White Paper

The Advent of Novel Treatment Options for Multiple Myeloma: A Critical Juncture for Multiple Myeloma Patients in South Korea

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List of abbreviations and acronyms

ABBREVIATIONS	DEFINITIONS
ADC	Antibody drug conjugate
BCMA	B-cell maturation antigen
BsAb	Bispecific antibodies
CAR-T	Chimeric antigen receptor T-cell
CR	Complete response
FDA	Food and Drug Administration
GDP	Gross domestic product
HIRA	Health Insurance Review and Assessment agency
HTA	Health technology assessment
ICER	Incremental cost-effectiveness ratio
mAb	Monoclonal antibody
MFDS	Ministry of Food and Drug Safety
MM	Multiple myeloma
MOHW	Ministry of Health and Welfare
NCCN	National Comprehensive Cancer Network
ORR	Overall response rate
OS	Overall survival
PFS	Progression-free survival
RRMM	Relapsed/refractory multiple myeloma
SCT	Stem cell transplantation
SEER	Surveillance, Epidemiology and End Results Program

Executive summary

Multiple myeloma (MM) is a rare and complex hematological cancer that causes multi-organ complications and affects patients' quality of life. The incidence and prevalence of MM in Korea have been increasing due to improved detection and its ageing population, along with significant increases in the socioeconomic cost of MM in Korea. In this white paper, we discuss the burden of MM in South Korea, the current treatment landscape and novel treatment options, unmet needs, barriers to access of novel MM treatment options and recommendations for the way forward.

The MM treatment landscape has evolved significantly from conventional chemotherapy to induction therapy with triplet regimens including proteasome inhibitors, immunomodulatory drugs, and high-dose steroids. The past decade has seen the emergence of anti-CD38 monoclonal antibodies and BCMA-targeted immunotherapy. However, access to these novel immunotherapy options in Korea is limited, and bortezomib-containing triplet regimens remain the primary induction regimen for both transplant-eligible and transplant-ineligible patients.

Despite the improved outcomes with current treatment options, there remains unmet needs in MM patients, such as tolerability concerns, need for new treatment options that lead to deep and prolonged response, limited access to treatment options and lack of local treatment guidelines. The use of quadruplet therapy, particularly the addition of anti-CD38 monoclonal antibody to triplet therapy, has shown promising results in previously untreated MM patients, both transplant-eligible and transplant-ineligible, in terms of progression-free survival, time to disease progression, and minimal residual disease negativity. BCMA-targeted immunotherapy, such as CAR-T therapy and bispecific antibodies, has also emerged as a highly promising novel treatment in patients who have received at least three prior lines of therapy and are refractory to proteasome inhibitors and immunomodulatory drugs.

The reimbursement landscape for MM treatment in Korea is at a critical juncture. Recent policy changes, such as the 'three tracks parallel process' that is aimed at streamlining drug regulation, reimbursement assessment and pricing, and the selective reimbursement scheme with copayment rates of 30% to 80% are intended to enhance patient access to innovative treatments. However, it remains unclear if these initiatives apply to MM treatment and challenges such as decreased healthcare investment, low ICER threshold and the exclusion of patient perspectives in value assessment of treatment options persist. Further, our projection analysis revealed that if anti-CD38 monoclonal antibody were reimbursed in the first-line, 968 deaths could be prevented and the worsening of this disease could be avoided in 2,434 patients over the next 5 years.

It is critical to address these gaps to ensure that MM patients in Korea have timely and equitable access to the latest and most effective treatments. We propose the following 8 recommendations to enhance the patients' access to effective MM treatments in Korea. By improving access to new treatments for MM patients, clinical outcomes for these patients in Korea will be enhanced compared to those in other countries.

Recommendations:

1. **Increase healthcare investment in Korea along with investments in infrastructure**
2. **Accelerate patient access to breakthrough treatments through 'three tracks parallel process'**
3. **Enhance clarity regarding reimbursement schemes and their relevance on MM**
4. **Update ICER threshold to be aligned with current economic capacity**
5. **Incorporate patient perspectives on the value of treatment in decision-making**
6. **Develop MM treatment guidelines specific to local landscape**
7. **Generate and utilize real-world evidence**
8. **Enhance patient outcomes through support and education**

Korea's recent healthcare policy reforms and its increased economic capacity are promising developments. Nonetheless, it is imperative to ride this momentum and address unmet needs by increasing investments in healthcare infrastructure and expedite patient access to breakthrough treatments, enhancing the outcomes of MM patients in Korea.

Introduction

Over the last decade, **incidence and prevalence** of MM in Korea has been **increasing**.

By 2030, there will be **~3,000 new cases diagnosed** annually and **22,500 people will be living with MM**.

Patients who relapse or become refractory to their current MM treatment have worse prognosis; it is critical that effective treatments are introduced in earlier lines to delay progression to RRMM.

Promising novel treatment for MM has emerged

In **newly-diagnosed transplant-eligible patients**, addition of anti-CD38 to bortezomib-containing triplet regimens (**DVTd vs VTd**) led to **45% reduction in risk of death** (OS HR 0.55, 95% CI 0.42-0.73) Reference: CASSIOPOEIA, Moreau et al, Lancet Oncol 2024.

In **newly-diagnosed transplant-ineligible patients**, addition of anti-CD38 to lenalidomide-dexamethasone (**DRd vs Rd**) led to **33% reduction in risk of death** (OS HR 0.67, 95% CI 0.55-0.82) Reference: MAIA, Facon et al, EHA 2024.

Unable to access novel MM treatment in Korea

Access to novel immunotherapy options in Korea is limited.

Only **52%** (13/25) of treatment regimens recommended in international guidelines are reimbursed in Korea.

Anti-CD38 treatment regimens are not reimbursed in first-line.

Barrier to reimbursement

The ICER threshold in Korea was established using the 2007 per-capita GDP and remains unchanged, despite a more than **60% increase** in Korea's GDP per capita by 2022.

The average wait time from regulatory approval to public reimbursement of drugs is approximately **18 months in Korea** and **only 3 months in Japan**.

BENEFITS IF ANTI-CD38 IS REIMBURSED IN FIRST-LINE TREATMENT

Our projection analysis revealed that if anti-CD38 monoclonal antibody were reimbursed in the first-line, 968 deaths could be prevented and worsening of this disease could be avoided in 2,434 patients over the next 5 years.

