Multiple Myeloma Overview: Novel therapies, the role of biomarkers and imaging, operational aspects

Giovanni Piazzi, Biol. Sc., PMP, Senior Director, Therapeutic Strategy Lead, Therapeutic Science and Strategy Unit, QuintilesIMS

Jorge Acosta, MD, Associate Medical Director, Oncology, Medical Strategy and Science, Therapeutic Science and Strategy Unit, QuintilesIMS

Brad Smith, Ph.D., VP, Translational Medicine, Strategic Drug Development, Advisory Services, QuintilesIMS

Nathalie Faye, MD, Ph.D, Medical Director, Europe, MEDIAN Technologies

Bhavish Lekh, MSc, BSc, Global Feasibility Lead, Clinical Planning and Analytics, Therapeutic Science and Strategy Unit, QuintilesIMS
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Executive summary

The treatment of multiple myeloma (MM) is complex and challenging due to the nature of the disease itself and the rapid advances in drug development, stem cell transplantation, and supportive care. These factors have contributed to improving the overall survival of MM patients in the last 30 years.¹

MM accounts for 1% of all cancers and 13% of all hematologic malignancies, with approximately 86,000 new cases of MM occurring annually worldwide. This malignant neoplasm primarily affects elderly individuals with a median age at the time of diagnosis of around 70 years.² Active MM is consistently preceded by precursor states of monoclonal gammopathy of undetermined significance and smoldering MM, which represent a continuum of progression of the tumor burden in the absence of symptoms or signs of end-organ damage.³ The current standard practice for patients diagnosed with smoldering MM is observation, with therapy only being initiated once the disease progresses to symptomatic active MM.⁴ Clinical research in MM has been very active, and this trend is expected to continue in the coming years.

MM is a highly complex genomic disease. Next-generation sequencing genomic studies have revealed extreme complexity in the MM cancer genome, making the indication less amendable to easy identification and targeting of oncogenic drivers. The implementation of any biomarker in MM is further complicated by the presence of multiple disease stages through progression and various phases of treatment. Imaging is of crucial importance for diagnosis and initial staging, as well as for therapeutic monitoring.

This white paper provides a comprehensive overview of novel therapies being investigated for the treatment of MM patients and of current research from the biomarker prospective. The imaging section provides a comprehensive overview of state-of-the-art imaging of MM, with a focus on whole-body imaging techniques including X-ray, computed tomography, magnetic resonance imaging, and positron emission tomography (PET). Key operational aspects to be considered when planning MM studies are presented in the operational section.

Section 1: Medical overview

MM current treatment approaches

Treatment approaches in MM depend on “fitness,” with chronological age still being an important discriminator for selecting therapy. The initial evaluation of patients includes an assessment of eligibility for high-dose therapy (HDT) and autologous stem cell transplantation (ASCT) based on age, performance status, and comorbidities. In the past decade, one of the major advances in the management of MM has been the introduction
of novel agents including proteasome inhibitors and immunomodulatory drugs as part of frontline treatment in both transplant and non-transplant candidates.\textsuperscript{5,6} These drugs have markedly improved the rate of complete response (CR) without substantially increasing toxicity. Moreover, and importantly, time to progression (TTP), progression-free survival (PFS), and overall survival (OS) have significantly increased. The use of combination regimes introducing novel agents in well-consolidated chemotherapy schemes is now the standard of care, both in ASCT regimens and in non-transplant settings.

However, despite great improvement of the therapeutic landscape in MM, it remains an incurable disease with an important shortening of life expectancy.\textsuperscript{7} Future development of second- and third-generation immunomodulatory drugs, proteasome inhibitors, new drug families such monoclonal antibodies or histone deacetylase inhibitors, and better tools for patient management will enable continued improvement in outcomes in these patients.

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Novel therapies and drugs in development

Immunomodulatory drugs

Immunomodulatory drugs (IMiDs) are a class of therapies that directly affect MM cells and the bone marrow microenvironment, leading to modulation of cytokines, inhibition of angiogenesis, and augmentation of immune effector numbers and function (T cell, NK-cell, and NK-T). Recently, interaction of IMiDs with cereblon, an ubiquitin ligase component responsible for substrate binding, was shown to be crucial for direct cytotoxic and immune related effects. T cell co-stimulation by lenalidomide or pomalidomide is cereblon-dependent and employs two downstream transcription factors, Ikaros (IKZF1) and its paralog Aiolos (IKZF3). Lenalidomide and pomalidomide also inhibit Treg proliferation. In addition to their effects on T cells, IMiDs are shown to augment NK cell antibody-dependent cellular cytotoxicity (ADCC) via increasing NK cell FasL and Granzyme B expressions. These properties make IMiDs perfect companions to the clinical activities of monoclonal antibodies (mAbs) and to the immune-based cellular therapies.

Proteasome inhibitors

Proteasome inhibitors have significantly improved outcomes in patients, regardless of whether they are eligible for transplantation. The proteasome inhibitor bortezomib is active in relapsed or refractory myeloma. On the basis of results of a phase 3 trial, bortezomib was approved for the treatment of myeloma in patients who had received at least one previous therapy. This phase 3 study showed that the addition of bortezomib to melphalan–prednisone was associated with significant improvement in outcomes in patients with newly diagnosed myeloma who were ineligible for high-dose therapy. The median time to progression (the primary end point) was 7.4 months longer in the bortezomib group than in the control group (hazard ratio, 0.48; P<0.001). This benefit was seen across all subgroups of patients, as defined according to baseline demographic and disease characteristics.

