The Treatment of Relapsed and Refractory Multiple Myeloma

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Relapsed and refractory multiple myeloma (MM) constitutes a specific and unmet medical need. Median survival ranges from as little as 6 to 9 months, and responses to treatment are characteristically short. Patients with relapsed/refractory disease are defined as those who, having achieved minor response or better, relapse and then progress while on salvage therapy, or experience progression within 60 days of their last therapy. In the era prior to the development of novel biologically based therapies for MM, relapse from successive treatment regimens resulted in progressively shorter response durations, which typically reflected emerging drug resistance, as well as changes in disease biology within each patient, with tumor cells expressing a more aggressive phenotype, higher proliferative fraction and lower apoptotic rates.

Both bortezomid- and lenalidomide-based therapies are expecially active, with bortezomib in particular being shown to provide a platform for combinations able to overcome resistance in this setting. The addition of novel and conventional agents to the treatment backbone of lenalidomide, thalidomide, and bortezomib are areas of active study, with participation in clincial trials a clear priority for such patients. Clinical challenges in the relapsed/refractory population include light chain and IgA isotype, renal failure, extramedullary disease, hyposecretory myeloma, and advanced bone disease.

Introduction

Relapsed and refractory multiple myeloma (MM) constitutes a specific and unmet medical need. Median survival ranges from as little as 6 to 9 months, and responses to treatment are characteristically short. Patients with relapsed/refractory disease are defined as those who, having achieved minor response or better, relapse and then progress while on salvage therapy, or experience progression within 60 days of their last therapy. In the era prior to the development of novel biologically based therapies for MM, relapse from successive treatment regimens resulted in progressively shorter response durations, which typically reflected emerging drug resistance, as well as changes in disease biology within each patient, with tumor cells expressing a more aggressive phenotype, higher proliferative fraction and lower apoptotic rates.

Although several prognostic factors have been identified for newly diagnosed myeloma, factors that retain prognostic value in the context of relapsed/refractory disease remain to be comprehensively defined. Nonetheless, within the overall adverse prognosis of relapsed/refractory MM, patients with poorer risk include those with t(4;14) or t(14;16) translocation(s), deletion of chromosomes 17 or 13, hypodiploidy, high β_2 microglobulin, and low serum albumin. Additional clinical challenges in the relapsed/refractory population include light chain and IgA isotype, renal failure, extramedullary disease, hyposecretory myeloma, and advanced bone disease.

The advent of novel therapies targeting disease biology and tumor microenvironment has significantly improved the outlook for patients with relapsed/refractory disease. Bortezomib, a first-in-class proteasome inhibitor, and the immunomodulatory agents thalidomide and lenalidomide now constitute "backbone" agents in this setting. A schematic representation of the main caspase-mediated pathways for the direct anti-MM effect of these agents, in addition to dexamethasone, is shown in **Figure 1** (see Color Figures, page 517). Bortezomib reflects a paradigm of drug development where accelerated approval emerged from studies in the relapsed/refractory patient population in 2003, followed by full approval in the relapsed setting in 2005; combinations that include bortezomib are now a priority in this patient population. Details regarding selected studies of bortezomib, thalidomide, and lenalidomide, alone and in combination with each other, and standard antineoplastic agents as well as other agents in active clinical development are included in **Table 1** and briefly reviewed here.

Bortezomib

Following a successful and rapid phase 1/2 development program, the international, randomized phase 3 APEX trial compared bortezomib with high-dose dexamethasone in 669 patients with relapsed and relapsed/refractory MM. The trial was stopped when the interim analysis demonstrated the superiority of bortezomib in terms of response rates, median time to progression (TTP), and survival.[1] Final results confirmed these findings, as well as superior overall response rates (ORR; 43%), including a 15% complete and near complete response rate (CR/nCR) with bortezomib monotherapy. Moreover, this updated analysis with extended follow-up confirmed that use of bortezomib

Table 1. Selected studies of bortezomib, thalidomide, and lenalidomide.

