Future Directions of Next-Generation Novel Therapies, Combination Approaches, and the Development of Personalized Medicine in Myeloma

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ABSTRACT

Despite tangible progress in recent years, substantial therapeutic challenges remain in multiple myeloma (MM), particularly for patients at high risk for early relapse or death and for those with advanced multi-drug resistant disease and refractoriness to currently available combination regimens. Addressing these challenges requires identification of novel classes of anti-MM agents, their incorporation into safe and more effective combination regimens, and development of efficient algorithms to select the most appropriate therapeutic options for the clinical and molecular features of individual patients at a given time during their disease. Ideally, these goals can be facilitated by preclinical identification of the “driver” molecular lesions on which different myeloma subtypes exquisitely depend, and by informative preclinical models simulating the clinical setting(s) in which trials will be conducted. Large prospective studies of patients treated uniformly with contemporary clinical regimens are essential, but there is also a major need for flexibility in studying new regimens in the future. Long-term patient follow-up and integrated annotation of clinical (safety and efficacy) and correlative (molecular, biochemical, etc) data are also critical. Novel molecular profiling techniques will likely identify more clinically and biologically discrete subsets of patients with recurrent, even if infrequent, lesions. This molecular heterogeneity, combined with the increasing numbers of candidate therapeutic targets and respective investigational agents, may pose formidable challenges for the development and implementation of personalized medicine in MM. This review discusses these challenges, as well as potential strategies to address them, with the aim of making significant improvement in the clinical outcome of patients with MM.


INTRODUCTION

During the last 10 years, several randomized controlled trials in different clinical settings of multiple myeloma (MM) have shown that regimens containing bortezomib, thalidomide, or lenalidomide increase the progression-free—and in many cases overall—survival of patients as compared with regimens used in the prethalidomide era. Therefore, the improved overall survival of patients with MM diagnosed between 2001 and 2006 (which does not yet fully account for the impact of lenalidomide or its combination with bortezomib on patient outcome) versus before 2000 can be attributed, at least in part, to these novel agents and not just to concurrent advances in supportive care, such as the use of bisphosphonates for bone disease.

However, the overall survival curves in the postthalidomide era contain two concerning features, namely, their lack of an identifiable plateau and their early and sometimes steep drop-off. These features respectively suggest that currently available treatment options for myeloma are unlikely to be curative for a large portion of patients, and that a substantial proportion of patients at high risk for early relapse or death do not receive maximal benefit from currently available combination regimens. It should be noted that these observations might change favorably with additional follow-up after the 2006 US Food and Drug Administration (FDA) approval of lenalidomide or after the introduction and broader use of bortezomib-lenalidomide combinations in clinical practice. Nevertheless, a conservative projection on the basis of currently available experience is that a substantial portion of high-risk patients may not receive maximal benefit even from double or triple combinations of novel agents with or without conventional agents. Thus, only a small subset of patients, including those with standard-risk features, will ever likely achieve a curative outcome.

Therefore, substantial therapeutic challenges remain. This review article discusses, on the basis of...
Information available to date, some of the directions that may help address these challenges in the future. Emphasis is placed on the ongoing efforts to identify novel classes of anti-MM agents, incorporate them into safe and more effective combination regimens, and develop efficient algorithms to select the most effective therapeutic options that match the clinical and molecular features of individual patients at any given point in the course of their disease.

NOVEL AGENTS FOR THE TREATMENT OF MYELOMA

The major leaps in improving clinical outcome in MM over the last decade have been primarily driven by the successive introduction of new agents that not only exhibited anti-MM activity as monotherapy but also importantly demonstrated lack of cross-resistance with previously available classes of drugs. Following this successful blueprint, research for additional classes of novel therapeutics has continued in the MM field. The spectrum covered by these agents is quite broad. Attempting to classify them by any individual criterion (eg, documented or hypothesized putative targets and mechanisms of action, safety and efficacy profiles in preclinical studies, current phase of clinical development) may not comprehensively reflect their heterogeneous, but often overlapping, features or accurately reflect their potential for providing clinical benefit in this disease.