Carfilzomib is a second generation selective proteasome inhibitor that has demonstrated activity in patients with MM. Prospective trials have demonstrated response rates of 40 to 50 percent on bortezomib-naïve cases and 15 to 20 percent in bortezomib-refractory cases. Higher response rates have been seen with combination therapy, such as carfilzomib, lenalidomide, dexamethasone (KRD). In the phase III ENDEAVOR study, 929 patients were randomized to receive carfilzomib as a 30-minute infusion along with dexamethasone (n = 464) or bortezomib and dexamethasone (n = 465). Carfilzomib was administered at a starting dose of 20 mg/m² on days 1 and 2 of cycle 1. In the control arm, patients received bortezomib at 1.3 mg/m². The majority of patients received bortezomib subcutaneously. The advantage in PFS seen with carfilzomib was consistent across subgroups. The median OS was 24.3 months in the bortezomib arm but had not yet been reached in the carfilzomib arm (HR, 0.79; P = .066). However, at the time of the primary analysis, survival data were not yet mature. The ORR was 77% with carfilzomib versus 63% with bortezomib. The complete response rate with carfilzomib was 13% versus 6% with bortezomib. The rate of very good partial response or better with carfilzomib was 54% compared with 29% with bortezomib.
Carfilzomib was initially approved by FDA on July 20, 2012 to treat patients for patients with MM who have received at least two prior therapies, including bortezomib and an immunomodulatory agent, and have demonstrated disease progression on or within 60 days of the completion of the last therapy. On July 24, 2015, FDA approved carfilzomib in combination with lenalidomide and dexamethasone to treat patients who have received at least one to three prior lines of therapies. On January 21, 2016, FDA approved yet another indication for carfilzomib to be used in combination only with dexamethasone for patients with relapsed and/or refractory MM who have received 1 to 3 previous therapies. This decision also converted carfilzomib’s monotherapy accelerated approval in this setting to a full FDA approval.

On November 19, 2015, the European Medicines Agency approved it in combination with lenalidomide and dexamethasone to treat patients who have received at least one prior therapy. On May 27, 2016, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion recommending a change to the terms of the marketing authorization, i.e. carfilzomib in combination with either lenalidomide and dexamethasone or dexamethasone alone is indicated for the treatment of adult patients with MM who have received at least one prior therapy.

Ixazomib is an oral proteasome inhibitor that has demonstrated activity in patients with MM. The combination of ixazomib plus lenalidomide and dexamethasone has been evaluated in two phase 1 studies and in a phase 3 trial. In a multicenter phase 3 trial (Tourmaline-MM1), 722 adults with relapsed MM were randomly assigned to receive IRd versus Rd plus placebo [129]. To be included, patients had to have relapsed after one to three prior therapies and could not be refractory to lenalidomide or proteasome inhibitor-based therapy. Cycles of IRd were administered every 28 days as ixazomib (4 mg on days 1, 8, and 15), lenalidomide (25 mg on days 1 through 21), and dexamethasone (40 mg on days 1, 8, 15, and 22). Therapy was continued until disease progression or unacceptable toxicity. At a median follow-up of 15 months, the addition of ixazomib improved the overall response rate (78 versus 72 percent) and complete response rate (12 versus 7 percent), progression-free survival (median 21 versus 15 months; hazard ratio 0.74; 95% CI 0.59-0.94), and duration of response (21 versus 15 months). Overall survival data are not yet mature.

Ixazomib is approved by the U.S. FDA in November 2015 for use in combination with lenalidomide and dexamethasone (IRd) for the treatment of patients with MM who have received at least one prior therapy.

On September 16, 2016, CHMP has adopted a positive opinion, recommending the conditional approval of ixazomib capsules in combination with lenalidomide and dexamethasone for the treatment of adult patients with MM who have received at least one prior therapy. As of today, if the European Commission ratifies the CHMP’s opinion and authorization is granted, Ixazomib will be the first and only oral proteasome inhibitor approved for use across Europe.
**Vaccination strategies**

Two separate vaccination approaches have been developed. The first approach employs peptide-based vaccines. The pioneer of these approaches used idiotype proteins (Id) which appeared to be attractive and specific targets. Unfortunately, this approach has – up to now – not resulted in significant therapeutic effects most likely due to the poor immunogenic nature of the protein as well as low expression of these proteins on the plasma cell surface. There have been efforts to increase immunogenicity via the use of keyhole limpet hemocyanin (KLH), granulocyte macrophage colony stimulating factor (GM-CSF), and tetanus toxoid fragments. In the case of idiotypic proteins, a study investigating the benefit of using idiotype pulsed dendritic cells (DCs) generated from CD34 progenitors showed good tolerability and safety in 11 patients, yet poor biological response was seen in about half, some with increase in humoral response and fewer with T cell activity.15 Again, a Phase II study investigated stimulation of dendritic cells *ex vivo* with idiotypic proteins (Mylolvenge), in a way similar to that by the FDA approved prostate cancer treatment sipuleucel (Provenge), reporting an almost two year overall survival benefit. However, the study had limitations.16 There are ongoing active Id peptide vaccination trials in various forms such as idiotype pulsed DCs and Id-KLH.

On the other hand, subsequent identification of tumor associated antigens such as MAGE, NY-ESO1, WT-1, RHAMM-R3 and XBP-1 and their use as targets enabled generation of cellular responses when used individually and/or in combination in preclinical studies. Clinically, initial results using a single peptide based vaccine demonstrated that such vaccines can be used with few adverse effects and can elicit immune responses, but with modest effect on disease control. In particular, there is a focus on cocktails of fragments of peptides that have abundant expression on myeloma cells. In a preclinical study that used T cells from myeloma patients, peptide specific cytotoxic T lymphocytes were successfully generated using XBP-1, CD138 and CS1 as immunogens. This was more recently replicated using cells from smoldering myeloma patients, which also showed an enrichment in the effector memory CD8 T cell subset, suggesting potentially durable responses. Currently active peptide vaccination trials in myeloma include WT1, hTERT, MAGE-A3 with NY-ESO-1, MAGE-A3 with AS15 and MUC1. Efforts to enhance the immunogenicity of these vaccines included attempted combination with T cell therapy (see below). Although there were impressive immune responses, positive clinical outcomes were lacking.

