Multiple Myeloma

Findings from the AMCP Market Insights Program

Meeting Objectives

- Evaluate the impact of emerging MM therapies on clinically meaningful outcomes and payer strategies
- Understand MM specific managed care strategies around treatment pathways, access and affordability
- Assess the role of real-world data to better understand the impact of current and emerging treatments for patients with MM

Introduction

Multiple myeloma (MM) is a hematologic cancer of plasma cells, currently estimated to afflict 160,000 people worldwide.[1,2] Standard treatments include immunomodulatory drugs, proteasome inhibitors, and monoclonal antibodies.[3] A majority of newly diagnosed, transplant-eligible patients are treated with a three-drug regimen as outlined in the National Comprehensive Cancer Network (NCCN) guideline.[4] The goals of treatment are to reduce disease burden with induction therapy, prolong durability of response with maintenance therapy, reduce treatment side-effects, and extend overall survival. Despite the approval of several therapeutic agents in the past decade that have led to improved response rates and increased survival, MM remains incurable. A majority of patients will eventually relapse and cycle through different combinations of agents, which may increase both the clinical and economic burden.[5] Payers are faced with several factors impacting MM care, including the preferred sequencing of treatment, total cost of care, ability to improve overall survival, and management of treatment side-effects.

To understand the appropriate and cost effective treatment of MM, AMCP convened an expert panel of managed care stakeholders. Panelists included representatives from national and regional health plans, integrated delivery systems, hospitals, and pharmacy benefit managers (Figure 1). Participants discussed the changing landscape of MM, novel treatments, business considerations, coverage trends, and formulary management.

Evolving Paradigms

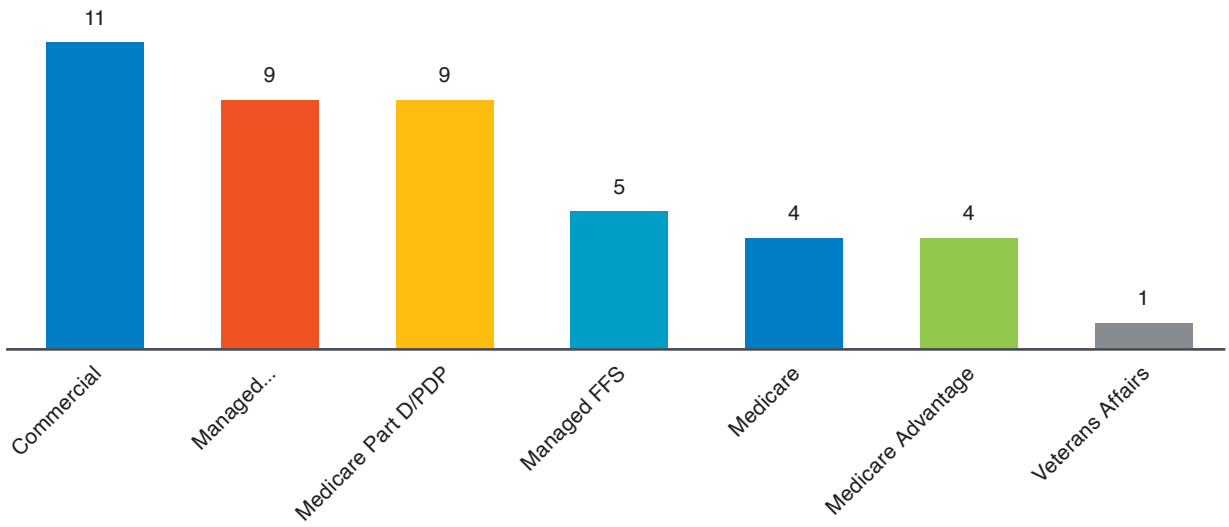
MM develops from a pre-malignant condition known as monoclonal gammopathy of undetermined significance (MGUS), which progresses to smoldering MM (SMM) and MM.[6] MM patients are further staged into risk categories, which predict prognosis and treatment response. High-risk MM patients often display a large degree of intra-tumoral genetic heterogeneity.[7] The contribution of cancer cell mutations and clone heterogeneity to disease progression and resistance to therapy is increasingly being recognized in the treatment of MM.[8] From a payer perspective, this is seen as a shift in practice as more oncologists prescribe treatment strategies that target activating the immune system for broad tumor recognition as opposed to targeting single genetic lesions.