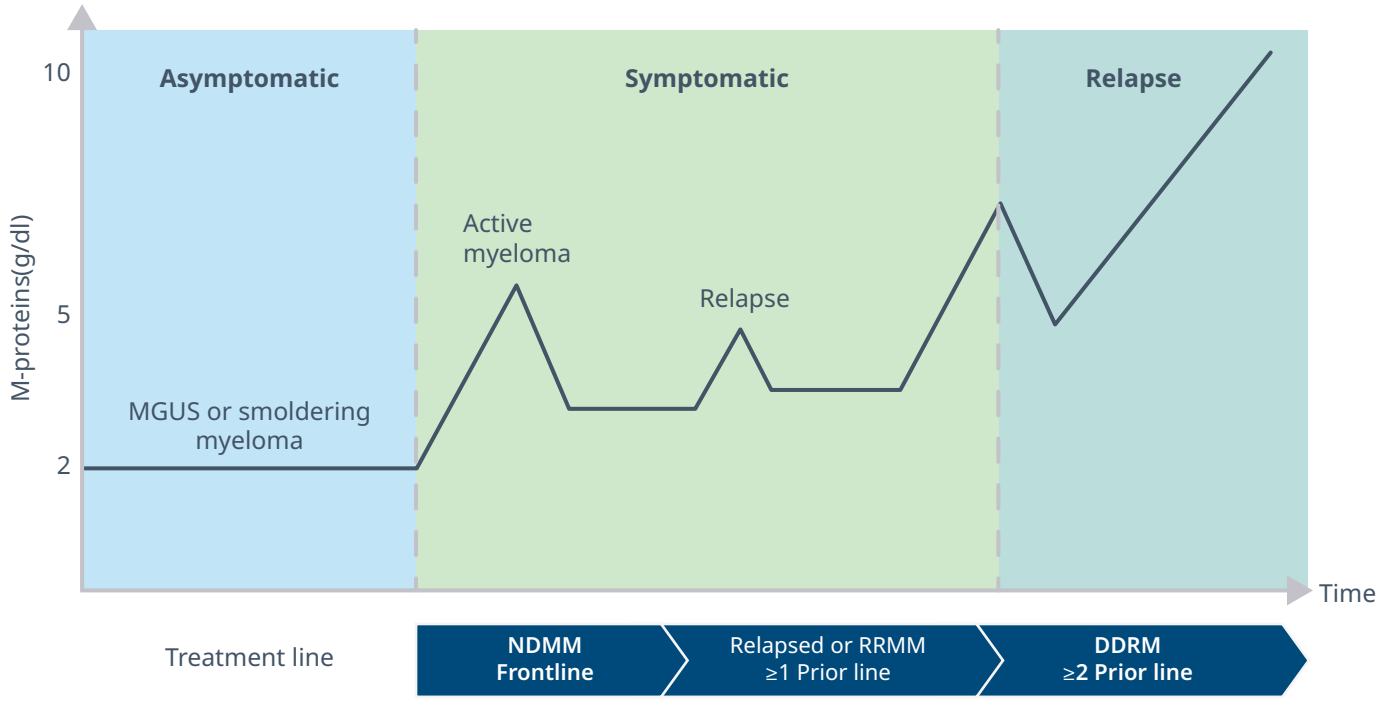
Burden of multiple myeloma in South Korea

Disease introduction

Multiple myeloma (MM) is a complex and rare haematological cancer, characterized by oncogenic transformation of plasma cells in the bone marrow. These abnormal plasma cells produce monoclonal immunoglobulins, which cause various complications, including bone pain, anaemia, hypercalcemia, and kidney dysfunctions. These complications disrupt the production of other blood cell types and lead to renal failure due to accumulation of an immunoglobulin M-protein in kidneys and bloodstream.[1]

Overview of disease stages of MM is presented in Figure 1 and is thought to develop from an asymptomatic phase of clonal plasma cell growth to the onset of symptomatic state that requires treatment.[1] Relapsed and/or refractory multiple myeloma (RRMM) is a critical stage that is characterized by ineffectiveness of treatment during salvage therapy or the progression of disease within 60 days of the last administered therapy.[2] RRMM indicates a situation where the disease is resistant to former therapeutic interventions and is a significant hurdle in managing disease progression. This is as patients have considerably poorer prognosis after they have relapsed or become refractory to their current treatment and it has been shown that it is increasingly difficult to induce durable response to treatment with each relapse, with MM patients showing declining response to treatment as they progress to the next line of therapy after treatment failure.[3-5] As such, it is crucial that effective treatment options are introduced in earlier lines to delay patient progression to RRMM.

Figure 1. Disease stages of multiple myeloma



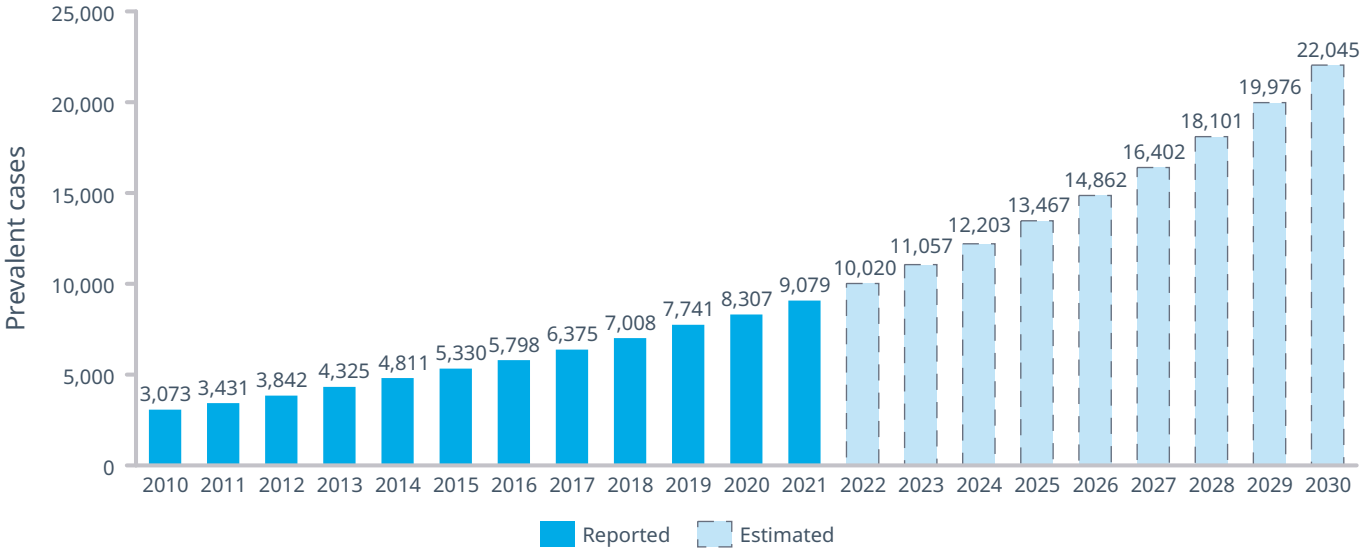
DRMM = heavily pretreated and/or double refractory multiple myeloma; MGUS = monoclonal gammopathy of undetermined significance; MM = multiple myeloma; NDMM = newly diagnosed multiple myeloma; RRMM = relapsed refractory multiple myeloma. Lines of therapy corresponding to the symptomatic/diagnosed, relapse and refractory relapse disease stages are discussed in Section 3.2 Adapted from: MYC inhibitors in multiple myeloma" by Martinez-Martin S et al. 2021.[6] CC BY 4.0 (https://creativecommons.org/licenses/by/4.0/)