Author N/n	Regimen	Response rate, % (CR + PR)	Time-to-event data	Key toxicities
Richardson[1,2] 333/315	8 3-wk cycles Btz 1.3 mg/m^2 days 1, 4, 8, 11 3 5-wk cycles days 1, 8, 15, 22	43 CR/nCR: 15	TTP: 6.2 mo OS: 29.8 mo DOR: 7.8 mo	Grade 3/4: thrombocytopenia 26/4%; neutropenia 12/2%; anemia 9/1%; peripheral neuropathy 7/1%; diarrhea 7/0%; fatigue 5/<1%; dyspnea 5/<1%
Orlowski[3] 322/310	8 3-wk cycles Btz 1.3 mg/m^2 days 1, 4, 8, 11 PLD 30 mg/ m^2 day 4	48 CR/nCR 14	TTP: 9.3 mo DOR: 10.2 mo	Grade 3/4: neutropenia 30%; thrombocytopenia 22%; anemia 9%; diarrhea 7%; asthenia 6%; fatigue 5%; hand foot syndrome 5%
324/303	3-wk cycles Btz 1.3 mg/m^2 days 1, 4, 8, 11	43 CR/nCR 11	TTP: 6.5 mo DOR: 7 mo	Grade 3/4: thrombocytopenia 15%; neutropenia 14%; anemia 9%; peripheral neuropathy 9%; neuralgia 5%
Chanan-Khan[4] 21	6 4-wk cycles Btz 1.3 mg/m^2 days 1, 4, 15, 18 PLD 20 mg/m^2 days 1, 15 Thal 200 mg daily	56 CR: 22	PFS: 10.9 mo OS: 15.7 mo	Grade 3/4: neutropenia 43/4%; thrombocytopenia 22/9%; anemia 22/0%
Zangari[7] 85/85	8 3-wk cycles Btz 1.0-1.3 mg/m^2 days 1, 4, 8, 11 Thal 50-200 mg/day from cycle 2 Dex 20 mg day of/day after btz for suboptimal response after 3 cycles	55 CR/nCR: 16	EFS: 9 mo OS: 22 mo	Most common grade 3/4 toxicities were thrombocytopenia and neutropenia. Nonhematologic toxicities included neuropathy.
Richardson[8] 24/21	8 3-wk cycles Btz 1.0-1.3 mg/m^2 days 1, 4, 8, 11 Len 5-20 mg days 1-14 Dex 20 mg day of/day after btz for PD	52 CR/nCR: 10	NR	Most common grade 3/4 toxicities were thrombocytopenia and neutropenia. Significant neuropathy did not occur and rates of DVT were low (<5%)
Kropff[10] 50/50	Btz as above Dex 20 mg day of/day after btz Cyclophosphamide 50 mg daily	82 CR/nCR: 12	EFS: 12 mo OS: not reached	Dose-limiting grade 3/4: thrombocytopenia 0/19%; infection 25/0%; peripheral neuropathy 19/0%; herpes zoster 17/0%; fatigue 15/0%; cardiovascular 9/0%; diarrhea 8/0%; orthostatic hypotension 6/0%
Reece[11] 21/20	28-d cycles Btz 0.7-1.5 mg/m^2 days 1, 8, 15, or days 1, 4, 8, 11 Cyclophosphamide 150/300 mg/m^2 days 1, 8, 15, 22 Prednisone 100 mg every other day	45 CR/nCR: 15	NR	Grade 3/4 (cycles 2-8 only): hyperglycemia 29/0%; neutropenia 24/5%; hypophosphatemia 19/10%; thrombocytopenia 14/5%
Berenson[12] 35/34	8 4-wk cycles Btz 0.7-1.0 mg/m^2 days 1, 4, 8, 11 Melphalan 0.025-0.25 mg/kg days 1-4	47 CR/nCR: 15	PFS: 8 mo	Grade 3/4: neutropenia 34/6%; thrombocytopenia 37/3%; anemia 23/6%; hypocalcemia 6/0%
Palumbo[13] 30/30	6 5-wk cycles Btz 1-1.6 mg/m^2 days 1, 4, 15, 22 Melphalan 6 mg/ m^2 and prednisone 60 mg/m^2 days 1-5 Thal 100 mg daily	67 CR/nCR: 17	NR	Grade 3/4: thrombocytopenia; febrile neutropenia; fatigue; anemia; pneumonia; vasculitis; infections; sensory neuropathy
Terpos[14] 44/41	4 4-wk cycles Btz 1.0 mg/m^2 days 1, 4, 8, 11 Melphalan 0.15 mg/kg days 1-4 Dex 12 mg/m^2 days 1-4, 17-20 Thal 100 mg/d	66 CR/nCR: 37	PFS: 9.6 mo	Grade $\geq$ 3: thrombocytopenia 20%; neutropenia 8%; anemia 7%; peripheral neuropathy 6%
Richardson[15] 30/25	3-wk cycles Btz 0.7-1.3 mg/m^2 and KOS-953 100-275 mg/m^2 days 1, 4, 8, 11	32 CR/nCR: 12	NR	Dose-limiting: grade 3/4 hepatotoxicity; grade 3 pancreatitis. Other grade 3/4 events included thrombocytopenia and elevated ALT (manageable with ursodiol).
Barlogie[16] 169/169	Thal 200-800 mg/day	30 CR: 2	2-year EFS: 20% 2-year OS: 48%	Grade > 2: CNS 25%, gastrointestinal 16%, peripheral neuropathy 9%
Palumbo[18] First relapse 62/62	Thal 100 mg/d continuously Dex 40 mg days 1-4 of each month	56	PFS: 17 mo 3-year OS rate: 60%	Tingling and numbness 19%; constipation 18%; sedation 13%
Second relapse and beyond 58/58		46	PFS: 11 m OS: 19 mo	
Dimopoulos[19] 53/53	3 4-wk cycles Thal 400 mg/d and Dex 20 mg/d days 1-5, 14-18 Cyclophosphamide 150 mg/m^2 every 12 hours days 1-5	60 CR/nCR: 5	TTP: 8.2 mo OS: 17.5 mo	Grade 3/4: neutropenia 18/8%