**Antibody therapies (mAb)**

The development of effective cytotoxic mAb therapies in MM has been hindered by the lack of distinctively and constitutively expressed target molecules on malignant plasma cells. Early studies demonstrated only minimal activity of anti-CD20 rituximab, which is expressed on 20% of plasma cells. This was followed by studies of several mAbs (against CD40, IGF-1R, CD56, CS1, CD138, CD74, IL-6R, CD38, TRAIL-R1). In this review, the authors focus on two mAbs that have already demonstrated promising clinical activity in MM, elotuzumab and daratumumab.
Elotuzumab – anti-CS1 (SLAMF7) antibody
CS-1 is a transmembrane glycoprotein expressed on normal and malignant plasma cell membranes as well as on NK cells. An IgG1 antibody targeting CS1, elotuzumab, has shown impressive *in vitro* activity against myeloma cells, killing them via antibody dependent cellular cytotoxicity (ADCC) while using the same receptor for activation of NK cells. This antibody does not have complement dependent cytotoxicity (CDC). The initial single agent phase I trial showed no clinical activity in a heavily pre-treated population. However, in conjunction with revlimid and dexamethasone, elotuzumab had an impressive 82% objective clinical response in relapsed patients after a median of three lines of prior treatment; median time to progression was still not reached after 16.4 months of follow-up. Recently, a large phase III study (ELOQUENT-2), involving 600 relapsed MM patients, confirmed the efficacy of the combination of elotuzumab plus lenalidomide and dexamethasone compared to lenalidomide and dexamethasone alone; progression free survival was 68% and 41% at one and two years (compared to 57% and 27% in controls). Interestingly, elotuzumab also showed activity against disease, with high risk cytogenetic features such as t(4;14) and del(17p) as well as, to a lesser extent, +1q21.

Combination trials with proteasome inhibitors showed promising results as well, albeit to a lesser degree. Several phase I studies are underway exploring roles of elotuzumab along with anti-KIR antibodies (lirilumab – BMS-986015) or anti-CD137 (urelumab – BMS 663513).

Elotuzumab was approved by FDA on November 30, 2015, in combination with lenalidomide and dexamethasone to treat patients with MM who have received one to three prior lines. On May 11, 2016, the European Medicines Agency granted the marketing authorization valid throughout the European Union in combination with lenalidomide and dexamethasone to treat patients who have received at least one prior therapy.

Daratumumab – anti-CD38 antibody
CD38 is a type II transmembrane glycoprotein with multiple proposed functions in cell adhesion, signaling and enzymatic (cellular nucleic acid metabolism) activity. This is expressed on a multiple hematopoietic and non-hematopoietic cell types. Among many hematopoietic cells that harbor this antigen are medullary thymocytes, subpopulations of both activated B and T lymphocytes, NK cells and dendritic cells.

Daratumumab is a fully human IgG1k monoclonal antibody directed against CD38, which has shown activity against myeloma cells in preclinical models. Among the proposed mechanisms of action of daratumumab, in addition to well described CDC and ADCC, are antibody dependent phagocytosis (ADCP), induction of autophagy/apoptosis, as well as loss of enzymatic activity.
In phase I/II study published by Lokhorst et al., impressive clinical responses were seen in a heavily pretreated patient population, with 64% double refractory to PIs and IMiDs and 76% having undergone ASCT. Daratumumab as a single agent yielded 36% overall response rate in 16 mg/kg arm and remarkably, in the responder group, 65% remained progression free after 12 months.

On November 16, 2015, FDA granted accelerated approval for daratumumab to treat patients with MM who have received at least three prior treatments, including a proteasome inhibitor and an immunomodulatory agent, or who are double-refractory to a proteasome inhibitor and an immunomodulatory agent. Daratumumab was the first anti-CD38 monoclonal antibody approved for treating MM.

On May 20, 2016, the European Medicines Agency granted Daratumumab conditional approval for relapsed refractory MM after at least two previous treatments with a proteasome inhibitor and an immunomodulatory agent.

On November 16, 2015, FDA granted accelerated approval for daratumumab, which was the first anti-CD38 monoclonal antibody approved for treating MM.

On July 2016, FDA granted a Breakthrough Therapy Designation for daratumumab in combination with lenalidomide and dexamethasone, or bortezomib and dexamethasone, for the treatment of patients with MM who have received at least one prior therapy. Breakthrough Therapy Designation was granted to daratumumab based on data from two Phase 3 studies. The MMY3004 (CASTOR) clinical trial which has evaluated daratumumab in combination with bortezomib and dexamethasone, compared to bortezomib and dexamethasone alone, in patients with MM who received at least one prior therapy. The combination of daratumumab, bortezomib, and dexamethasone resulted in significantly longer progression-free survival than bortezomib and dexamethasone alone, with a risk of disease progression or death that was 61.4% lower in the daratumumab group than in the control group. The MMY3003 (POLLUX) clinical trial which has evaluated daratumumab in combination with lenalidomide and dexamethasone, compared to lenalidomide and dexamethasone alone, in patients with MM who received at least one prior therapy. Overall, the addition of daratumumab prolonged progression free survival and was associated with a 63% lower risk of disease progression or death than lenalidomide and dexamethasone alone. In addition to the priority review FDA has also granted a Standard Review for daratumumab in combination with pomalidomide and dexamethasone for relapsed or refractory MM following at least 2 prior therapies, with a proteasome inhibitor and an immunomodulatory agent.

Two additional antibodies that target CD38 are SAR650984 (isatuximab) and MOR03087 (MOR202; MOR), which are under clinical development as monotherapy or in various combinations.
Several new mAbs are under development for various cell member targets. The first is B cell maturation antigen (BCMA), a protein of TNF receptor superfamily, which is crucial for long term survival of plasma cells through its binding B cell activating (BAFF) and proliferating (APRIL) factors.

Antibodies against CD138 (syndecan) seem limited by the soluble forms of CD138. However, when a mAb was combined with tubulin polymerization inhibitor maytansinoids, there were significant preclinical as well as early clinical effects in a phase I trial. Antibodies targeting CD56 and CD74 are in early stages of clinical development.

**Bispecific T cell engagers (BiTEs)**

A new area of antibody research has recently focused on bispecific T cell engagers (BiTEs). These combine the specificities of two antibodies by simultaneous binding to multiple epitopes, one of which involves the engagement and activation of T cells via their CD3 molecules. The first bispecific antibody generated specifically against myeloma was developed by combining single-chain variable fragments (ScFv) of a mAb that binds normal and malignant plasma cells (Wue-1) and a mAb against CD3, forming BiTE product (bscWue-1+CD3). This led to design and development of other BiTEs. A promising bispecific engager that is currently under clinical investigation targets BCMA via a defucosylated antibody that is conjugated to monomethyl aurastatin F (MMAF, GSK2857916).