Disease burden

INCIDENCE AND PREVALENCE OF MM IN KOREA

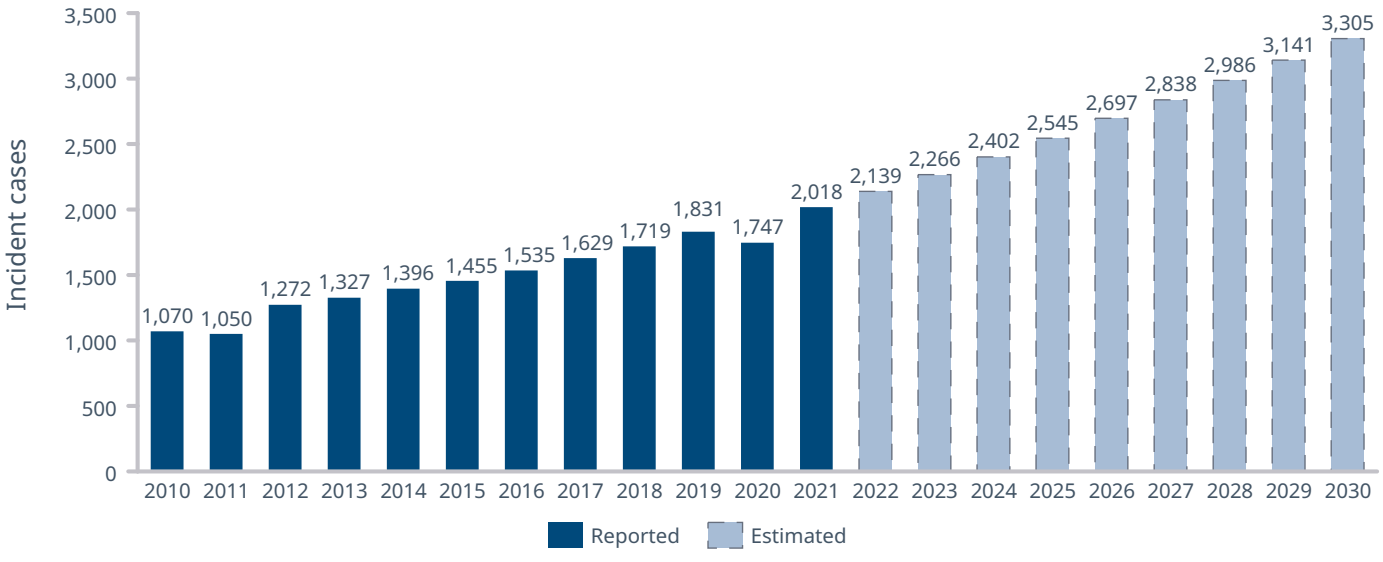
MM accounts for approximately 0.9% of all cancers in Korea.[7] With improved detection coupled with the ageing population in Korea,[8] the incidence and prevalence of MM has been respectively increasing by an average of 5% and 10% annually over the last decade (Figures 2 and 3). As such, it is estimated that there will be ~22,500 people living with MM in Korea and ~3,000 new cases diagnosed annually by 2030.

Figure 2. Number of people living with multiple myeloma in Korea from 2010-2030



Source: Cancer statistics in Korea 2010-2020[9-20], IQVIA analysis

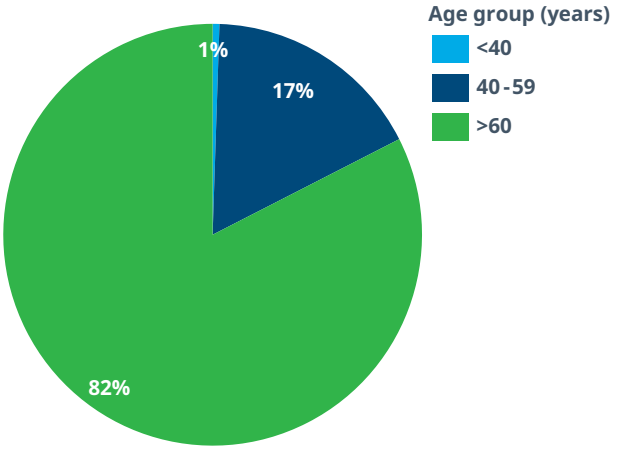
Figure 3. Number of newly diagnosed multiple myeloma cases in Korea from 2010-2030



Source: Cancer statistics in Korea 2010-2020[9-20], IQVIA analysis

Furthermore, the incidence of MM increases with age. In 2022, patients over 60 years of age accounted for 82% of newly diagnosed cases while patients under 40 years of age accounted for only 1% (Figure 4).[7] According to the Surveillance, Epidemiology and End Results (SEER) data, MM was most frequently diagnosed among people aged 65 to 74.[21] Given the ageing demographics of the Korean population, the incidence of MM is likely to continue increasing for years to come.[22] As such, lack of optimal treatment coupled with rising incidence of the disease will lead to a strain on healthcare resources and impact patients' and caregivers quality of life, resulting in greater economic burden due to lost productivity and high medical costs.

Figure 4. Multiple myeloma incident cases distributed by age group in Korea



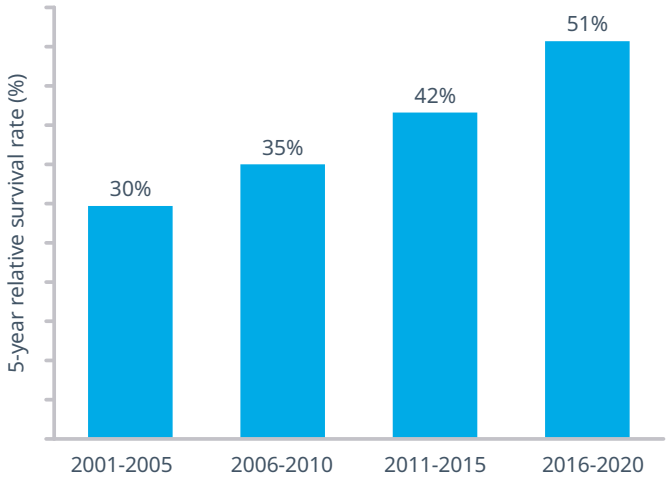
Source: GLOBOCAN 2022[7]

Along with the development and introduction of new treatments, the survival of patients with MM has improved significantly in Korea over the past two decades where the 5-year relative survival rate of MM patients in Korea improved from 30% prior to 2005 to 51% in the period of 2016 to 2020 (Figure 5).[16] Nonetheless, there is room for further improvement of patient outcomes as the 5-year relative survival rate of MM patients in Korea is still lower than that in other developed markets, such as United States (~60%), where various innovative treatments are available for patients.[16,23]

"It takes about 2 years for a new drug to become available in the US but almost 6 years for approval and reimbursement in Korea. Since its availability is late, use in Korea patients is late and this leads to the differences in outcomes in Korea patients (compared to other countries)."