Table continued on next page

Table 1. Selected studies of bortezomib, thalidomide, and lenalidomide. (Continued)

Author N/n	Regimen	Response rate, % (CR + PR)	Time-to-event data	Key toxicities
Offidani[20] 50/50	6 4-wk cycles Thal 100 mg/d Liposomal doxorubicin 40 mg/m^2 day 1 Dex 40 mg days 1-4, 9-12	76 CR/nCR: 32	OS: not reached PFS: 22 mo EFS: 17 mo	Grade ≥ 3: neutropenia 16%; nonhematologic toxicities 12%; venous thromboembolic disease 12%; severe infection 16%
Weber[23] 171	4-wk cycles Len 25 mg days 1-21 Dex 40 mg days 1-4 and 9-12, 17-20 (cycles 1-4)	59 CR: 13	TTP: 11.1 mo OS: 29.6 mo	Grade ≥ 3: neutropenia 36%; DVT/PE 18%; thrombocytopenia 12%; anemia 12%; pneumonia > 10%; atrial fibrillation 6%; fatigue 6%; diarrhea 5%
Dimopoulos[24] 176	As above	59 CR/nCR: 17	TTP: 11.3 mo OS: not reached	Grade ≥ 3: neutropenia 27%; thrombocytopenia 10%; anemia 6%; DVT 5%
Richardson[25] 67 (once daily) 35 (twice daily)	4-wk cycles Len 30 mg once daily or 15 mg twice daily, days 1-21 Dex 40 mg for 4 d every 14 d for suboptimal response	18 CR/nCR: 6 (Once daily) 14 CR/nCR: 0 (Twice daily)	DOR: 19 mo (once daily), 23 mo (twice daily) PFS: 4.6 mo (combined) OS: 27 mo (combined)	Grade 3/4 (once daily): neutropenia 49/12%; thrombocytopenia 15/16%; leukopenia 36/2%; lymphopenia 31/6%; anemia 15/2% Grade 3/4 (twice daily): neutropenia 57/11%; thrombocytopenia 26/17%; leukopenia 34/0%; lymphopenia 31/9%; anemia 11/3%

Abbreviations: CR, complete response; PR, partial response; Btz, bortezomid; nCR, near CR; TTP, time to progression; OS, overall survival; DOR, duration of response; PLD, pegylated liposomal doxorubicin; Thal, thalidomide; PFS, progression-free survival; EFS, event-free survival; Dex, dexamethasone; Len, lenalidomide; PD, progressive disease; NR, not reported; ALT, alanine transaminase; CNS, central nervous system; DVT/PE, deep venous thrombosis/pulmonary embolism

resulted in a 6-month survival advantage (29.8 months vs 23.7 months), despite more than 62% of crossover to bortezomib from the high-dose dexamethasone arm.[2]

