively recruiting participants

a slightly higher incidence of serious AEs in the carfilzomib group (48% vs 36%), but a lower incidence of neuropathy.[10]

The ASPIRE trial evaluated carfilzomib in combination with lenalidomide and dexamethasone (carfilzomib group) compared with lenalidomide and dexamethasone alone (control group) in 792 patients with relapsed/refractory disease. PFS was significantly improved in the carfilzomib group compared with the control group (26.3 vs 17.6 months, respectively), as was ORR (87.1% vs 66.7%). Median OS was not yet reached in either group at interim analysis, but 24-month OS was higher with the carfilzomib group than in the control group (73.3% vs 65%). The AE profile was similar to that of the ENDEAVOR trial, and there was a similar incidence of grade 3 or higher AEs between the 2 treatment arms, although carfilzomib-treated patients reported a better health-related quality of life. The results of this trial prompted the FDA in 2015 to expand approval of carfilzomib to include patients with relapsed multiple myeloma who have received at least 1-3 prior lines of therapy.[11]

Another coup for proteasome inhibitors came with the approval of ixazomib in the relapsed/refractory setting in combination with lenalidomide and dexamethasone. Ixazomib is an oral proteasome inhibitor, reversible like bortezomib, but with a significantly shorter half-life. The phase 3 randomized, double-blind TOURMALINE-MM1 trial compared the combination of ixazomib, lenalidomide, and dexamethasone with the lenalidomide and dexamethasone combination in 772 patients with relapsed/refractory disease and the approval marks the first all-oral combination for multiple myeloma.

Results presented at the 2015 annual meeting of the American Society of Hematology (ASH) showed that during a median follow-up of 14.8 months, median PFS was significantly improved in the ixazomib arm compared with the lenalidomide-dexamethasone control group (20.6 vs 14.7 months, respectively), with median times to progression of 1.1 and 1.9 months, respectively. ORR was 78.3% in patients treated with the ixazomib combination, compared to 71.5% with doublet therapy. The benefit of ixazomib was found to be most pronounced in patients with high-risk cytogenetics. The most frequent AEs experienced by patients in the ixazomib arm included diarrhea, rash and constipation. The rates of grade 3 AEs were comparable with doublet and triplet combination therapies and, although neuropathy occurred slightly more frequently with ixazomib, there were fewer cases of renal failure.[12]

Three other phase 3 TOURMALINE trials are ongoing; -MM2 is evaluating ixazomib triplet therapy in newly diagnosed patients, and –MM3 and –MM4 are studying ixazomib as maintenance therapy in patients who have and have not undergone SCT.

HDAC inhibitors have synergistic impact on proteasomal degradation

Another therapeutic strategy came to fruition in 2015, with the approval of the first histone deacetylase (HDAC) inhibitor panobinostat. HDACs are enzymes that control a type of epigenetic modification of the DNA – a secondary level of regulation that dictates when and where genes are expressed. In the case of HDACs, that modification is the removal of acetyl groups from the histone protein "spool" around which the DNA "thread" is wound in the nucleus of nondividing cells. Deacetylation is thought to tighten the spool making the genes within the DNA less available for transcription.

High levels of HDAC activity have been shown to be associated with the silencing of tumor suppressor genes, leading to the development of various forms of cancer, including multiple myeloma. Thus, inhibiting HDAC activity could help to reactivate these genes on an epigenetic level.[13]

Numerous HDAC inhibitors are being developed, including panobinostat, which is a pan-HDAC inhibitor that has broad-spanning inhibitory activity across many members of the HDAC enzyme family. Though single agent activity proved disappointing, promising synergistic activity with proteasome inhibitors culminated in its approval in combination with bortezomib and dexamethasone in patients with relapsed/refractory disease.

Approval was based on a subgroup analysis of the PANORAMA-1 trial among 193 patients who had received at least 2 prior therapies. Median PFS in the combination arm (10.6 months) was almost twice that of the bortezomib-dexamethasone doublet arm (5.8 months), with a tumor shrinkage rate of 59% compared with 41% and ORR of 51% compared with 41%. The efficacy of panobinostat comes at the cost of significant toxicity, with higher rates of grade 3-4 and serious AEs and approval was issued with a Boxed Warning and Risk Evaluation and Mitigation Strategy to help clinical oncologists manage AEs.[14]