— Hematologist 3

Figure 5. Multiple myeloma 5-year relative survival rate in Korea from 2001–2020



Source: Kang et al, 2023[16]

FINANCIAL IMPACT OF MM ON PATIENTS

With the increasing prevalence and incidence of MM, the socioeconomic cost of this disease has risen significantly. It has been reported that the socioeconomic cost of this disease, including direct medical costs, non-direct medical costs of transportation and nursing costs, costs of productivity loss and premature deaths, increased substantially from US$118M (~133 billion KRW) in 2011 to US$200M (~226 billion KRW) in 2015.[24]

Furthermore, the financial impact of the disease extends beyond medical costs and it has been reported that the annual productivity loss for MM patients and caregivers accounted for approximately 10% to 18% of the total cost of illness.[25] This is not surprising given that MM patients experience significant productivity loss in the first year following diagnosis due to disease symptoms and from undergoing chemotherapy with doublet and triplet regimens.[26]

Although the outlook for patients with MM has improved considerably over the last decade, there remains room for further improvement of MM patient outcomes in Korea. Compounded with the challenge of managing patients who ultimately relapse, there is a need for more effective therapies to aid management of this disease in Korea.Evolution of MM treatment and the current treatment landscape in Korea

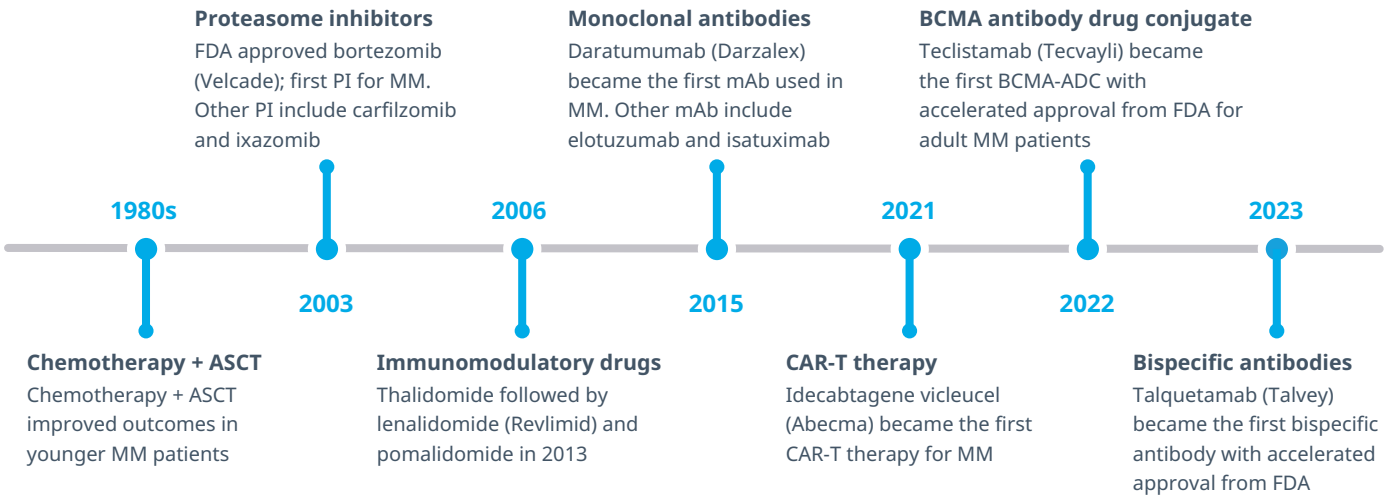
Evolution of multiple myeloma treatment and the current treatment landscape in Korea

The MM treatment landscape has changed dramatically over the last three decades from the use of conventional chemotherapy to the introduction of triplet regimens incorporating proteasome inhibitors such as bortezomib, immunomodulatory drug thalidomide or lenalidomide, and high-dose steroids as the standard induction regimen (Figure 6).[27] The past decade has also been termed the “immune era” for multiple myeloma, with the advent of anti-CD38 monoclonal antibodies.[28]

In recent years, B Cell maturation antigen (BCMA)-targeted immunotherapy, including BCMA-targeted Chimeric antigen receptor T-cell (CAR-T) therapy, BMCA-antibody drug conjugates and bispecific antibodies, has emerged as highly promising novel treatments in patients who have received at least three prior lines of therapy and are refractory to proteasome inhibitors and immunomodulatory drugs.

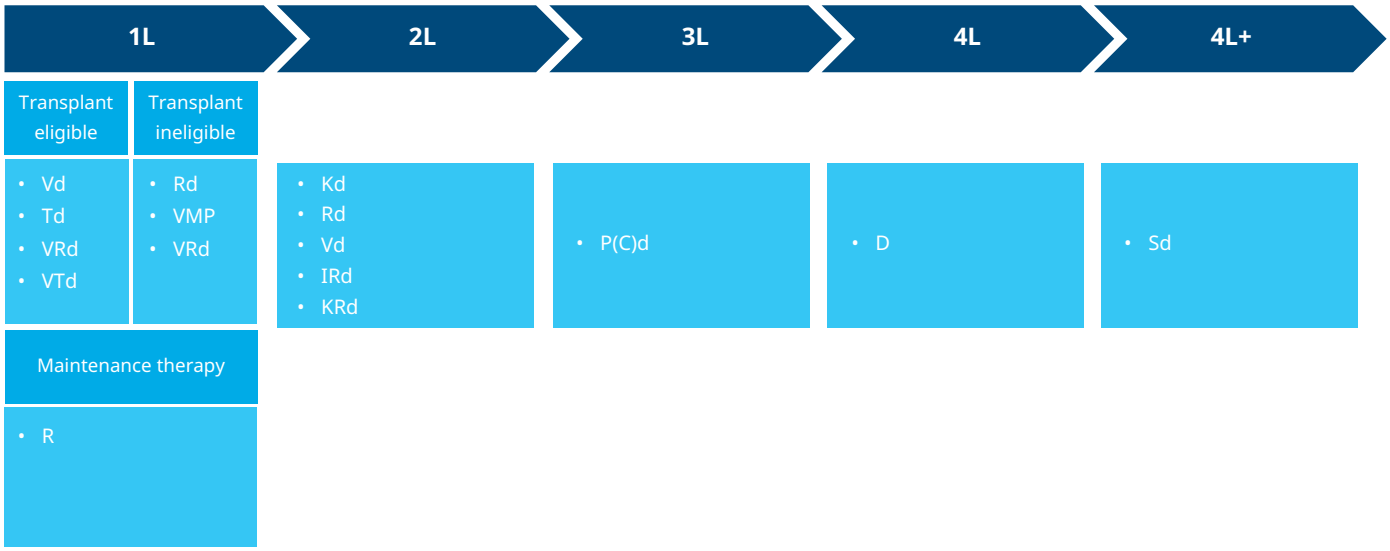
Despite the emergence of these promising novel treatment options over the last few years that have been recommended in international guidelines,[29] access to the immunotherapy options in Korea are limited. Although anti-CD38 combination regimens are available for use in first line treatment, due to lack of reimbursement, triplet regimens containing bortezomib remain the primary induction regimen in Korea for both transplant-eligible and transplant-ineligible patients (Figure 7).