"We need to recognize that multiple myeloma is not one disease"
– Physician

Pharmaceutical treatments for MM typically includes three general classes of drugs: immunomodulatory agents, proteasome inhibitors, and anti-CD38 monoclonal antibodies.[3] The panelists noted a decline in the use of two-drug regimens, and that triplet therapy (bortezomib, lenalidomide, dexamethasone (VRd) or daratumumab, lenalidomide, dexamethasone (DRd)) appears to be the mainstay for most patients who are newly diagnosed with MM because of the overall survival (OS) benefit. Treatment selection is largely based upon the individual patient's clinical presentation, comorbidities, risk stratification and the experience of the oncologist. Unfortunately, currently-approved therapies are not curative for most patients. While combination treatments and autologous stem cell transplant can often lead to effective control of MM, most patients will relapse over time.

"If you have 10 providers, you'd see 10 different ways of treating MM patients."
– IDN

Figure 1. Market Insights Forum Participant Mix



Advances in understanding myeloma biology have led to new treatment strategies to target specific surface antigens on MM cells, such as the B-cell maturation antigen (BCMA). BCMA appears to be essential for the survival of long-lived plasma cells but it is almost absent in other cells, making BCMA an attractive therapeutic target.[9] Several cell-based gene therapy approaches like chimeric antigen receptor-modified (CAR)-T-cells, antibody-drug conjugates, and bispecific antibodies (BsAb) represent new immunotherapy strategies in MM with varying benefits and considerations (Table 1).[10] Although the availability of effective new regimens in MM is welcomed by physicians and payers, it also imposes challenges. The panelists noted that, as the number of treatment options increases, it is important to understand the sequence that is most effective and to be able to compare overall survival and quality-adjusted life-years of different treatment sequences.

"There is not great data to compare what is standard of care, or the right order for using the newer agents."
– IDN

Additionally, the high upfront investment in cell and gene therapies, uncertainty surrounding long-term durability, and adverse events remain concerns among payers. The panelists highlighted their concern for significant treatment-related adverse events, such as cytokine release syndrome, and commented that many are considering the cost of managing treatment toxicities into total cost-of-care calculations and value-based payment agreements.

"There is hope around the benefits of new therapies, but also uncertainty regarding their long-term durability, safety and effectiveness."
– Regional Health Plan

Additionally, panelist noted that treatment selection can be impacted by the limited distribution of products or caused by the distance that patients must travel to receive treatment (e.g. CAR-T therapy), which can vary greatly by region.

Innovation and Research

In recent years the Food and Drug Administration (FDA) has increasingly approved drugs and biologics through the Accelerated Approval Program and on the basis of surrogate endpoints.[11] A surrogate endpoint is an intermediate

Table 1. Comparison of Immunotherapy Strategies for Multiple Myeloma[10]

	Antibody-Drug Conjugates	Bispecific Antibodies	CAR-T
Pros	"Off the shelf" product	"Off the shelf" product	High response in the relapsed refractory setting
	Independent from host immune function	High response in the relapsed/ refractory setting	Only one treatment required
	No delay in administration	No delay in administration	
	Can be given in the community setting	May be given in the community setting	
Cons	High cost	High cost	High cost
	Continuous therapy	Continuous therapy	Long production time (4–6 weeks)
	Higher doses may be required for antigen downmodulation	CRS and ICANs toxicity	CRS and ICANs toxicity
	Payload mediated toxicity		Requires conditioning therapy
	Potential lower response rate		Require adequate lymphocyte count and function

endpoint intended to predict for patient-centered or clinically meaningful outcomes.[12] When used as primary outcomes, surrogate endpoints enable clinical trials of smaller sample size, shorter duration, and lesser cost than trials with clinically meaningful primary endpoints. While overall survival is the gold standard of clinical endpoints in cancer studies, it requires a larger sample size and longer follow-up when compared to measuring progression-free survival (PFS). PFS is commonly used as the primary survival endpoint in MM trials. The panelists discussed recent evidence that shows minimal residual disease (MRD), overall response rate, complete response rate, and stringent complete response may be useful as surrogate endpoints to estimate PFS benefit for patients with newly-diagnosed MM.[13]