SECOND-GENERATION PROTEASOME INHIBITORS AND NEW IMMUNOMODULATORY THALIDOMIDE DERIVATIVES

It is notable that an important category of emerging agents either is made up of structural analogs of or compounds that hit the same target as (perhaps with incremental pharmacodynamic/pharmacokinetic variations) anti-MM drugs currently approved by the FDA. Pomalidomide and second-generation proteasome inhibitors, including carfilzomib, salinosporamide A (NPI-0052), and MLN9708/2238, are examples within this broad group. Pomalidomide (formerly known as CC-4047 or immunomodulatory thalidomide derivative (IMID)-1) is a derivative of and structurally similar to thalidomide. Its direct anti-MM activity was first demonstrated preclinically by Hideshima et al. Subsequent studies have shown that pomalidomide maintains key aspects of the mechanism of action of lenalidomide, including the dual activation of caspase 8 and caspase 9 apoptotic signaling and ability to synergize in vitro with proteasome inhibitors, such as bortezomib. Phase I clinical studies of pomalidomide plus low-dose dexamethasone showed activity in patients with MM resistant to other anti-MM agents, including thalidomide, lenalidomide, and bortezomib. The second-generation proteasome inhibitor carfilzomib binds irreversibly to the β5 subunit of the 20S proteasome (unlike the reversible binding of bortezomib or its orally bioavailable analog MLN2238/MLN9708) and has demonstrated clinical activity (primarily in bortezomib-naive or -exposed patients, but less so in those truly resistant) with a favorable safety profile and notably lower rates of peripheral neuropathy. Ongoing clinical studies of pomalidomide and second-generation proteasome inhibitors will determine which or how many will receive FDA approval. An intriguing questionyet to be answered regarding the latest generation of IMIDs or proteasome inhibitors is whether their use in patients naïve to other agents of this drug class (eg, in the upfront setting) would produce efficacy and safety results comparable or superior to those produced by the prototypic members of each class. For example, given that carfilzomib and bortezomib have the same molecular target (specifically, the β5 proteasome subunit) but produce different rates of peripheral neuropathy, there are intriguing questions as to the molecular basis for this different safety profile and whether carfilzomib could emerge in the future as the proteasome inhibitor of choice for patients at high risk for treatment-emergent neuropathy. Answers to such questions will have important implications for the long-term use of these agents in clinical practice and the sequence in which they may be used in subsequent treatment. Compared with currently available FDA-approved prototypes, new-generation IMIDs and proteasome inhibitors may conceptually represent only an incremental advance, but they may provide more treatment options (and potentially some safer ones), which could translate into substantial benefit over time. This may provide an important additional bridge until the point at which yet newer novel classes of drugs with greater anti-MM activity are identified.

NOVEL CLASSES OF ANTI-MM AGENTS IN CLINICAL DEVELOPMENT

Another notable category of novel agents in development for MM involves inhibitors of histone deacetylases (HDACs; eg, vorinostat, romidepsin, panobinostat), mammalian target of rapamycin complex 1 (mTORC1; temsirolimus/CCI779, everolimus/RAD001, ridaforolimus/AP23573), and heat shock protein 90 (hsp90; tanespimycin, AUY922, IPI504 as well as perifosine) and the monoclonal antibody (mAb) elotuzumab (against surface marker CS1; also referred to as SLAMF7 or CD319). No member of these classes of compounds is currently FDA approved specifically for MM. However, FDA approval has been granted for other indications to vorinostat, romidepsin (cutaneous T-cell lymphoma), temsirolimus, and everolimus (renal cell carcinoma). These agents hit targets validated in preclinical MM studies and show variable degrees of encouraging clinical data in combination with other anti-MM agents. For some of these regimens, phase III trials are ongoing (eg, bortezomib-dexamethasone with ν without panobinostat [NCT01023308] or perifosine [NCT01002248], bortezomib with ν without vorinostat [NCT00773747], lenalidomide-dexamethasone with ν without elotuzumab [NCT01239797]) or being planned. Results from these studies will determine their future role in the management of MM. Other agents approved by the FDA for other diseases and currently in clinical trials in MM include the anti−receptor activator of nuclear factor kappa-B ligand (RANKL) mAb denosumab and the alkylating agent bendamustine.