Figure 6. Evolution of MM treatments



ADC, antibody-drug conjugates; ASCT, autologous stem-cell transplantation; mAB, monoclonal antibody
Source: International Myeloma Foundation,30 Dima et al 2022[27]

Figure 7: Korea treatment algorithm



Source: Korea Ministry of Food and Drug safety,[31] IQVIA analysis

D = daratumumab; IRd = ixazomib-lenalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; P(C)d = pomalidomide-cyclophosphamide-dexamethasone; R = lenalidomide; Rd = lenalidomide-dexamethasone; Sd = Selinexor-dexamethasone; Td = thalidomide-dexamethasone; Vd = bortezomib-dexamethasone; VMP = bortezomib-Melphalan-Prednisone, VRd = bortezomib-lenalidomide-dexamethasone; VTd = bortezomib-thalidomide-dexamethasone

Unmet needs in multiple myeloma patients

TOLERABILITY CONCERNS WITH CURRENT TREATMENT OPTIONS

Although the outlook for patients with MM has improved considerably over the last decade, there remain concerns with adverse effects of current frontline triplet regimen options, such as fatigue, fever, gastrointestinal side effects and peripheral neuropathy,[32] especially as MM patients tend to be more advanced in age.

Bortezomib-containing triplet regimens are currently the preferred frontline regimen in Korea.[33] However, use of bortezomib also led to increased occurrence of adverse events. The SWOG S0777 trial demonstrated significant improvements in both progression-free survival (PFS) and overall survival (OS) for bortezomib-lenalidomide-dexamethasone (VRd) compared with Rd in patients without intent for autologous stem cell transplant (SCT). Nonetheless, intravenous administration of bortezomib was associated with a substantial rise in grade 3 or worse neuropathic and gastrointestinal adverse events. Consequently, there was greater discontinuation of treatment due to adverse events with the triplet regimen, a significant drawback in tolerability compared to the Rd regimen.[34,35] Similarly, a prospective observational study of 177 transplant-ineligible MM patients in Korea showed that the addition of bortezomib to melphalan and prednisone (VMP) led to a notable increase in rates of peripheral neuropathy and gastrointestinal toxicity. Development of peripheral neuropathy was the leading cause of treatment discontinuation, highlighting the lack of tolerability of current treatment options.[36] The lack of tolerability not only leads to treatment discontinuation but also impacts social and functional activities which increases psychological burden of disease and treatment on patients.

"The main drugs being used now have quite a lot of toxicity, that is one of the significant unmet needs. (This is) One of the reasons why patients suffer and why they can't get subsequent lines of treatment"

— Hematologist 4

NEED FOR NEW TREATMENT OPTIONS THAT LEAD TO DEEP AND PROLONGED RESPONSE

The main goals of front-line treatment is to achieve remission, delay disease progression and prevent recurrence while maintaining patients' quality of life.[2] However, a real-world retrospective study of 11,500 patients with newly-diagnosed MM in Korea between 2010 to 2019 found that not only did ~50% of patients who received 1L treatment advanced to 2L, crucially, ~20% progressed to 4L treatment and beyond indicating the need for more effective treatment options to achieve deep and prolonged response.[37] The shortening time to next treatment with each subsequent line of treatment received also imply that prognosis remains poor for patients who relapse or become refractory to earlier treatment.[37]

"If the effective treatment is given at first line and disease is removed, it becomes the setting where cure can be considered even though it wasn't a curable disease technically. It is accepted now that reserving good drugs for later lines is not ideal."

— Hematologist 1

Consequently, it was unsurprising that a 2016 survey conducted by the Korean Multiple Myeloma Patient Group showed that among the 65 survey participants, 32% of surveyed patients expressed that they were actively seeking new treatment options after exhausting all previously available treatments.[38] MM patients in Korea have also expressed dissatisfaction with the first-line therapy as frequent recurrences significantly contribute to the frustration and distress experienced by them and their families.[39] Their continued search for alternative treatment options highlights the critical need for persistent efforts in introducing new effective treatments that are more optimal for patients.

LIMITED ACCESS TO TREATMENT OPTIONS AND LACK OF LOCAL TREATMENT GUIDELINES

Despite continued innovation, improvements in patient outcomes are hindered by treatment availability in Korea. Out of 25 multiple myeloma (MM) treatments recommended by NCCN guideline across various lines of therapy, only 13 (52%) were reimbursed in Korea (Table 1), emphasizing the difficulties patient encounter in accessing novel frontline treatment and the limited options for treatment sequencing.

"The biggest problem of reimbursement in Korea is that a fixed regimen has to be used. The reimbursement criteria considers whether it's monotherapy or combination therapy and in what line of therapy... treatment effectiveness may be increased by adding other drugs in some patients, but the regimen may then not be reimbursed."

— Hematologist 2

The landscape of MM treatment is rapidly changing as novel treatment options become available. However, there is a lack of local MM treatment guidelines in Korea. Treatment guidelines are essential to ensure a consistent and a standardized approach in managing patients based on available treatment options and optimize patient outcomes. These guidelines should be based on the latest research and clinical data, and should be updated regularly to reflect the evolving landscape of MM treatment specific to Korea. This will guide healthcare professionals in providing the best possible care to their patients and improve the overall quality of life for those affected by MM in Korea.