**Immune checkpoint inhibitors (PD-1/PD-L1 Axis)**

Immune checkpoint inhibitors targeting PD-1 (pidilizumab, pembrolizumab and nivolumab) on T cells or its cognate ligand, PD-L1, on tumor cells have established activities in many different types of cancers. Whereas the initial postulated mechanism of action of the checkpoint blockade was primarily via the engagement of T cells that are being regulated by peripheral tolerance, a growing body of evidence suggests important roles of antigen presenting cells and activation of NK cells. The preliminary results of a Phase I study with nivolumab that enrolled multiple hematologic malignancies reported disappointing results with no objective responses according to IMWG criteria in 27 myeloma patients. However, 67% of patients remained stable within a population where two-thirds of MM patients were heavily pretreated with more than three lines of treatment. Another PD-1 antibody, pidilizumab (CT-011), was investigated via a phase I trial that enrolled 17 patients with various hematological malignancies and has yielded stable disease in the single myeloma patient in the cohort, however, with a durable response for more than 13 months.

There are also clinical studies looking into safety and efficacy of pembrolizumab, primarily in combination with IMiDs. Recently, preliminary results of a phase II trial with pembrolizumab with pomalidomide was presented and reported 50% objective response, including near complete and very good partial responses in a double refractory (RRMM) patient population, hence the combination with pomalidomide and dexamethasone has promising therapeutic activity and an acceptable safety profile in heavily treated RRMM patients. Currently there are several clinical studies investigating the use of immune
checkpoint inhibitors in various combinations in MM, the majority being PD-1 trials. In addition, there is a growing interest in its cognate molecule, PD-L1, as this is the part of the signaling pathway that is harbored on the tumor itself and, at least in theory, has the additional potential for ADCC; this ligand was shown to be expressed on malignant plasma cells. In addition, PD-L is also expressed on other cells, as well such as on plasmacytoid DCs (pDC) and myeloid derived suppressor cells (MDSC), both of which play a role in the immunosuppressive state in myeloma.

Adoptive T cell therapies (ACT)

Early studies suggested that early lymphocyte count recovery after auto-SCT correlated with improved disease control. Several trials involved ex vivo co-stimulation of autologous T cells via immunomagnetic beads (anti-CD3/CD28 beads), which, in the presence of interleukin-2, led to significant activation and expansion of T cells. Infusion of these cells after myeloablative bone marrow conditioning and autologous stem cell transplantation led to early lymphocytosis. In trials using peripheral blood there is no clear evidence for a tumor specific T cell enhancement effect and no impact on outcome. This was probably related to nonspecific stimulation of the entire T cell repertoire, including regulatory T cells. However, it was also noted during early trials that vaccination responses were enhanced in patients receiving ex vivo expanded T cells. This led to a series of trials using various antibodies (Idiotype, MAGE, hTERT, Survivin), all of which were associated with enhanced antibody and cellular immunity against the vaccine.

Recently, Borrello and colleagues have shown for the first time that expanding the subset of marrow-infiltrating T lymphocytes (MILs) can led to clinical antitumor immunity. The results are encouraging, but experience with ACTs awaits confirmation in larger trials.

Chimeric antigen receptor (CAR) T cells

Single chimeric antigen receptor T cell based therapy (CART) represents a huge leap in immune therapy. CART cells, constructed by fusing the single chain variable fragment (scFv) of a monoclonal antibody (mAb) specific for a surface antigen with an intracellular signaling domain have shown activity in several CD-19 related diseases.

The MHC-independent tumor recognition, in vivo expansion, and memory cell generation confers on these cells a clear advantage over naked antibodies or adoptively transferred tumor-reactive T cells. A successful example of CD19 targeted CAR-T cell approach was recently published, suggesting activity of this therapy. Even though plasma cells do not have a strong CD-19 expression, Garfall et al. have observed a low, but nevertheless more frequent expression than previously reported on malignant plasma cells. Targeting this population via the use of CTL019 cells (lentivirus transduced autologous T cells harboring CD3-zeta/CD137 based anti-CD19 chimeric receptor), they reported remission in a 43-year-old with nine prior lines of treatment; they also report treating another nine patients, with more than half being in remission.
Additional attempts using other targets in MM have been less successful and have been attributed to the lack of expression of the target antigen on relevant clones. There are others that have not yet been attempted due to low expression. However, as in the case of CD19 directed CARs, there may be a role for this strategy even for weakly expressed antigens or perhaps due to dynamic nature of surface antigen expressions. At present, it remains unclear whether simultaneous targeting of multiple antigens (such as CD38, CS1, BCMA, CD138, etc.) will be needed to eliminate the malignant clone.

**TCR transgenic T cells**

Infusion of auto-engineered T cells with affinity enhanced TCR specific for a common peptide shared between two cancer testis antigens (NY-ESO-1 and LAGE-1) in MM was recently reported. Patients needed to have HLA-A2 and their MM cells expressed NY-ESO-1 and/or LAGE-1. A total of 24 patients were treated and at last follow up, eight remained in remission with a median PFS of 19.1 months and median OS of 32 months. The duration of response is reasonable and seems better than would be expected in this population. Initial laboratory data suggest that the infused cells remain functional in the absence of IL-2 and without exhaustion for up to one year. Relapsed patients were both antigen negative (indicating mutational change in the target) and positive (probably reflecting T cell exhaustion). However, as these cells are HLA dependent, this approach has a limited utility compared to CART cells.

**Cytokines**

**Interleukin–6 (IL-6)**

Interleukin-6 (IL-6) is a cytokine that has been under spotlight in myeloma since the late 1980s as a driver for myeloma, which raised the question of the benefit of targeting this cytokine for therapeutic purposes. A phase I/II dose escalation study with chimeric monoclonal anti-IL-6 antibody (CLB IL6/8) resulted in a reduction of endogenous production, an effect that was attributed to the blockage of a positive feedback loop. A phase II randomized, double blind, placebo-controlled study compared another anti-IL-6 antibody, siltuximab (CNTO 328), in combination with bortezomib, to bortezomib and placebo combination. There are multiple other studies looking at different combinations of IL-6 blockade in conjunction with other standards of care such as bortezomib, VD, VRD and VMP.