Combination approaches have since been an area of active investigation and the results of a large phase 3 study comparing bortezomib and pegylated liposomal doxorubicin (PLD) with bortezomib alone in 636 relapsed patients was recently reported.[3] TTP was significantly longer with the combination than with bortezomib alone (9.3 months vs 6.5 months, respectively). A recent update confirmed a favorable response rate for the combination (ORR 52%, CR/nCR 17%) versus single-agent bortezomib (ORR 44%, CR/nCR 13%), with a longer duration of response (DOR) (10.2 months vs 7.0 months) and most importantly a survival advantage. Toxicities were somewhat higher with the combination, including higher rates of grade 3 or higher thrombocytopenia and neutropenia; rates of peripheral neuropathy were similar in the two treatment arms. These results provided the basis for the recent U.S. Food and Drug Administration (FDA)-approval of the combination of bortezomib with PLD for the treatment of patients with MM who have received at least one prior therapy and not previously received bortezomib. Bortezomib and PLD have also been combined with thalidomide. In a study of 21 patients with MM, ORR was 56% with 22% CR. Responses were seen regardless of prior exposure to bortezomib, doxorubicin, or thalidomide. Progression-free survival (PFS) and overall survival (OS) were 10.9 and 15.7 months, respectively. Toxicities proved manageable; there were no deep venous thromboses (DVTs) with prophylaxis and no significant peripheral neuropathy was reported.[4]

Both the phase 2 SUMMIT[5] and CREST[6] trials added dexamethasone for suboptimal response to bortezomib alone. Overall responses ranged from 27%[5] for single-agent bortezomib up to 50%[6] with the addition of dexamethasone. Dexamethasone was also added for suboptimal response in studies of bortezomib and thalidomide (VTd),[7] and lenalidomide and bortezomib (RVd).[8] In 85 patients treated with VTd, the ORR was 55%, with 16% CR/nCR; event-free survival (EFS) and OS were 9 and 22 months, respectively. The most common grade 3/4 toxicities were thrombocytopenia and neutropenia, with manageable neuropathy.[7] In the RVd study of 36 relapsed and refractory patients, responses were similar (ORR), despite prior thalidomide and bortezomib use in most patients.[8] This study was based on the preclinical rationale that activation of caspase-8 by lenalidomide would cooperate with the dual bortezomib-triggered activation of caspase-8 and (predominantly) caspase-9 to trigger an enhanced anti-MM effect (**Figure 1**; see Color Figures, page 517), a construct that also provides a platform for other combinatorial strategies.[9] Remarkably, no significant neuropathy was seen, despite duration of therapy as long as 3 years. Bortezomib and dexamethasone have also been combined with cyclophosphamide.[10] In 50 patients, ORR was 82%, with 12% CR/nCR; EFS was 12 months and OS was not reached at the time of presentation. Dose-limiting grade 3/4 toxicities with this combination included thrombocytopenia, infection, peripheral neuropathy, herpes zoster, fatigue, cardiovascular, diarrhea, and orthostatic hypotention.[10] In a smaller study including prednisone in place of dexamethasone, the ORR was 45% with CR/nCR 15%.[11]

Bortezomib has also been combined with low-dose melphalan. In 21 evaluable patients, the ORR was 47%, with 15% CR/nCR; PFS was 8 months. Grade 3/4 toxicities included neutropenia, thrombocytopenia, anemia, and hypocalcemia.[12] When thalidomide and prednisone were added to this combination, ORR increased to 67%, but there was little change in the CR/nCR rate (17%). Toxicities with this combination included thrombocytopenia, febrile neutropenia, fatigue, anemia, pneumonia, vasculitis, infections, and sensory neuropathy.[13] The combination of bortezomib, melphalan, thalidomide, and dexamethasone also reported a similar ORR (66%), but here the CR/nCR rates appeared higher (37%); PFS was 9.6 months. Toxicities grade 3 or higher included thrombocytopenia, neutropenia, anemia, and peripheral neuropathy.[14]

Bortezomib in combination with the heat-shock protein (HSP)-90 inhibitor tanespimycin has also shown promise. Responses were seen in 32% of patients, including 12% CR/nCR. Importantly, durable responses were seen in patients who were bortezomib naïve as well as those who had been previously treated with bortezomib, and even patients who were refractory to bortezomib.[15] Interestingly, rates of neuropathy were low, and no grade 3 neuropathy has been reported to date. Studies of bortezomib and numerous other novel agents are ongoing or planned, including other small molecules, such as perifosine and histone deacetylase inhibitors (SAHA and LBH), as well as monoclonal antibody–based approaches.