"Since everything is decided in the reimbursement criteria, the options in which doctors can choose are very limited. If doctors can choose what treatment option to use and which combination, improved outcomes could be expected."

— Hematologist 4

Table 1: Treatment options recommended in the NCCN guidelines and available in Korea

TREATMENT REGIMEN	NCCN GUIDELINES	SOUTH KOREA
D	O	O
DKd	O	
DPd	O	
DRd	O	
DVd	O	
DVCd	O	
DVMp	O	
DVTd	O	
IRd	O	O
IsaKd	O	
IsaPd	O	
Kd	O	O
KRd	O	O
Pd	O	O
PVd	O	
R	O	O
Rd	O	O
Sd	O	O
Td	O	O
V	O	
Vd	O	O
VCd	O	
VMP	O	O
VRd	O	O
VTd	O	O

DKd = daratumumab-carfilzomib-dexamethasone; DPd = daratumumab-pomalidomide-dexamethasone; DRd = dratumumab-lenalidomide-dexamethasone; DVd = daratumumab-bortezomib-dexamethasone; DVCd = daratumumab-cyclophosphamide-bortezomib-dexamethasone; DVMP = daratumumab-bortezomib-melphalan-prednisone; DVTd = daratumumab-bortezomib-thalidomide-dexamethasone; IRd = ixazomib-lenalidomide-dexamethasone; IsaKd = isatuximab-carfilzomib-dexamethasone; IsaPd = isatuximab-pomalidomide-dexamethasone; Kd = carfilzomib-dexamethasone; KRd = carfilzomib-lenalidomide-dexamethasone; Pd = pomalidomide-dexamethasone; PVd = pomalidomide-bortezomib-dexamethasone; R = lenalidomide; Rd = lenalidomide-dexamethasone; Sd = Selinexor-dexamethasone; Td = thalidomide-dexamethasone; V = bortezomib; Vd = bortezomib-dexamethasone; VCd = bortezomib-cyclophosphamide-dexamethason; VMP = bortezomib-Melphalan-Prednisone, VRd = bortezomib-lenalidomide-dexamethasone; VTd = bortezomib-thalidomide-dexamethasone. Source: NCCN guidelines Multiple Myeloma v2.2024[29]

Promising novel treatment options for multiple myeloma patients

The emergence of novel treatment options has been a significant development in the field of MM treatment, particularly as we enter the current "immune era" following the approval of novel immunotherapy options, including anti-CD38 antibodies and anti-BCMA immunotherapy.

IMPROVED CLINICAL OUTCOMES WITH THE ADDITION OF ANTI-CD38 MONOCLONAL ANTIBODY

The use of quadruplet therapy, particularly the addition of anti-CD38 monoclonal antibody to triplet therapy, has shown promising results in previously untreated transplant-eligible MM patients. The randomized phase III CASSIOPOEIA trial showed that addition of anti-CD38 monoclonal antibody daratumumab to bortezomib, thalidomide and dexamethasone (DVTd vs VTd) led to improvements in PFS and OS.[40–42] At median of 80 months follow up, median PFS was significantly longer in DVTd-treated patients at 83.7 months compared with 52.8 months in those treated with VTd alone. Estimated 72-month overall survival rates were 86.7% (95% CI 83.5-89.3) in the DVTd group compared with 77.7% (95% CI 73.9-81.0) in the VTd group.[41,42] Discontinuation rates during induction and consolidation was slightly lower in the DVTd group than in the VTd group, and the occurrence of serious adverse events, including infection, was similar between both groups.[40]

These results concur with a recent retrospective multicenter study in transplant-eligible newly-diagnosed MM patients in Korea; compared with the current standard of care (VRd), a significantly greater proportion of patients achieved very good partial response or better with DVTd treatment (93% vs 68%), while 16% of patients treated with VRd experienced relapses compared with 2% in the DVTd group.[43] These findings support the use of front-line quadruplet regimen containing anti-CD38 monoclonal antibody for transplant eligible newly-diagnosed MM.

The improved clinical outcomes with addition of anti-CD38 monoclonal antibody in frontline treatment was also demonstrated in transplant-ineligible patients.[44]

In the ALCYONE trial, the addition of daratumumab to bortezomib, melphalan and prednisone (DVMP vs VMP) resulted in 58% reduction in risk of progressive disease of death that reached statistical significance, higher overall response rates (91% vs 74%) and almost double in complete response (CR) rates.[45,46]

The MAIA phase III trial showed that addition of daratumumab to lenalidomide and dexamethasone (DRd vs Rd) led to significant improvements in survival benefit in newly diagnosed MM patients who were transplant ineligible. At median follow up of ~7.5 years, DRd treatment reduced the risk of death by a third compared with Rd treatment. Median overall survival was 90.3 months in the DRd group vs 64.1 months in the Rd group. Median time to next treatment was significantly longer in the DRd group compared with that in Rd group (not reached vs 42.4 months). Overall, 78% of patients in DRd group discontinued treatment compared with 94% of patients in Rd groups.[47,48]

The alleviation of disease symptoms allows patients to participate in daily activities and is also crucial to their treatment satisfaction, compliance and quality of life. Patient reported outcomes from the phase III trials have shown that addition of anti-CD38 monotherapy led to improvement in pain and health related quality of life. These benefits were observed since early phases of treatment and was sustained in the long-term.[49,50] The addition of daratumumab in induction therapy has therefore been demonstrated to be effective and tolerable and is the standard induction therapy for transplant-ineligible patients.

"(Anti-CD38 monoclonal antibody) It's the treatment that should be used from first line. We have experience with it; it doesn't have many side effects and has high treatment effect, so it's the treatment that should be used universally and quickly."

— Hematologist 2

NEED FOR NOVEL TREATMENT OPTIONS TO BE USED IN EARLIER LINES OF TREATMENT

Anti-CD38 antibodies are currently accessible for 4th line treatment in Korea,[31] however, there is mounting evidence to support the use of effective treatment options in earlier lines rather than saving it for later lines of treatment.

A recent retrospective study by Fonseca et al[5] in newly diagnosed MM patients found that a substantial proportion of patients who received frontline treatment were unable to move on to subsequent lines of therapy. It was reported that 56% of nontransplant patients and 21% of transplant patients received only a single line of therapy, and only 8% of nontransplant patients and 22% of transplant patients received a fifth line of treatment. While it was unclear if attrition rates were due to disease progression or not, higher attrition rates were associated with older age, cardiovascular or pulmonary circulation disorders, and renal impairment. These findings highlight the importance of defaulting to optimal treatment regimens for newly diagnosed patients, as opposed to "saving" for later lines of therapy, as many patients may not receive subsequent lines of therapy and the overall clinical impact may be muted.