**Interleukin-15 (IL-15)**

Interleukin-15 (IL-15) is a cytokine that has a critical role in CD8 memory cell and NK cell development, proliferation and activation, making it an attractive target. A complex with superagonistic activity against this cytokine, ALT-803 was recently developed, which in preclinical models was able to employ specifically CD8 memory cells. Although NK cells are also activated, the anti-myeloma activity was independent of this activation. A phase I/II study looking into the safety and efficacy of ALT–803 in RRMM is currently under investigation, with another one exploring its role in the setting of post-allogeneic SCT relapse in hematological malignancies.
Histone deacetylases

Histone deacetylases (HDACs) deacetylate the lysine residues of both histones and non-histone proteins. Histone acetylation results in a loose local chromatin structure that regulates gene-specific transcription. Non-histone proteins can also be acetylated, leading to dynamic changes in their activity and stability. For these reasons, HDAC inhibition has emerged as a potential approach for the treatment of MM. Specifically, combination treatment with HDAC inhibitors and proteasome inhibitors or immunomodulatory drugs shows remarkable anti-MM activity in both preclinical and clinical settings. However, the clinical studies using non-selective HDAC inhibitors also cause unfavorable side effects in patients, driving development of more isoform- and/or class-selective HDAC inhibitors to enhance tolerability without diminishing anti-MM activity, thereby improving patient outcomes in MM.

Panobinostat is a histone deacetylase (HDAC) inhibitor that inhibits the enzymatic activity of HDACs. Inhibition of HDAC activity results in increased acetylation of histone proteins, an epigenetic alteration that results in a relaxing of chromatin, leading to transcriptional activation. The efficacy and safety of panobinostat in combination with bortezomib and dexamethasone were evaluated in a randomized, double-blind, placebo-controlled, multicenter phase III study in 768 patients with relapsed or relapsed and refractory MM who had received 1-3 prior lines of therapies. The median PFS (95% CI) was 12.0 months and 8.1 months, respectively. Overall survival was not statistically significantly different between the two treatment groups. The median OS was 40.3 months in the panobinostat + bortezomib + dexamethasone arm and 35.8 months in the placebo + bortezomib + dexamethasone arm. The overall response rate using modified EBMT criteria was 59% in the panobinostat + bortezomib + dexamethasone arm and 39% in the placebo + bortezomib + dexamethasone arm demonstrating activity in heavily treated MM population.

Both vorinostat (a potent broad oral HDAC inhibitor approved in the United States in 2006 for the treatment of patients with cutaneous T cell lymphoma) and panobinostat have demonstrated some activity against MM, and due to the benefits reported with panobinostat, on February 23, 2015, the FDA and on September 11, 2015, the EMA granted accelerated approval to panobinostat in combination with bortezomib and dexamethasone for the treatment of patients with relapsed and refractory MM who have received at least two prior regimens, including bortezomib and an immunomodulatory agent.

BTK inhibitors

Bruton tyrosine kinase (Btk) is a non-receptor enzyme of the Tec kinase family that is expressed among cells of hematopoietic origin, including B cells, myeloid cells, mast cells and platelets, where it regulates multiple cellular processes including proliferation, differentiation, apoptosis, and cell migration. Functional null mutations of Btk in humans cause the inherited disease, X-linked agammaglobulinemia, which is characterized by a lack of mature peripheral B cells. Conversely, Btk activation is implicated in the pathogenesis of several B-cell malignancies. Taken together, these findings have suggested that inhibition of Btk may offer an attractive strategy for treating B-cell neoplasms.
Ibrutinib is a first-in-class, once-daily, oral, covalent inhibitor of Bruton’s tyrosine kinase (BTK), an enzyme overexpressed in malignant plasma cells, whose expression may positively regulate the myeloma stem cell-like population. Ibrutinib is being studied alone and in combination with other treatments in several blood cancers. In MM preliminary data from the ongoing Phase 1/2b PCYC-1119 trial suggested that the combination of ibrutinib plus carfilzomib with or without dexamethasone was well tolerated in relapsed or refractory MM patients with an initial objective response rate (ORR) of 62%. Clinical activity was observed at the 840-mg dose of ibrutinib in heavily pretreated patients with relapsed or relapsed/refractory MM (RRMM), when combined with weekly dexamethasone.12

Knowledge of the critical importance of Btk in tumour biology and the clinical profile observed with ibrutinib has encouraged the development of second-generation Btk inhibitors as a therapy for B-cell malignancies.

Section 2: Biomarker considerations and opportunities

Background on biomarkers
The adoption of genomic patient diagnosis, targeted drugs and precision medicine has been surprisingly rapid in many cancer indications, including some hematology/oncology indications such as non-Hodgkin’s Lymphoma. MM is unique in this regard in oncology. Until recently, the common, approved therapies have been chemotherapies, the IMiDs (namely thalidomide and lenalidomide), and the proteasome inhibitors (namely bortezomib). These therapies have multiple mechanisms of action not necessarily linked to a single target or predictive biomarker. The recent drug approvals in MM continue this trend for effective drugs that broadly target classes of proteins (such as histone deacetylase inhibitors, or HDACs) or immune-related proteins rather than single oncogenic drivers. In addition, while MM has had well-defined cytogenetic prognostic biomarkers in guidelines for some time, these have not been linked to therapies or widely incorporated into treatment decisions. More recently, gene expression signatures have become available to replace these risk classifiers but again, have not been broadly adopted.

Next-generation genomic profiling has emerged in MM, promising to move MM into the new precision medicine age. However, next-generation sequencing (NGS) studies have revealed extreme complexity in the MM cancer genome. MM therefore provided an interesting challenge for biomarkers in drug development and routine patient care.
Patient diagnosis and risk classification

The introduction and use of the SLiM IMWG practice guidelines in 2014 have enabled early treatment of patients likely to develop CRAB myeloma-defining characteristics. However, prognosis in MM is also based upon a number of biomarkers and scoring systems that have a significant impact on patient outcomes.