Thalidomide

In a seminal study of 169 patients with relapsed or refractory multiple myeloma, thalidomide 200–800 mg per day yielded responses (≥50% reduction in M-protein) in 30% of patients with a 2% CR rate; 2-year EFS and OS in this study were 20% and 48%, respectively. Toxicities of grade 3 or higher included central nervous system (CNS), gastrointestinal, and peripheral neuropathy.[16] This is but one study included in a review of 42 studies with target doses of single-agent thalidomide ranging from 50 mg/day to 800 mg/day. In the 1629 patients included in the intention-to-treat analysis, the ORR (50% or greater M-protein reduction) for single-agent thalidomide was 30%; 2% of patients showed a 90% or greater reduction. Across studies, grade 3/4 adverse events included constipation, somnolence, neutropenia, and neuropathy and toxicities appear both cumulative and dose dependent. The incidences of somnolence, peripheral neurotoxicity, and thromboembolism were all higher at doses higher than 200 mg/day, and worsened over time.[17]

The clinical benefit of thalidomide increases significantly when it is combined with other agents. For example, thalidomide in combination with dexamethasone has become one of the most commonly used front-line regimens in the U.S. for patients with MM and was approved by the FDA for this indication in 2006. The combination also shows significant activity in recurrent disease; Palumbo et al investigated the combination of thalidomide and dexamethasone in MM patients at first relapse (n = 62) and at second relapse and beyond (n = 58), with an ORR of 56% for patients at first relapse and 46% for patients beyond first relapse. PFS was 17 months, with 3-year survival at 60% for the first group; for the second, EFS was 11 months, and OS was 19 months. For both patient populations, major toxicities included neuropathy, constipation and sedation.[18]

As with bortezomib, thalidomide and dexamethasone have also been combined with cyclophosphamide and PLD. Thalidomide, cyclophosphamide, and dexamethasone resulted in an ORR of 60% with 5% CR/nCR.[19] TTP was 8.2 months, and OS was 17.5 months. Grade 3/4 neutropenia was reported in 26% of patients. ORR for the combination of thalidomide, PLD, and dexamethasone was 76%, with 32% CR/nCR. EFS and PFS were 17 and 22 months, respectively, and OS was not reached. Significant toxicities included neutropenia, DVT, and severe infection.[20]

As alluded to above, an important safety consideration with thalidomide is the risk of DVT, which increases substantially when thalidomide is combined with corticosteroids and some chemotherapeutic agents, but not bortezomib.[21]

Lenalidomide

In an effort to reduce the toxicity and enhance the activity of thalidomide, thalidomide analogs have been synthesized. Lenalidomide is an immunomodulatory derivative of thalidomide that shows higher *in vitro* potency and greater activity than thalidomide in MM cell lines, suggesting that it may be effective in thalidomide-resistant patients.[22] After considerable promise and excellent tolerability was shown in a series of phase1/2 trials, two phase 3 trials comparing lenalidomide plus high-dose dexamethasone to high-dose dexamethasone alone have been reported. In the North American study (MM-009), 171 patients were treated with lenalidomide plus dexamethasone; the ORR of 59% with 13% CR was encouraging. Moreover, TTP was 11.1 months, and median OS was 29.6 months. Of note, grade 3 or higher toxicities were neutropenia, DVT (including pulmonary embolism), thrombocytopenia, anemia, pneumonia, atrial fibrillation, fatigue, and diarrhea.[23] In the European study (MM-010), 176 patients were treated with lenalidomide plus high-dose dexamethasone. ORR was again remarkable at 59%, with 17% CR/nCR. TTP in this study was similar (11.3 months), and OS has not been reached. Reported grade 3 or higher toxicities also included neutropenia, thrombocytopenia, anemia, and DVT.[24]

The dosing schedule with lenalidomide was extensively investigated to provide a platform for the above trials; specifically, in a large randomized phase 2 study, patients received either a single daily dose of 30 mg or two doses of 15 mg each. Intermediate-dose dexamethasone was added for suboptimal response. The ORR was 18%

with the single daily dose and 14% for the twice-daily dose; CR/nCR rates were 6% and 0%, respectively. With single daily dosing, the DOR was impressive at 19 months, and similar with twice-daily dosing, where the DOR was 23 months. For both groups combined, the PFS was 4.6 months and the OS was 27 months. Dexamethasone was added in more than half of the patients, and response was improved in approximately 40%, commensurate with the synergism seen with this combination. Grade 3/4 toxicities for the two groups were similar and included neutropenia, thrombocytopenia, leucopenia, lymphopenia, and anemia. The addition of low-dose dexamethasone stabilized or improved response in approximately half of those progressing on lenalidomide alone and was generally well tolerated, although DVT was reported in 2 patients. Importantly, DVT occurred rarely in this study, and only when dexamethasone was added, with significant peripheral neuropathy occurring in just 2%.[25]