From a payer perspective, most panelists reported taking a conservative approach to the use of surrogate endpoints to support their formulary and coverage policies in MM. They expressed a preference for using clinically meaningful outcomes (such as overall survival) but acknowledged that the value of surrogate endpoints where clinically meaningful outcomes are not available. Others noted they only consider validated surrogate outcomes in their formulary evaluations, particularly for oncology drugs approved on the basis of progression-free survival without evidence of improvement in survival. Other panelists commented on the value of recently-published health technology assessments (e.g., ICER and NICE) in oncology to support coverage decisions. Additionally, several panelists questioned if there is still a need for the use of surrogate endpoints in MM clinical trials now that many treatment options are available, in addition to concern that cost-effectiveness models based on extrapolations of immature survival data from short-term studies could lead to inaccurate budget modeling.

"Being a bit more rational in terms of strategy in developing clinical trials is important. The use of surrogate endpoints is imperfect…However, there is real-world data to support that MRD negativity is a "viable surrogate for PFS" in multiple myeloma"
– Physician

The vast majority of decisions in the relapse/refractory MM (RRMM) population are being dictated by clinical practice guideline and pathways, although payers are seeking a broad range of real-world evidence (RWE) around how best to use newer MM immunotherapies (Table 2). From a payer perspective, the highest impact of RWE will likely be on the safety and effectiveness of a medication in larger more heterogeneous populations, and used to support regulatory submissions and supplement clinical trial evidence.

Payer Strategies

The ongoing rise in health care spending continues to have a profound effect on the US economy and health care payers. The Centers for Medicare and Medicaid Services project that by 2028, health care expenditures will climb to $6.2 trillion, or about $18,000 per person, and will represent about 20 percent of GDP.[14] The panelists emphasized that payers use

Table 2. Real World Evidence Needs for Innovative MM Therapies

Real-world evidence are providers/payers seeking in MM
Financial models
Heterogenic patient populations
Impact on absenteeism
Independently generated RWE
Negative trial outcomes
Overall survival
Patient reported outcomes
Pragmatic trial of all prescribers and treatments
Quality of life
Sequence of drug treatment options
Site of care
Total cost of care impact

a variety of approaches to manage the total cost of MM care and the appropriate use of treatments. Prior authorization (PA) is the most likely used utilization management strategy, followed by limiting medication prescribing to a hematologist/oncologist. Formulary coverage criteria is commonly limited to the FDA-approved indications but may be more restrictive than the product label due to limited evidence of benefit and/or safety concerns. Payers are interested in limiting formulary coverage to a set of preferred products, which would be driven by clinical expert guidance, clinical evidence, guidelines and organizational contracting strategies. But panelists also acknowledged numerous challenges remain around selecting preferred formulary products in MM that will be influenced by the type and size of the organization, site of care options, differences in product dosing (e.g. IV vs. SQ), chair time availability in infusion clinics, provider contracts, patient specific characteristics and also influenced by the heterogeneity of MM.

"We are currently focused on developing preferred products for one type of cancer and will expand preferred status into other cancer types from there."
– Regional Health Plan