There is also a continuously expanding constellation of novel agents that have undergone variable degrees of preclinical evaluation, but so far, their clinical development is in earlier stages. Some agents hit pathways or targets overlapping with those affected by the agents already described, but they also have additional effects (for instance, dual inhibitors of mTORC1/2 or composite mTORC1/2−phosphoinositide 3-kinase inhibitors [NVP-BEZ235] have profiles of activity distinct from classical rapamycin analogs, which hit only mTORC1). Other agents target previously credentialed pathways but at distinct molecular levels and engender differential biologic effects. For instance, the NEDD8−activating enzyme inhibitor MLN4924 targets the neddylation pathway (upstream of the 20S proteasome), triggering
molecular sequela and preclinical anti-MM activity distinct from established 20S proteasome inhibitors. Other novel agents include mAbs against MM cell surface antigens (eg, CD38, CD40, CD138, CD200), growth factors (eg, anti–interleukin-6 antibody siltuximab/CNTO 328), or mediators of bone disease in MM (eg, anti–dickkopf-related protein 1 [DKK-1] antibody BHQ88055 or activin receptor antagonist ACE-01156); inhibitors of intracellular signaling cascades implicated in myeloma cell proliferation, survival, drug resistance, and/or interaction with the bone microenvironment, for instance, kinase inhibitors against cyclin-dependent kinases57; MEK58; fibroblast growth factor receptor 353; Aurora kinases (eg, MLN8237 or others60-62); and telomerase inhibitors (eg, imetelstat/GRN163L). Although the adverse clinical outcome in patients with MM with t(4;14) was originally attributed to overexpression and additional mutations of FGFR3, recent data suggest a major putative role for the histone methyltransferase MM-SET63,64 and raise the possibility that it could be a bona fide therapeutic target for this subset of MM. Other molecularly defined subsets of MM also conceivably harbor therapeutically tractable molecular lesions, but it is not yet clear which of these lesions are essential for MM cell survival in each of these subsets.

Therapeutics targeting tumor-microenvironment interactions or cancer cells with stem cell–like features or enhancing antitumor immunity remain high on the list of preclinical and clinical interest. Beyond the aforementioned agents against MM bone disease, several agents targeting tumor-microenvironment interactions have been developed, including agents with minimal, if any, direct targeting of tumor cells. Examples include agents targeting the tumor-associated vasculature (eg, defibrotide60) and other mAbs (eg, anti-ICAM1 Ab BI-505, studied in trial NCT01025206) against key adhesion molecules. The immunostimulatory effects of thalidomide derivatives56 have sparked new interest in antitumor immunotherapy, including not only many previously mentioned mAbs but also mAbs against killer-cell immunoglobulin-like receptors (KIRs), with the intent of neutralizing their inhibitory effect on natural killer cell function and augmenting antitumor immunity67; infusions of haplo-identical KIR ligand-mismatched natural killer cells in the setting of autologous stem-cell transplantation (ASCT)68; dendritic cell vaccines69; immunotherapy against cancer/testis antigens expressed in MM70; and other emerging targets.71 Targeting of tumor stem-cell populations has been attempted with mAbs against CD20 or by targeting other antigens with relatively restricted expression within the tumor stem-cell compartment (eg, cancer-testis antigens). It has been proposed that cancer stem cells are functionally dependent on pathways such as Hedgehog, Notch, and Wnt as well as on telomerase function. Inhibitors of these pathways have been tested preclinically in MM.72-26 Hedgehog inhibitors (eg, GDC-0449) have clinical activity in neoplasias (eg, basal cell carcinoma, medulloblastoma) with mutual activation of the pathway,77,78 a finding not yet detected in MM.