A retrospective observational study of newly-diagnosed Korean MM patients from 2010 to 2017, found that drop-off rates (proportion of patients not reaching next line) increased from 56% to 68% with each subsequent line among patients who have not received SCT and ranged from 41% to 54% among patients who have received at least one SCT.[51] The increase in drop-off rate with each additional line of therapy highlights the need to utilize the most effective therapies in earlier lines of treatment as patients may not survive to receive them in later lines of treatment.

"It's better to induce the deep response in patients from first line of treatment rather than waiting until the fourth line of treatment…then patients' PFS and OS will improve."

— Hematologist 2

"I think it's a principle to use more effective drug earlier in advance, before having tolerability issues, to increase proportion of patients cured."

— Hematologist 4

TARGETING BCMA WITH NOVEL TREATMENT OPTIONS FOR RELAPSED AND REFRACTORY MULTIPLE MYELOMA HOLDS PROMISE

One of the emerging treatment strategies for RRMM is to target BCMA, a protein that is highly expressed on the surface of malignant plasma cells. CAR-T therapy involves genetically modifying a patient's own T-cells to recognize and kill BCMA-positive plasma cells and have shown promising results in clinical trials for patients with RRMM. In a multicenter study of 127 patients with RRMM, ABECMA, the first FDA-approved anti-BCMA CAR-T therapy, achieved an overall response rate (ORR) of 72% and a CR rate of 28%. An estimated 65% of patients who achieved CR remained in CR for at least 12 months.[52] In another study, Carvykti, another anti-BCMA CAR-T therapy, was evaluated in 97 patients with RRMM and achieved an ORR of 98% and a CR rate of 76%. Among the patients who achieved CR, 76% remained in CR for at least 22 months.[53]

"When patients are on the fourth or fifth lines of treatment, there are few drug options left. Bispecific antibody or CAR-T treatment should be readily accessible in Korea for such patients."

— Hematologist 2

More recently, bispecific T-cell antibodies (BsAb) have received regulatory approval and present as an active therapeutic option for RRMM patients by direct T-cell activation and subsequent tumor cell killing. Following results of the MaJesTEC-1 study, teclistamab, an anti-BCMA BsAB, recently received FDA-approval for RRMM patients who received at least 3 lines of treatment including anti-CD38, proteasome inhibitor and lenalidomide.[54,55] After a median follow-up of 14 months, the overall response rate was 63% and 39% of patients achieved a CR or better, with a median progression-free survival of 11 months and median duration of response was 19 months. This study showed a high rate of deep and durable response in patients RRMM disease with acceptable tolerability profile, even among those who have been triple-class exposed.[54]

Current policies related to reimbursement provide a way forward for novel multiple myeloma treatment but gaps are still present

In South Korea, the reimbursement landscape for MM treatment has been evolving, marked by both advancements and persisting challenges. While recent policy changes show promise in enhancing patient access to innovative treatments, significant gaps in the reimbursement framework still limit the full potential of these advancements. This section explores the current state of healthcare investment, policies impacting MM treatment access, the existing reimbursement framework, and the role of patient advocacy in shaping treatment accessibility.

DECREASED HEALTHCARE INVESTMENT IN KOREA DESPITE INCREASING INCIDENCE OF CANCER

Despite increasing number of cancer cases from 2021 and 2022,[56,57] there was a 4% decrease in the national cancer budget in Korea from 99,004 billion Won in 2020 to 94,975 billion Won in 2021.[58,59] This financial shift could have significant repercussions, especially in pharmaceutical and healthcare spending. The reduction in the cancer-related budget raises concerns about its potential impact on the approval and reimbursement of novel MM treatments as financial constraints may limit the allocation of resources to newer, often more expensive, therapies, hindering their accessibility to patients. Compounding this challenge is Korea's comparatively lower investment in health spending per capita when juxtaposed with other developed markets like Japan and Australia. A comparison in Table 2 underscores the need for an increase in health spending in Korea, recognizing the vital role it plays in supporting novel treatments and ensuring optimal patient care.

LACK OF CLARITY ON WHETHER RECENT HEALTHCARE POLICY CHANGES THAT COULD POTENTIALLY LEAD TO QUICKER ACCESS TO NOVEL TREATMENTS APPLY TO MM

The Ministry of Health and Welfare (MOHW) recently unveiled a Regulatory Innovation Plan for the New Bio-Health Industry which aims to enhance access and expedite the commercialization of innovative treatments for rare and incurable diseases, such as regenerative medicine.[60] As part of the healthcare policy reformation, the government is set to implement a 'three tracks parallel process' aimed at streamlining drug regulation, reimbursement assessment, and pricing. This initiative focuses specifically on drugs addressing life-threatening diseases, orphan drugs or those presenting significant clinical improvements. To qualify for this expedited process, candidate drugs must meet specific criteria, including the treatment of life-threatening diseases or clearly demonstrate superior clinical efficacy.[60] However, it is important to note that while some of these criteria may apply to MM treatments, MM is currently not recognized as a rare disease in Korea. The Korea Disease Control and Prevention Agency's rationale for excluding MM from the rare disease category include a relatively higher disease prevalence, lower severity, and financial burden, among others.[61] Nonetheless, while the criteria for classifying diseases as rare are undergoing reevaluation,[62] the 'three tracks parallel process' could potentially affect the speed at which patients gain access to MM treatments.

Table 2: Healthcare spending relative to GDP (US dollars)

	JAPAN	SOUTH KOREA	AUSTRALIA
GDP per capita ($)	33,806	33,192	65,434
Health spending per capita ($)	4,347	3,260	7,055
Health spending per capita (% of GDP per capita)	12.9	9.8	10.8

Source: IQVIA analysis

UNCERTAIN IMPACT OF POLICY CHANGE ON MM PATIENTS' FINANCIAL BURDEN

In 2014, the MOHW introduced policy changes to improve access of non-reimbursed costly novel treatments, by introducing a selective reimbursement scheme.[63] Evaluation drugs for inclusion in this scheme are based on clinical usefulness, cost-effectiveness and social demand for reimbursement of the drugs.[64] However, it remains uncertain whether this policy is applicable to MM treatments, as there have been no guidelines or details published regarding the evaluation of drugs based on the criteria mentioned nor treatments that qualify for selective reimbursement. By introducing copayment rates of 30% to 80%, the selective reimbursement scheme aimed to increase patient access to treatments that is clinically effective but has low cost-effectiveness. This policy has been reported to apply to treatments for cancer, cardiovascular disease, cerebrovascular disease, and rare diseases that are not included in the list of reimbursed drugs but are judged to be essential for the treatment of 'important' conditions that would otherwise go untreated. While the introduction of copayments was intended to facilitate patient access to crucial treatments and alleviate the financial burden of patients using non-reimbursed expensive novel treatments, there is a lack of clarity on which treatments meet the criteria, and it is unclear whether this scheme applies to MM treatments.[63]

OUTDATED ICER THRESHOLD AND LACK OF TRANSPARENCY SLOWS PATIENT ACCESS TO MM NOVEL TREATMENTS

An explicit incremental cost-effectiveness ratio (ICER) threshold value is not published in Korea, instead, the Health Insurance Review and Assessment agency (HIRA) relies on per-capita gross domestic product (GDP) in reimbursement decision making.[65] This ICER threshold was based on the per-capita GDP from 2007 and has not been updated even though the Korea GDP-per-capita has increased more than 60% as of 2022.[66,67] This low ICER threshold is thus outdated and insufficient to meet the demands of modern healthcare and economic growth.