In order to improve the consistency of care that is provided to patients across providers, payers have been active in developing clinical oncology pathways, including for MM. In many organizations, these pathways are now integrated into the EMR system, which can better influence prescribing decisions. The panelists described use of pathways from various sources ranging from third-party vendors, payer-developed pathways, and provider-developed pathways. They also underscored the importance of having expert clinical teams in place to review the evidence for MM treatments and to provide guidance on treatment pathways. Several payers described the use of disease-specific working groups as an example of managing the growing complexity of care in MM. In general, disease- state working groups are collaborative multidisciplinary teams that meet regularly to review clinical trial information. Panelists described key working group functions around monitoring trends, informing the Pharmacy and Therapeutics (P&T) process and supporting custom treatment pathway development and maintenance, including treatment sequencing. The work groups were credited with allowing payers to consider evolving clinical evidence more quickly and facilitate more timely updates to the formulary and treatment pathways that support improved access for patients. Another activity for payers to consider implementing is around providing more clinician education about MM and the evidence for newer treatments. Regional payers (with fewer staff resources) stated they are partnering with third-party oncology management organizations to bring in additional clinical expertise to support management of MM treatments.

"Employers are asking for every option to better manage specialty medications. And you better be able to show you have ticked all of the boxes: UM, specialty distribution, quantity limits, PA etc."
– Regional Health Plan

Payers are planning to use generic-first programs and biosimilars in pathways to improve affordability, but there is mixed interest in switching current patients. For example, panelists discussed the availability of generic bortezomib, which was first approved by the FDA in January 2018 although is marketed for intravenous administration only. A study published in 2020 demonstrated that switching from subcutaneous to generic intravenous bortezomib could reduce the cost of bortezomib.[15,16] The panelists discussed that this kind of preferred generic opportunity could be

an option in select patient populations, including but not limited those who have not developed bortezomib-induced peripheral neuropathy with the subcutaneous formulation. Additional generic competition in MM treatment options is expected over the next five years for subcutaneous bortezomib, lenalidomide and carfilzomib.[16]

Reducing the costs of prescription drugs and improving supply chain stability have become areas of focus as a solution to reduce the total cost of care. Panelists discussed the need and commitment to bring more supply stability and immunotherapies to patients by investing in the infrastructure to support the engineering of cellular products. The discussion highlighted an example from a partnership between an academic research institution and integrated delivery system to develop specialized manufacturing facilities to engineer T cells for administration to their delivery system patients.

"Part of the justification for investing in cellular lab technology is reducing the total cost of care and improving CAR-T supply."
– IDN

Focusing on providing care for patients in the most cost effective setting is an area of interest for both payers and employers. Costs of intravenous drug therapy and reimbursement rates can be higher in the hospital outpatient department when compared to the physician office or with home infusion. Several panelists shared that they had already implemented site-of-care policies for oncology medications. Others were still in the planning phases. But providers and patients had mixed feedback on the value of the oncology site-of-care programs currently in place

"We are seeing site of service strategies in the multiple myeloma market: with mixed push back from providers and patients."
– IDN

Special Pharmacy Carve-Out

Innovation in treating MM is being impacted by the trend to carve-out specialty medications. Rising medical costs are a significant concern for employers and there is interest in identifying different insurance plan designs that limit the impact of the pharmacy benefit on the overall cost of care. Panelists discussed the growing use of carve-out and benefit exclusions by self-insured organizations for select specialty medications, including some cancer treatments. Proponents of carve-outs say they gives employers more transparency into their pharmacy benefits and allow them greater understanding and control of spending, more informed deal negotiation, and lower total cost of care. But the panelists raised concerns around the potentially unknown impact of these benefit designs on patients' out-of-pocket cost and access. Panelists noted that financial assistance programs that help patients pay for specialty medications vary in eligibility requirements, and carve-outs and benefit exclusions may limit the amount of support patients are eligible to receive.

"Employers simply cannot afford this… There is no longer a clinical coverage review – it is just a benefit exclusion. They seem willing to take the PR hit."
– Regional Health Plan

Panelists highlighted another example of more restrictive formulary practice in the Tennessee Medicaid program… CMS recently announced that Tennessee will be able to implement a commercial style, closed-drug formulary that does not cover certain drugs[18] – a common practice for private insurance and Medicare.