It is thought that the synergistic activity between proteasome and HDAC inhibitors relates in part to the effects of a specific HDAC enzyme, HDAC6. Resistance to proteasome inhibitors is thought to be mediated by the activation of the unfolded protein response, in which undegraded proteins are organized at a single location in the cell and form an aggresome. This triggers an alternative degradation pathway called autophagy in which the proteins are destroyed in the lysosome. HDAC6 plays an important role in this response since it binds both ubiquitinated proteins and the cellular motor dynein and mediates protein transport to the aggresome. Thus, targeting both HDACs and the proteasome has the potential to target both pathways of protein degradation. Other mechanisms of synergy have also been reported.[15]

Several other HDAC inhibitors are being evaluated in clinical trials (Table). Ricolinostat is a more selective inhibitor that targets just HDAC6. Data from 2 phase 1b trials of this drug were reported at ASH in late 2015. In combination with bortezomib and dexamethasone it was well-tolerated and achieved an ORR of 33%, with many patients experiencing durable responses of 6 months or more. When combined with lenalidomide and dexamethasone in the second study, ORR was 55%.[16,17]

Monoclonal antibodies finally hit home

Monoclonal antibodies directed against specific tumor-associated antigens have engendered significant therapeutic advances in other tumor types. Their utility in multiple myeloma has been hindered by the lack of an ideal antigen that is distinctly but constitutively expressed on multiple myeloma cells, leading to a number of clinical disappointments.

That has changed in recent years, with the discovery of two novel targets – CD38 and signaling lymphocyte activation molecule F7 (SLAMF7) – which are broadly expressed on multiple myeloma cells, but not on other myeloid and lymphoid cells.

Several monoclonal antibodies targeting these proteins have been developed, with elotuzumab (SLAMF7) and daratumumab (CD38) the most advanced in clinical development, adding two more approvals to the multiple myeloma docket in 2015. They bind to multiple myeloma cells and induce cell death through a number of different mechanisms, including antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC). Elotuzumab has also been shown to target SLAMF7 on NK cells and boosts their antitumor activity as an important component of its efficacy in multiple myeloma.[18,19]

Elotuzumab was approved in combination with lenalidomide and dexamethasone in the relapsed/refractory setting based on the results of the phase 3 ELOQUENT-2 study in 321 patients. During a median follow-up of 24.5 months, median PFS was 19.4 months with elotuzumab, compared with 14.9 months with lenalidomide and dexamethasone alone, and ORR was 79% and 66%, respectively. Common grade 3/4 AEs in the elotuzumab arm included lymphocytopenia, neutropenia, fatigue, and pneumonia.[20]

Though elotuzumab displayed limited single-agent activity, daratumumab proved notably more effective in this regard. In the ongoing SIRIUS trial, ORR was 29% among 106 patients, with responses lasting an average of 7.4 months. Median PFS and OS were 3.7 months and 17.5 months, respectively and it was well tolerated.[21]

These antibodies and several other CD38-targeting agents continue to be evaluated in a range of clinical trials (Table), including a phase 3 trial of daratumumab in combination with lenalidomide and dexamethasone in patients with relapsed/refractory disease (NCT02076009). Updated results from a phase 1/2 trial of this combination were presented at ASH and highlighted the deep and durable responses that this drug combination evokes. The ORR was an impressive 81%, with 63% of patients experiencing very good partial response or better. Responses occurred rapidly – median time to response was 1 month – and median DOR had not been reached.[22]

Immunotherapy paves the way ahead

In recent years, indirectly targeting tumors by boosting the anti-tumor immune response and reversing the immunosuppressive effects of the tumor microenvironment have proved a powerful therapeutic strategy. The success of immunomodulating agents and monoclonal antibodies provides proof-of-principle that immunotherapies have significant potential in the treatment of multiple myeloma as well.

A variety of approaches are being used, including vaccines, drugs targeting cytokines, particularly IL-6 and IL-15, and therapies that modulate the bone marrow microenvironment to improve ingress of immune effector cells. Most promising are the immune checkpoint inhibitors that block inhibitory signaling pathways on cytotoxic T cells and prevent the tumor from inactivating these key effectors of the immune response. These drugs have already had a substantial impact on the treatment of several other tumor types.

The programmed cell death-1 (PD-1) targeting agent, pembrolizumab has emerged as the front-runner, with ongoing phase 3 trials in the relapsed/refractory and front-line settings. Nivolumab, atezolizumab (MPDL3280A), and the cytotoxic T-lymphocyte antigen 4 (CTLA-4)-targeting drug ipilimumab are also being evaluated in several different trials (Table).

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