**IMPORTANCE OF INFORMATIVE PRECLINICAL MODELS**

Having a plethora of investigational agents under preclinical or clinical evaluation does not necessarily translate into clinical progress. Many of the most promising investigational agents for MM are variants of existing FDA-approved therapies for this disease, whereas other novel agents that mechanistically depart from the well-established path of thalidomide derivatives and proteasome inhibitors have not yet demonstrated potent single-agent activity in heavily pretreated patients with MM. In fact, a broader concern is that preclinical results, even highly promising ones, translate only infrequently into clinical success. Indeed, fewer than 10% of agents entering phase 1 testing in any cancer receive FDA approval for any indication.79 It may therefore be sobering but prudent to recognize the possibility that more preclinical and clinical work will be needed before new classes of anti-MM monotherapies become widely available. For some investigational agents, alternative dose, route of administration, and scheduling might perhaps reveal improved single-agent anti-MM efficacy. For all investigational agents, it is otherwise important to stringently consider at a preclinical level how critical the corresponding targets are for MM cell biology and which patient subsets would have the highest likelihood of benefit from such therapeutic intervention. Molecular targets with differential expression in MM (v normal tissues) may be completely unattractive for therapeutic interventions if they are functionally redundant for tumor cell viability. Functional studies identifying the “driver” molecular lesions on which tumor cells exclusively depend should be an elemental criterion in selecting targets for therapeutic testing. To remain informative, preclinical models should be fine-tuned to optimize their relevance to the clinical settings in which trials will be conducted. Tumor-microenvironment interactions can confer drug resistance to diverse drug classes and may contribute to the suboptimal clinical translation of otherwise exciting preclinical results. Therefore, in vivo studies (both for xenographs and genetic models) should ideally be orthotopic (ie, reflect anatomic distribution of lesions in patients with MM).80 Notably, recent studies have shown that nonmalignant accessory cells of the tumor microenvironment can render MM cells more sensitive to certain classes of therapeutics, which presumably target key pathways triggered in tumor cells by their milieu.80 In vitro screening for anti-MM agents should therefore be performed not against MM cells cultured in isolation but rather in the presence of nonmalignant accessory cells. The risk is that otherwise, agents that are subject to this previously underappreciated microenvironment-dependent synthetic lethality may be filtered out of preclinical and clinical pipelines, depriving the field of some potentially useful candidate therapeutics.80

Clinical testing of a novel agent in unselected patient populations may dilute any efficacy signal (even a potent one), if it is restricted to relatively infrequent subsets of patients with MM. Identification of candidate biomarkers of response or resistance should be pursued, when feasible, as early as possible in preclinical development through studies across different subtypes, using large cell-line panels (not withstanding under-representation of cases of hyperdiploid MM) and/or primary MM tumor cells. Candidate markers derived from such exploratory studies should not be used to restrict or exclude patient enrollment in ensuing clinical trials; rather, such studies should help enrich them for patient subsets with the highest likelihood of response, allowing for prospective validation by comparisons of outcome in patients with versus without the markers of interest.

Novel agents (alone or in combination) are expected to be explored not only in induction regimens but also to augment the depth of response to conditioning regimens, for consolidation as well as maintenance. Since early reports of positive efficacy data for single-agent lenalidomide as maintenance after ASCT,8,9 studies of maintenance use of proteasome inhibitors (alone or in combination with lenalidomide) and other agents have been eagerly awaited. Alternative schedules and even route of administration (eg, growing experience with subcutaneous administration of bortezomib81) could conceivably facilitate such studies.
ROLE OF COMBINATION REGIMENS IN THE FUTURE OF MM TREATMENT

Because the identification of new active agents does not occur at a steady or predictable rate, combination regimens for MM are essential to improve the rates, depth, and durability of clinical responses to established agents. Several randomized clinical trials have supported this concept, demonstrating increased progression-free and/or overall survival with doublets or triplets combining thalidomide/lenalidomide or bortezomib with alkylators, anthracyclines, or glucocorticoids, compared with corresponding single agents or doublets. Furthermore, high rates and depth of response have been observed with the bortezomib-lenalidomide doublet (with or without addition of dexamethasone) with triple or quadruplet combinations based on the bortezomib-lenalidomide backbone (eg, liposomal doxorubicin or cyclophosphamide), added to lenalidomide, bortezomib, and dexamethasone [RVD]; and with other permutations of conventional and recently established anti-MM agents, including bortezomib, thalidomide, and dexamethasone, lenalidomide, adriamycin, and dexamethasone, and recent versions of the Total Therapy program (eg, TT4 and TT5 trials NCT00734877 and NCT00869232, respectively). Importantly, safety profiles of such combinations have become key discriminators, as illustrated by the results of the EVOLUTION (Evaluation of Velcade, Dexamethasone and Lenalidomide, With or Without Cyclophosphamide Using Targeted Innovative Oncology Strategies in the Treatment of Front-Line MM) study in distinguishing the relative value of these regimens. On the basis of encouraging early clinical experience with newer generation IMIDs (eg, pomalidomide) and proteasome inhibitors (eg, carfilzomib), it is anticipated that these agents will also be incorporated in similar combinations and assume the positions of their corresponding first- or second-in-class agents. This direction is also supported by preclinical evidence, which shows that the original concept of combining proteasome inhibitors with thalidomide derivatives to achieve enhanced direct anti-MM effects not only applies to bortezomib and lenalidomide but also represents an overall class effect.