Partnering to Address Risk and Access

From a payer perspective, there was agreement around the opportunity for value-based contracting (VBC) and alternative payment models in MM, which underscored that some level of risk sharing in this area is needed. Some panelists commented that, due to the limited data on treatment sequencing with none of the current treatments being curative, VBC could be an important tool for expanding access and supporting RWE generation. Most agreed that the collaborative effort inherent in VBC agreements was seen as promising and demonstrates a willingness to engage in innovative approaches. However, it was also discussed that challenges remain around the operations and implementation of VBCs and efforts should be continued to lower the complexity of these agreements.

"One thing they do know is that MM disproportionately affects older and minority patients, who have more than double the risk of developing the disease."
– Physician

To effectively address health inequities in MM, healthcare organizations are realizing the value of partnerships and, increasingly, cross-industry partnerships. Health care payers and providers are working to better understand social factors that affect patient health. Pharmaceutical companies can play an active role in addressing health inequities in MM, including identifying and supporting underserved patient populations. Pharmaceutical companies are well-positioned to identify social risk factors and unmet social needs and can have an important role in addressing and mitigating those needs in partnership with payers.

Summary

For payers, coverage criteria development for preferred treatment and sequencing for MM medications becomes increasingly complex with the increasing number of new therapeutic options due to the current clinical evidence gaps. Payers are looking to better understand how MM treatments can be sequenced in the most optimal way to maximize patient survival, minimize toxicity, and manage the total cost of care. As payers focus on a longer-term perspective and seek to assess clinical effectiveness and cost-effectiveness, their view on the value and acceptability of surrogate endpoints in MM clinical trials has diminished. They are looking to RWE to fill in evidence gaps. As such, pharmaceutical companies stand to gain from the development of an RWE strategy for new product launches and future areas of focus for post-marketing trials should include minority groups that were underrepresented within preapproval trials. Expect to see greater impact from integrated delivery networks that offer comprehensive health plans and from investments in engineering cell and gene therapies as a solution to the rising total cost of care and supply chain challenges. Payers continue to implement traditional utilization management techniques and contracting strategies to manage MM treatments, but they are open to new risk-sharing arrangements and are responding to current specialty medication trends and employer expectations with more restrictive benefit designs.

The availability of new immunotherapy therapies, including bispecific antibodies, CAR-T, and conjugated antibodies, has marked a turning point in the treatment of patients with MM. These approaches are expected to play an essential role in the treatment of MM in the next years and to have far-reaching implications for payers.

Disclosures

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References

1. Ludwig H, Novis Durie S, Meckl A, Hinke A, Durie B. Multiple Myeloma Incidence and Mortality Around the Globe; Interrelations Between Health Access and Quality, Economic Resources, and Patient Empowerment. *Oncologist*. 2020 Sep;25(9).

2. The American Cancer Society Cancer Statistics Center. Multiple Myeloma Estimates. Accessed Sept. 13, 2021 at https://cancerstatisticscenter.cancer.org/#!/cancer-site/Myeloma.

3. Rajkumar SV. Multiple myeloma: 2020 update on diagnosis, risk-stratification and management. *American journal of hematology*. 2020;95(5):548-567.

4. Kumar SK, Callander NS, Adekola K, Anderson L, Baljevic M, Campagnaro E, Castillo JJ, Chandler JC, Costello C, Efebera Y, Faiman M, Garfall A, Godby K, Hillengass J, Holmberg L, Htut M, Huff CA, Kang Y, Hultcrantz M, Larson S, Liedtke M, Martin T, Omel J, Shain K, Sborov D, Stockerl-Goldstein K, Weber D, Keller J, Kumar R. Multiple Myeloma, Version 3.2021, NCCN Clinical Practice Guidelines in Oncology. *J Natl Compr Canc Netw*. 2020 Dec 2;18(12):1685-1717.

5. Mikhael J. Treatment Options for Triple-class Refractory Multiple Myeloma. *Clin Lymphoma Myeloma Leuk*. 2020;20(1):1-7.

6. Kyle RA, Durie BGM, Rajkumar SV, Landgren O, Blade J, Merlini G, et al. Monoclonal gammopathy of undetermined significance (MGUS) and smoldering (asymptomatic) multiple myeloma: IMWG consensus perspectives risk factors for progression and guidelines for monitoring and management. *Leukemia*. (2010) 24:1121–7. 10.1038/leu.2010.60.