Currently, approximately 15% of MM patients will survive 0-2 years while 20% may survive longer than 10 years. Prognostic factors in practice today include ECOG performance status, tumor burden and tumor biology, determined by well-established genomic alterations identified by fluorescence in situ hybridization (FISH) or karyotype testing. Additional common prognostic factors include age, LDH levels, macroglobulin levels, and composite scores such as the International Staging System (ISS state). The prognostic genomic alterations consist of either IgH translocations or genomic imbalances such as hyperdiploid, chromosomal gains or deletions. Research and debate to determine which genomic alterations are truly independent prognostic biomarkers or are dependent on other alterations is ongoing. For example, some of the translocations, such as the t(4;14) translocation, have been shown to be linked to other alterations while the Del17 alteration is believed to be a truly independent biomarker for a poor outcome. Some of the rarer alterations, such as the t(14;16) translocation, are now being identified as significant risk factors with important disease information.

One further source of complexity is that the cytogenetic probes or tests used to identify these alterations are not fully standardized and results may vary. Recently, Hebraud et al. extended the analysis of single genomic prognostic factors to combinations of two or more biomarkers. The group reported that certain combinations of Del17 and t(4;114) alterations were more predictive and also confirmed that Del17 was an independent poor prognostic factor. However, the use of these cytogenetic prognostic factors in determining choice of therapies or patient treatment has not been fully adopted. Reports do support the use of certain combinations of proteasome inhibitors and IMiDs in some high risk patients (t4:14) but not others (Del17). However, these cytogenetic factors have not been commonly included in drug clinical studies and are not found on drug labels. In summary, there continues to be a lack of understanding of the complex genetics and biology of these cytogenetic factors and their use in MM.

Gene expression signatures for improved risk assessment

A potential replacement or addition to the MM cytogenetic prognostic classifiers are the gene expression signatures that have been independently identified by multiple groups in the past five years. Prognostic gene expression signatures for MM have been described by at least two research groups, with the MyPRS score available in the United States and the SKY-92 test available in the EU. However, adoption of these tests has been limited due to a number of factors. Concerns regarding the extent of clinical validation for the tests are not helped by the lack of overlap in gene lists among the three signatures. In addition, the tests are lab developed tests without regulatory approval and are not supported from a large number of labs. A 2014 publication questioned the accuracy of the tests as well.

Prognosis in MM is also based upon a number of biomarkers and scoring systems that have a significant impact on patient outcomes.
Despite these concerns, the gene expression signatures offer a prognostic solution that may be technically superior and better reflect the MM biology of the individual patient compared to the cytogenetic tests. Further evidence of clinical validation and broader availability may improve the adoption of this attractive alternative.

**Genomic profiling and opportunities for treatment selection**

The development and adoption of next-generation sequencing and high throughput genomic profiling of cancer patients is rapidly transforming patient care in some indications and cancer centers. A groundbreaking report in 2011 by Chapman et al.\(^39\) first identified an actionable mutation in the BRAF gene in a small number of MM patients using a NGS approach. Subsequent reports expanded genomic profiling of MM patients, including analysis of tumor heterogeneity and clonal evolution.\(^40,41\) The results of these studies demonstrated that MM is a highly complex genomic disease, often with multiple founder clones and changing driver alterations. These studies cast doubt on the future development of precision medicine in MM based upon easily identifiable and targetable genomic driver alterations. However, further genomic studies are underway and outcomes from commercial NGS tests, such as the Foundation Medicine HemeOne test, will determine if this approach will become a diagnostic option for MM patients. A more holistic approach that combines cytogenetics and additional genetic tests may be a more feasible alternative, as proposed by Prideux et al.\(^42\)

**Section 3: Imaging**

Like in other cancers, imaging in MM is crucial for the diagnosis, initial staging, follow up and evaluation of recurrence.

For decades, to be diagnosed with MM and start treatment, patients needed to have the presence of “end-organ” damage such as destructive bone lesions. With the availability of several new treatments for MM, it became urgent to identify patients who could benefit from therapy before potentially irreversible organ damage occurred. There is also the potential that early therapy may improve survival.

The International Myeloma Working Group (IMWG) issued updated criteria in 2014 for MM and allows the use of modern imaging methods to make an earlier diagnosis.\(^33\)
**Diagnosis and staging**

**Whole body X-ray (WBXR)**

The initial imaging evaluation in patients with suspected MM for the last 40 years has been the radiographic skeletal survey or whole-body X-ray (WBXR). Despite validation with staging systems, low cost, and wide availability, WBXR is quite limited in its technical capacity to evaluate bony structures, and lytic lesions are only apparent on conventional radiography when 30% to 50% of bone mineral density has already been lost.43

Patients with early myeloma who have very small lytic lesions or diffuse marrow involvement may escape detection and delay treatment.

**Whole body low dose CT (WBLDCT)**

Several useful attributes have contributed to the expanding use of CT in patients with MM, such as rapid acquisition time and development of low radiation dose protocols.

CT has a 4% to 33% higher detection rate of lytic lesions compared with X-ray. The results are more variable concerning lesions in the skull and ribs. In some studies, detection of this type of lesions was lower with CT, whereas other studies suggested better detection in those regions.44

As with X-ray, WBLDCT may not detect diffuse marrow involvement with homogenous cortical bone appearance that could be mistaken for osteoporosis in an elderly, at-risk population.

**Whole body MRI (WBMRI)**

Magnetic resonance imaging (MRI) can provide distinct information compared to WBXR and WBLDCT, as bone marrow infiltration and distinct patterns of marrow infiltrates that have been found to correlate with findings on bone marrow biopsy.45

Whole body coverage is necessary, as 50% of lesions would be missed by imaging the spine alone.46 MRI has a superior focal lesion detection rate (as much as 82% higher) compared with WBXR.44 MRI can detect changes in marrow density and identify marrow infiltration patterns before development of any bone destruction in patients with monoclonal gammopathy of undetermined significance or smoldering myeloma.47,48

The recent consensus statement from the International Myeloma Working Group has recommended WBMRI for diagnosis of all patients suspected of having MM. Patients with more than one lesion >5 mm should be considered as having symptomatic disease requiring therapy, whereas previous recommendations recognized only cortical lytic lesions on X-ray or CT for treatment.49
Diffuse involvement of the bone marrow is also better detected by conventional WBMRI, but can be most often a subjective diagnosis based on comparison of marrow signal with intervertebral discs.