Other notable combinations integrate agents that have not been approved by the FDA for MM treatment but have shown encouraging rates and depth of response in combination with existing anti-MM regimens. Examples include the previously mentioned combinations of HDAC inhibitors with bortezomib or lenalidomide and dexamethasone, elotuzumab plus lenalidomide and dexamethasone, and hsp90 inhibitors plus bortezomib. The pleiotropic effects of HDAC and hsp90 inhibitors on multiple proteins critical for oncogenesis and drug resistance conceivably account for their roles as sensitizers to other anti-MM agents. HDAC inhibition suppresses expression of diverse oncogenic transcripts, blunts compensatory transcriptional responses mounted by MM cells attempting to escape the proapoptotic effect of bortezomib, and leads to hyperacetylation and decreased function of hsp90, hypoxia-inducible factor 1-alpha, and other oncogenic proteins. Consistent with these observations, combinations of vorinostat (also known as suberoylanilide hydroxamic acid) with bortezomib have shown enhanced preclinical anti-MM activity. This has been subsequently confirmed with other HDAC inhibitors as well. HDAC inhibition also affects the aggresome, an alternative pathway for intracellular protein degradation. The transcriptional and protein homeostasis effects of HDAC inhibitors could conceivably cooperate to enhance the anti-MM activity of bortezomib, including clinical responses even in bortezomib-refractory patients. The combination of elotuzumab with lenalidomide was made based on the notion that the immunostimulatory effect of lenalidomide would enhance the antibody-dependent cellular cytotoxicity triggered by elotuzumab.

The emergence of several potent triplet or quadruplet anti-MM combinations is reminiscent of successes with similarly complex regimens for other hematologic malignancies (eg, Hodgkin’s lymphoma, diffuse large B-cell lymphoma). Will IMID/proteasome inhibitor regimens such as RVD (with > 90%, > 70%, and > 50% rates of partial, very good partial, and complete or near-complete responses, respectively, in newly diagnosed MM) improve the long-term outcome of patients with high-risk features? Will RVD—by itself or in combination with another agent (potentially an HDAC inhibitor, the hsp90 inhibitor perifosine, or elotuzumab)—provide a DNA-damaging chemotherapy-free induction regimen that will improve clinical outcome with ASCT? Are there subsets of patients with MM for whom RVD-based therapy could provide comparable outcome with or without ASCT? Conversely, are there patient subgroups for whom the rates and depth of response to RVD would be comparable to those with treatment with only a bortezomib- or lenalidomide-based approach; if so, could these patients benefit from the sequential or alternative use of drugs of these classes rather than the deployment of all possible classes of active anti-MM agents early on in the course of disease? Studies such as the IFM-DFCI (French Francophone Myeloma Intergroup—Dana-Farber Cancer Institute) study of RVD with versus without ASCT (NCT01208662) or the trial of bortezomib and dexamethasone with versus without lenalidomide (NCT00522392) and other future trials will help address these questions, in terms of not only rates and depth of response but also safety profile, progression-free survival, and ideally overall survival. With regard to the latter end point, the need for long-term follow-up and the potential confounding effect of heterogeneous salvage therapy across treatment arms are recognized; they pose fundamental clinical research challenges, although to date, in comparative studies of novel therapies, concordance between progression-free and overall survival has been consistently observed.

Delivering the appropriate overall intensity of treatment to those patients who need it most and sparing other patients, particularly elderly patients or those with other comorbid conditions, from a potentially increased risk of adverse effects and higher cost will require prospective identification of those patients who have a high probability of major clinical response with single-agent or doublet treatment compared with more complex combination regimens. These questions lie at the heart of another major frontier for translational research in MM, namely, the concept of personalized medicine.