It is noteworthy that the combination of lenalidomide with higher-dose dexamethasone is associated with a higher risk of DVT, particularly with concomitant use of erythropoietin.[26] Moreover, this risk appears to be elevated in patients who have had prior therapy with thalidomide, and effective thromboprophlaxis is thus vital.[27]

Special Populations

Given that patients with relapsed/refractory MM typically are symptomatic, with potential comorbidities, and have characteristically resistant disease, relapsed/refractory disease remains especially challenging to treat. Features also include older age, renal disease, adverse cytogenetics (including chromosome 13 deletion), elevated β_2 microglobulin, low serum albumin and extramedullary disease. Bortezomib and lenalidomide have each been shown to be safe and effective in older patients with relapsed/refractory MM.[28,29] Thalidomide is reported to be safe and effective in elderly patients in the frontline setting, but caution is needed and lower doses are required.[30] Both bortezomib[31] and thalidomide[32] have been shown to be safe and effective in patients with renal impairment, and to reverse renal dysfunction in some patients with relapsed/refractory MM. Lenalidomide has yet to be extensively studied in patients with significant renal dysfunction, as it is actively excreted through the kidneys; patients with serum creatinine higher than 2.5 mg/dL were excluded from pivotal trials, although preliminary studies in renal failure have suggested dose reduction is feasible in such patients.

Both bortezomib and lenalidomide have been shown to overcome the poor prognosis conferred by the deletion of chromosome 13.[33,34] Bortezomib has also been shown to overcome the poor prognostic factors of elevated β_2-microglobulin and low serum albumin,[28] as well as being active in patients with advanced bone disease, plasmacytoma and extramedullary involvement.

Future Therapies

The pathophysiology of MM is now understood in significant detail at the molecular level.[9] Knowledge of many of the cell-signaling pathways has led to the development of agents targeting novel pathways.[9] For example, MM cells are sensitive to the interruption of intracellular signaling by HSP-90 inhibitors.[35] Histone deacetylase inhibitors exert anti-MM activity by inducing apoptosis in MM cells and inhibiting interleukin-6 (IL-6) secretion by bone marrow stromal cells.[36] Both TRAIL-apo2L[37] and 2-methoxyestradiol induce apoptosis of MM.[38] The macrolide antibiotic clarithromycin suppresses IL-6, which is a growth factor for MM and, although it does not demonstrate single-agent activity, it is being investigated in combination with thalidomide or lenalidomide and dexamethasone in a series of studies (ClinicalTrials.gov; identifiers NCT00182663 and NCT00151203). A new generation of proteasome inhibitors has now entered clinical trials with the promise of greater potency and less toxicity, as well as the ability to overcome bortezomib resistance, and the list of novel agents continues to rapidly increase as new targets are identified. For example, monoclonal antibodies offer an exciting adjuvant role, with combination approaches being especially attractive. Further investigation of these novel strategies, both alone and in combination, for the treatment of MM is clearly warranted as part of a continued effort to improve patient outcome. Participation in clinical trials is thus key and a cornerstone of patient management in the relapsed and refractory setting.

Conclusions

Until recently, management strategies for patients with relapsed/refractory MM have been limited to conventional chemotherapy and occasionally autologous stem cell transplantation. Given that patients with recurring disease typically are more symptomatic, with potential comorbidities, may be older, and are characteristically resistant to treatment, relapsed and refractory disease remains especially challenging to treat. With the introduction of novel, targeted therapies and the demonstration that combinations with these and other agents are especially active, even when the constituent drugs have been used singly or as doublets before, the potential to improve responses in this patient population has increased. However, new combinations of agents must ultimately show improvement in time-to-event outcomes, including TTP and OS, and not just in response rates; indeed, phase 3 studies such as the combination of PLD and bortezomib are now showing such benefits. Treatment-associated toxicities and effects on quality of life should also be considered to inform decisions in terms of the treatment choice for an individual patient. A growing understanding of gene expression profiling, multiple cellular-signaling pathways, and microenvironmental events involved in the mechanisms underlying resistance has already significantly informed our progress to date. These

advances, together with the ongoing design of optimal combination therapies, will aid in the development of future approaches to combat this otherwise fatal disease, and further improve outcome.

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