7. Schürch CM, Rasche L, Frauenfeld L, Weinhold N, Fend F. A review on tumor heterogeneity and evolution in multiple myeloma: pathological, radiological, molecular genetics, and clinical integration. *Virchows Arch*. (2019) 476:337–51.

8. Keats JJ, et al. Clonal competition with alternating dominance in multiple myeloma. *Blood*. 2012; 120 (5): 1067–1076.

9. Cho SF et al. Front Immunol 2018;10:1821, Shah N, Chari A, Scott E, Mezzi K, Usmani SZ. B-cell maturation antigen (BCMA) in multiple myeloma: rationale for targeting and current therapeutic approaches. *Leukemia*. 2020;34(4):985-1005.

10. Barilà, G.; Rizzi, R.; Zambello, R.; Musto, P. Drug Conjugated and Bispecific Antibodies for Multiple Myeloma: Improving Immunotherapies off the Shelf. *Pharmaceuticals*. 2021, 14, 40.

11. FDA Approval and Regulation of Pharmaceuticals, 1983-2018. Darrow JJ, Avorn J, Kesselheim AS. *JAMA*. 2020 Jan 14; 323(2): 164-176.

12. DeMets DL, Psaty BM, Fleming TR When Can Intermediate Outcomes Be Used as Surrogate Outcomes? *JAMA*. 2020 Mar 24; 323(12):1184-1185

13. Daniele P, Mamolo C, Cappelleri JC, et al. Overall, complete, and stringent complete response rates and minimal residual disease as potential surrogates for progression-free survival in newly diagnosed multiple myeloma. Presented at: EHA2021 Virtual Congress; June 9-17, 2021. Poster EP1025.

14. NHE Fact Sheet Accessed September 20, 2021 at www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/NationalHealthExpendData/NHE-Fact-Sheet

15. Shah B. Jhaveri R, Sanchorawala V, et al. Successful transition from bortezomib subcutaneous to generic intravenous bortezomib: Cost savings initiative with global economic impact. ASCO. *J Clin Oncol* .38; 2020 (suppl; abstr e19375).

16. Jhaveri R, Sanchorawala V, Sloan JM, et al. Successful Transition from Bortezomib Subcutaneous (SubQ) to Generic Intravenous (IV) Borezomib: Cost Savings Initiative with Global Economic Impact. *Blood*. 2019; 134 (Supplement_1) 4758.

17. IPD Analytics. Life-cycle insights. March 2021. Accessed September 15, 2021. https://www.ipdanalytics.com.

18. CMS Approves Innovative Tennessee Aggregate Cap Demonstration to Prioritize Accountability for Value and Outcomes. Accessed Sept. 15, 2021 at https://www.cms.gov/newsroom/press-releases/cms-approves-innovative-tennessee-aggregate-cap-demonstration-prioritize-accountability-value-and.

How Will This Impact Your Current and Future Decisions?

- Challenges remain in understanding the appropriate sequencing of care based on available clinical data.
- Continued reliance on clinical expertise from guideline developers (NCCN) and specialists (HEM/ONC).
- Continued use of restrictive benefit designs from self-insured employers in response to rising specialty costs.
- Continued use of treatment pathways from various sources (e.g. third-party vendors, payer-developed pathways, and provider-developed pathways).
- Educate around MM treatment options and the impact on overall survival, treatment toxicity, and total cost of care.
- Engage payers in discussions around their strategic priorities.
- Expect a greater impact from integrated delivery networks and from investments in engineering cell and gene therapies.
- Expect a growing use of third party oncology vendors by smaller regional health plans.
- The acceptability of surrogate endpoints in MM clinical trials is being questioned, payers are looking for clinically meaningful outcomes.
- There is an opportunity for generics and biosimilars to improve affordability and access in MM care.
- There is an opportunity for RWE to fill in current evidence gaps and support financial modeling.
- Utilization management strategies will likely expand beyond prior authorization.