The diffusion-weighted MRI technique is based on the motion of water at a molecular level and provides excellent contrast between normal bone marrow and myeloma lesions. In normal adults, marrow fat predominates and shows a little signal on DWMRI. When the cellularity increases so does the signal.

**Figure 2:** Spine MRI sagittal views show multiple disseminated localizations on cervical and thoracic spine hypo intense on T1 (a), hyper intense on T2 (c) with intense enhancement after contrast media injection (b).
Figure 3: Whole body Coronal T1 (a) and superimposed Diffusion and T1 weighted images (b) show MM localizations on spine, pelvis bone and femurs.

Figure 4: Whole body coronal T1 (a) and MIP (maximum intensity projection) reconstructions inverted grey scale images (PET-like) show multiple lesions disseminated on spine.
Treatment monitoring

Prognosis in MM has been determined according to the use of WBXR for decades. WBXR and WBLDCT are morphological imaging modalities that neither provide functional information about disease response nor are sensitive to early changes in bone marrow during treatment.

Several studies are evaluating FDG-PET/CT and MRI as tools to assess response to therapy.

PET

Positron emission tomography (PET) alone or combined with CT can be used to follow patients for response to therapy. The most significant advantage in the use of PET/CT is to distinguish active and inactive disease.

During follow-up examinations, PET/CT imaging can distinguish persistent metabolically active lesions of clinical significance just after therapy, whereas lesions detected by MRI persist for a longer period of time (9–12 months) following therapy. Limitations of PET imaging include poor specificity to small lesions less than 0.5 cm in size and false-positive results such as inflammation, infection, brown fat or postsurgical changes. Hybrid techniques such as PET/MRI and PET/WBLDCT may add functional data but are also not yet in routine clinical practice.

Diffusion WBMRI

For focal lesions, changes in size and number can be easily assessed and for diffuse infiltration, signal changes are useful.

ADC measurement can also be used to distinguish good responders and non-responder. Early ADC increases in good responder and decreases in non-responders.

Section 4: Operational aspects

Clinical trial landscape

A search conducted in Citeline (a comprehensive source of real-time R&D intelligence for the pharmaceutical industry featuring a data collection of global clinical trials, clinical trial investigators profiles and drug development pipelines) in September 2016 – using the search criteria, “Oncology, MM, Open/Planned, Industry only studies” – found approximately 300 studies currently ongoing or planned within MM. Figure 5 indicates that the most planned or open studies within MM are located within the USA (174), France (47), Spain (43), Italy (39), Germany (37), Canada (36), Australia (32), United Kingdom (27), Japan (25) and Belgium (24).
Regionally, North America and Western European countries have the most studies that are currently open to enrolment or planned – these regions are used frequently for MM studies and thus present high overall competition. Asia-Pacific, South America and Central Eastern European countries are seen to have relatively fewer studies, however some have a good degree of historical experience within MM studies. Countries within these regions may still be of value in conducting prospective MM studies as competition for MM patients could be less of a risk, whilst maintaining an adequate level of historical experience (completed MM studies) to conduct trials within this indication (Figure 5).

Figure 5: Top 10 countries for open/planned MM trials, Citeline (September 2016)

A large proportion of these studies (>80%) are at the early stages of clinical development (phase I/II), indicating the current high level of interest in finding new treatment approaches for MM patients (Figure 6).

Figure 6: Number of open/planned MM studies by phase, Citeline (September 2016)
Further analysis of these studies indicates that the top five sponsors conducting the most (open/planned) studies within MM as of September 2016 were: Celgene (62), Takeda (30), Amgen (23), Johnson & Johnson (23), and Bristol-Myers Squibb (17; Figure 7). The top five primary drugs being used within MM studies are: dexamethasone (41), lenalidomide (31), carfilzomib (18), pomalidomide (16), and ixazomib citrate (14).

Figure 7: Top 10 sponsors and drugs involved in MM studies, Citeline (September 2016)

Country ranking
The success of an MM clinical program depends on the selection of the right countries and sites to be included; in fact, careful country/site identification represents the major mechanism by which patient recruitment can be facilitated. Initial country/site recommendations for a given trial should be based on a data-driven process, which includes a country ranking algorithm and site tiers based on weighted variables tailored to the success of the specific studies. Using a variety of data sources, QuintilesIMS has developed a preliminary country ranking algorithm for MM studies that includes the characteristics and key success factors summarized in the Table 1.

Table 1: Country ranking algorithm data points and source

<table>
<thead>
<tr>
<th>Data points</th>
<th>Source</th>
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<tbody>
<tr>
<td>QuintilesIMS’s historical start-up timeline</td>
<td>QuintilesIMS’s regulatory database 2016</td>
</tr>
<tr>
<td>Five-year prevalence</td>
<td>GLOBOCAN 2012</td>
</tr>
<tr>
<td>Age standardized incidence rate</td>
<td>GLOBOCAN 2012</td>
</tr>
<tr>
<td>Past enrolment rates in MM studies</td>
<td>QuintilesIMS’s investigator database 2016</td>
</tr>
<tr>
<td>QuintilesIMS’s indication experience (overall studies)</td>
<td>QuintilesIMS’s investigator database 2016</td>
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Table 2 provides an overview of the country tiers for MM based on the data points utilized in Table 1. The data points to be included in the algorithm and the resulting tiers are linked to the success factors and the objective of each single program.

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
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<tbody>
<tr>
<td>Australia, Canada, Czech Republic, France, Germany, Italy, Japan, New Zealand, South Korea, Spain, United Kingdom, United States</td>
<td>Austria, Belgium, Bulgaria, China, Denmark, Greece, Hungary, Israel, Netherlands, Poland, Romania, Russian Federation, Sweden, Switzerland, Turkey and Ukraine</td>
<td>Argentina, Brazil, Egypt, Finland, Ireland, Latvia, Lebanon, Lithuania, Malaysia, Mexico, Norway, Philippine, Portugal, Serbia, Singapore, Slovakia, South Africa, Taiwan and Thailand</td>
</tr>
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QuintilesIMS’s experience

Figure 8 provides an overview of QuintilesIMS experience in MM.