PERSONALIZED TREATMENT IN MM: ARE WE THERE YET?

Future Directions
The clinical and biologic heterogeneity of MM leaves little room for rigidly uniform “one-size-fits-all” therapeutic approaches for all patients. Administering the right treatment to the right patients at the right point during the course of their disease is of paramount importance, but this is not a recently discovered concept in MM or beyond. In fact, the International Staging System, widely available cytogenetic techniques (metaphase karyotype, fluorescent in situ hybridization), and more recently the mSMART (Mayo Stratification for Myeloma
and Risk-Adapted Therapy) algorithm—and University of Arkansas for Medical Sciences gene expression–based high-risk scores are examples of platforms intended to eventually facilitate the individualized management of MM. The current resurgence of the question of personalized treatment in MM reflects the recent expansion of the anti-MM therapeutic armamentarium, which has altered the significance of some classical prognostic markers, and concurrent advances in the molecular characterization of MM. Both of these developments are key prerequisites for more efficient individualized therapeutic algorithms in a neoplasm as complex and heterogeneous as MM.

Indeed, in recent years, long-standing experience with more established metaphase karyotype and fluorescent in situ hybridization data has been complemented by comprehensive data on gene expression profiles, chromosomal amplifications or deletions, DNA mutations, and methylation profiling on CD138+ MM tumor cells from different MM clinical settings (newly diagnosed, relapsed, and relapsed refractory patients), including cohorts of uniformly treated patients. Notwithstanding some different results across various groups (likely resulting from different analytic approaches), a consensus has emerged on identifying certain key MM genetic events that are not considered initiating events in myelomagenesis, for example (which are present in the overwhelming majority of p53 lesions that are characteristic of the different subtypes of MM are not currently addressed by specific targeted therapies, either because they represent deletions of tumor suppressor genes or because they are amplifications (eg, c-MAF, MYC) or mutations (eg, RAS) of oncogenes for which no specific targeted therapies are currently available in advanced stages of clinical development. More emphasis should perhaps be placed on therapies that create a synthetic lethality in the context of these currently intractable targets, as well as on therapeutic targeting of RNA expression/function (eg, shRNA or siRNA constructs).

Enacting these intermediate steps will also require patient and comprehensive implementation at both clinical and laboratory research levels. Large prospective studies of patients treated uniformly with contemporary clinical regimens are essential, though the need for flexibility in studying new regimens in the future is recognized. Long-term patient follow-up and detailed annotation of clinical outcome is critically important and should not be restricted to tumor burden, time to and duration of response, or progression-free and overall survival. Information on certain specific clinical pictures (eg, aggressive extramedullary relapses or patient profiles evolving after therapy into monoclonal gammopathy of undetermined significance–like molecular profiles) is important to understand the molecular characteristics underlying these settings. Information should be collected on postrelapse salvage therapies, if these are not assigned to all patients uniformly or are not subject to new randomization within a given study. Baseline and serial correlative studies may include, but not be restricted to, integrated multidimensional molecular annotation (conventional cytogenetic data and results from gene expression profiles, mutation analyses, DNA copy number analyses, methylation profiles, and so on). In addition, better tools to monitor treatment responses both in and outside bone marrow will be important to avoid under- or overtreating patients. These tools include imaging studies (eg, positron emission tomography), multiparameter flow cytometry, and real-time quantitative polymerase chain reaction for minimal residual disease evaluation, which have provided informative data and also merit additional prospective evaluation. Collection and storage of samples for correlative studies should also allow for future testing with new and ideally more sensitive and specific molecular techniques that may not be available at this moment. Molecular testing should focus not only on the tumor and putative biomarkers of its response to treatment but also on patients’ normal cells to evaluate potential predisposition to adverse effects (as illustrated in the study by Broyl et al), including both short-term adverse effects and long-term complications of treatment or of the disease process itself. Such safety-oriented biomarkers could help modify the dose/schedule of individual agents or determine which partner drugs or sequences of administration are selected for combinations.