Figure 8: QuintilesIMS experience in MM

Since 2011, QuintilesIMS has provided Phase I-IV clinical services for:

- 36 MM studies
- 3104 subjects
- 1415 sites
- 33 countries worldwide

QuintilesIMS’s sites database

The high number of studies being conducted and planned in MM demands a high level of engagement with experienced sites in this indication. QuintilesIMS has an extensive database of investigators with MM experience, including a total of 1,239 sites across 45 countries. A total of 279 of these sites are QuintilesIMS Prime (77) and Partner (202) sites, which offer time savings during the start-up process and above-average recruitment during the active phase. Site relationships are important, as these help ensure efficient trial planning and conduct; a thorough understanding of patient pathways at the site level enables fast recruitment and maximization of referrals.
Recruitment rates
Based on an analysis of recruitment rates (patients per site per month, p/s/m) observed in MM trials, the median rate of 41 studies listed as completed in Citeline (September 2016) was 0.26 p/s/m. This rate is the same as the one observed at QuintilesIMS (sample size: 16 studies with status completed). Considering this observed median as a baseline figure for planning purposes, the predicted recruitment time for each trial should be determined based on the specific entry criteria and the predicted associated challenges to be addressed.

About QuintilesIMS and MEDIAN
QuintilesIMS’s team of oncology experts (oncologists, advisory services, biomarker experts, project leaders, therapeutic strategy leads, clinical leads, and feasibility leads) is well positioned to support the growth in clinical research in MM based on their experience in the indication, global coverage, relationship with a large site network, and understanding of the landscape.

MEDIAN Technologies, a central imaging review service provider, provides technology and service solutions that enable the proper assessments of MM patients.

Conclusions
Despite significant improvement in overall outcomes, MM remains incurable in majority of patients, prompting a continued search for additional therapeutic options. Treatment of MM presents a special therapeutic challenge because of the heterogeneity of this disease. New and innovative therapeutic options are being investigated, and the number of clinical trials to test drugs in development is expected to increase in the coming years. This will occur in parallel with the required adoption of genomic patient diagnosis, targeted drugs, and precision medicine, which is happening rapidly in many cancer indications but is lagging behind in MM.
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About the authors

Giovanni Piazzi, Biol. Sc., PMP
Senior Director, Therapeutic Strategy Lead, Therapeutic Science and Strategy Unit, Oncology, QuintilesIMS

Giovanni Piazzi has 23 years of clinical trials experience, including 15 years in the QuintilesIMS Oncology Therapeutic Area focusing exclusively on the execution and project management of large global oncology trials. Dr. Piazzi's experience as Clinical Project Manager encompasses a wide variety of different cancer types and project phases. In his current role as Therapeutic Strategy Lead, he combines strategic and operational expertise to help customers with delivery strategies for their oncology projects and programs. Prior to joining QuintilesIMS Dr. Piazzi worked at Synthelabò and SmithKline Beecham.

Jorge Acosta, MD
Associate Medical Director, Oncology, Medical Strategy and Science, Therapeutic Science and Strategy Unit, QuintilesIMS

Dr. Jorge Acosta is Board Certified Internal Medicine Specialist with training in Hematology. He graduated in Internal Medicine in Caracas (2006) at the Central University of Caracas, Venezuela. From 2006 to 2010, Dr. Acosta worked as clinical consultant in Internal Medicine and hematology attaché at the Instituto Medico La Floresta, Caracas. Currently, he is Associate Medical Director – Oncology Medical Strategy & Science Unit, responsible for medical monitoring, clinical guidance, and protocol writing for several trials in hematology, gene transfer therapy, and coagulation.
Brad Smith, PhD  
**VP, Translational Medicine, Strategic Drug Development, Advisory Services, QuintilesIMS**

Brad is VP of Translational Medicine in Advisory Services – Strategic Drug Development, at QuintilesIMS. In this position, Brad leads biomarker and companion diagnostic strategy and planning interactions throughout the organization, including clinical, laboratory, consulting, and commercial projects. He brings more than 21 years of experience in biological research in academia, biotechnology, and clinical services, including five years of experience in planning and design of clinical development plans and protocols for drug development. Prior to QuintilesIMS, Brad spent 10 years at Cell Signaling Technology, where he was responsible for technical and corporate development of biomarker and diagnostic businesses. He is the author of multiple basic research, translational medicine, and clinical publications and patents, and has PhD and held post-doctoral positions at Stanford University and the University of California, San Francisco.

Nathalie Faye, MD, PhD  
**Medical Director, Europe, MEDIAN Technologies**

Dr. Faye is a board-certified radiologist with over 10 years of experience in imaging for clinical trials. She trained and practiced as a clinical radiologist in different University hospitals in Paris, France, spent two years as an Assistant Professor of Radiology in Lille, France, and one year at Synarc Inc., a central core lab exclusively dedicated to clinical trials, in San Francisco. She has authored several publications in imaging. She obtained her PhD in physics and medical imaging at Paris University.
Bhavish Lekh, MSc, BSc
Global Feasibility Lead, Clinical Planning and Analytics, Therapeutic Science and Strategy Unit QuintilesIMS

Bhavish Lekh is continually developing his expertise and over the past eight years has been building on academic and industry knowledge within biochemistry, health care, and clinical research. In his current role, he provides expert feasibility guidance to clinical research studies and programs, to develop the most effective country and site strategies. Bhavish has experience in areas including project management, investigating industry views on regulatory compliance, working as a research assistant conducting experimental analysis on anti-apoptotic proteins involved in cancer development, and working as a health care assistant supporting emergency and trauma patients requiring rehabilitation. Prior to joining QuintilesIMS, he worked at Compliance Hub, the Queens Medical Centre’s Medical School, the Derbyshire Royal Infirmary, and the Derby City Hospital.