Correlative studies should ideally focus on biomarkers credentialized by stringent functional preclinical vetting before attempts for clinical validation. The specific method for evaluation of a candidate biomarker should be carefully optimized for the type of specimens that will be tested as well as in terms of sensitivity, specificity, and cost effectiveness. Importantly, the method of study of a given biomarker should be easy to implement beyond the walls of highly specialized tertiary care centers. MM cells in a given patient may exhibit substantial molecular heterogeneity and
drug responsiveness, with the emerging concept of cancer stem cells being a prime example. Developing tests that are not confounded by such heterogeneity will be a major frontier in the research of the years to come.

Many of these directions will not be easy to implement in the near future, and individualized treatment efforts in MM will continue to face major challenges, similar in nature to those in other disciplines. The numbers of clinically and biologically discrete subgroups of patients with MM will increase as more sensitive molecular techniques identify additional recurrent, even if infrequent, lesions. The overall complexity of the classifications and treatment algorithms will rise exponentially with identification of more candidate targets and respective investigational agents. Numerous combination regimens are already available, but correlative studies and mature follow-up of uniformly treated patients with MM (who now tend to live longer as a result of multiple lines of effective therapy) are often completed only after next-generation regimens with higher response rates have already been introduced. This partly reflects overall progress in the field, but it also calls for innovative clinical trial designs that will prevent biomarker discovery and validation efforts from becoming rapidly outdated because of potential shifts in clinical practice.

Another inherent challenge in MM and other cancers is that individualized management for the increasing number of ever smaller molecularly defined subsets may seem philosophically at odds with the perceived concept that evidence-based medicine should be rooted in average or median estimates of clinical outcome in large, yet heterogeneous, patient populations. The temptation to abandon the basic principles of randomized controlled clinical investigation should be avoided in the MM field. We should instead attempt to strike a balance, namely, continue to conduct large randomized studies (particularly for active agents and combinations with multitargeted effects that transcend multiple disease subtypes) and long-term follow-up but also pursue careful studies of smaller patient subgroups (especially those associated with dismal outcome) harboring critical driver molecular lesions and, if available, of highly selective investigational therapies against those targets, informed by innovative bench research. The degree to which this balance is achieved in the MM field will have a major impact on the direction of clinical practice in MM for the foreseeable future.

Although all authors completed the disclosure declaration, the following author(s) indicated a financial or other interest that is relevant to the subject matter under consideration in this article. Certain relationships marked with a “U” are those for which no compensation was received; those relationships marked with a “C” were compensated. For a detailed description of the disclosure categories, or for more information about ASCO’s conflict of interest policy, please refer to the Author Disclosure Declaration and the Disclosures of Potential Conflicts of Interest section in Information for Contributors.

**Employment or Leadership Position:** Faith E. Davies, Celgene (C), Johnson & Johnson (C) (speakers bureau) Consultant or Advisory Role: Constantine S. Mitsiades, Millennium Pharmaceuticals (C), Novartis (C), Bristol-Myers Squibb (C), Merck (C), Kosan Pharmaceuticals (C), Pharmion (C), Centocor (C); Faith E. Davies, Celgene (U), Novartis (U), Johnson & Johnson (U); Douglas Joshua, Celgene (U), Johnson & Johnson (U), Novartis (U); Jesus San Miguel, Celgene (C), Millennium Pharmaceuticals (C), Janssen (C), Novartis (C); Kenneth C. Anderson, Celgene (C), Onyx (C), Millennium Pharmaceuticals (C), Bristol-Myers Squibb (C), Merck (C), Novartis (C); Paul G. Richardson, Millennium Pharmaceuticals (U), Celgene (U), Bristol-Myers Squibb (U), Johnson & Johnson (U), Novartis (U) Stock Ownership: Kenneth C. Anderson, Acetylon Honoraria: Jesus San Miguel, Celgene, Janssen, Novartis, Millennium Pharmaceuticals Research Funding: Constantine S. Mitsiades, OSI Pharmaceuticals, Amgen, AVEO Pharma, EMD Serono, Sunesis, Gloucester Pharmaceuticals, Genzyme, Johnson & Johnson Expert Testimony: None Other Remuneration: Constantine S. Mitsiades, PharmaMar (licensing royalties)

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**AUTHORS’ DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST**

**AUTHOR CONTRIBUTIONS**

Manuscript writing: All authors
Final approval of manuscript: All authors
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