Drugs that seek reimbursement for diseases with alternative treatment options undergo pharmacoeconomic evaluation with reference to a low and outdated ICER threshold. The difficulties posed by the low cost-effectiveness threshold for pharmaceutical companies and Korean patients were discussed during the 2020 National Assembly Audit. Nonetheless, HIRA eventually declined the National Assembly's request to reassess necessity of adjusting the threshold and, in September 2021 instead opted to rely on "past assessment results", which is likely to be at similar threshold. The continued use of inadequate ICER threshold with limited transparency and predictability of the threshold will limit patient access to novel MM treatments.[67]

When evaluating a new drug, HIRA considers factors such as disease severity, social burden, impact on patients' quality of life, and drug innovation to determine the flexible application of ICER thresholds. A new drug is deemed innovative if it meets all the following: (i) when there is no alternative or therapeutically equivalent treatment available, (ii) when the drug shows significant clinical improvement in outcomes such as life extension, and (iii) when it is recognized by HIRA's Drug Reimbursement Evaluation Committee as an innovative drug or approved through the expedited review process by MFDS.[68] However, there is no indication of the upper limit of the flexible ICER threshold and the criteria for significant clinical improvement remains unclear. Given that the ICER threshold is a critical factor in reimbursement decision-making in Korea,[66,69] this ambiguity poses a significant obstacle to access of groundbreaking medicines that could potentially benefit patients with MM.Additional pharmacoeconomic data required during reimbursement decision-making process

ADDITIONAL PHARMACOECONOMIC DATA REQUIRED DURING REIMBURSEMENT DECISION-MAKING PROCESS

In 2021, HIRA implemented a change in its approach to the evaluation of expensive oncological medicines. Specifically for costly new drugs, the Oncology drug advisory committee within HIRA has now mandated

the submission of pharmacoeconomic data, such as budget impact assessments.[63] This signifies a tightening of the review criteria along with broader considerations of financial implications associated with these treatments. While this adjustment reflects a more comprehensive economic evaluation of treatments, there is a concern that it could potentially lead to further restrictions in access to costly novel treatments, as budgetary considerations are increasingly factored in reimbursement decision-making, aside from clinical efficacy and other criteria.

TIME LAG IN APPROVAL AND REIMBURSEMENT OF NEW MM TREATMENTS

It has been reported that compared to other developed countries such as the United States and Japan, Korea experiences a significantly slower approval and reimbursement timeline for new treatments.[70] The wide disparity in accessibility of new treatments is apparent where 85% of all new medicines approved since 2012 have become available in the United States while only 33% are available in Korea.[70] Furthermore, 22% of these new medicines were reimbursed by National Health Insurance in Korea which is less than half the number reimbursed in Japan.[70] The number of reimbursed drugs for MM in Korea is also significantly lower than in the United States or Europe.[71]

Compared with its neighbour, the average wait time from regulatory approval to public reimbursement of drugs is approximately 18 months in Korea and only 3 months in Japan.[70] This time gap between approval and reimbursement is also noted for novel MM treatments in Korea. For instance, the daratumumab monotherapy for fourth-line MM treatment was approved in November 2017 but only received reimbursement in April 2019.[72,73] This stands in contrast to the faster reimbursement timelines observed in countries like Japan, where DVd was approved in 2017 and slated for inclusion in the National Health Insurance reimbursement price list within 60-90 days.[74,75] Therefore, this delay in approval and reimbursement of novel MM treatments in Korea emphasizes the need for closer examination and potential reforms to enhance timely access to innovative therapies in the Korean healthcare system.

PATIENT AND EXPERT VOICES UNDERREPRESENTED IN THE REIMBURSEMENT DECISION-MAKING PROCESS

The current reimbursement decision-making process lacks the inclusion of patient representation. Presently, Drug Evaluation Committee meetings involve up to 19 members, comprising representatives from HIRA and the Ministry of Food and Drug Safety (MFDS), pharmacists' and doctors' associations, health professionals, consumer groups, and experts recommended by the MOHW.[63] This demonstrates a lack of inclusion of patients' perspectives when evaluating the value and necessity of innovative treatments. The absence of direct involvement from patient advocacy groups raises concerns about the comprehensiveness of the decision-making process and the representation of those directly affected by the outcomes of these evaluations. Furthermore, the expertise of reviewers in the MFDS differs from that of hematologic experts, highlighting the need for evaluation by the appropriate specialists.

The reimbursement landscape for MM treatment in Korea is at a significant crossroad. Recent policy changes, such as the 'three tracks parallel process', indicate a positive shift towards improving patient access to innovative treatments. However, challenges such as decreased healthcare investment, lack of transparency on when ICER is considered for reimbursement decisions, and the exclusion of patient voices in decision-making persist. It is critical to address these gaps to ensure that MM patients in Korea have timely and equitable access to the latest and most effective treatments.

> *"Most people involved in the assessment for approval in MFDS were not the specialist doctors of the disease, but pharmacists. Although the Ministry of Food and Drug Safety recently hired reviewers who are clinicians these days, there are very few of them."*
>
> *— Hemato-oncologist 1*

Recommendations to improve access to novel multiple myeloma treatments

The accessibility of innovative breakthrough MM treatments in South Korea is at a critical juncture. Addressing issues related to government regulation, pricing and reimbursement policies, the ICER threshold, and the valuation of novel treatments are imperative to improve patient outcomes. We put forward the following recommendations to enhance the patients' access to effective MM treatments in Korea.

1 Increase healthcare investment in Korea along with investments in infrastructure

Compared with other developed countries, the current health spending relative to GDP in Korea indicates room for increased investment. In Japan, the health spending in 2020 was 11.5% of GDP whereas in Korea, it is only 11.3% of GDP.[76,77] Increased financial commitment is crucial to facilitate introduction and access to clinically meaningful novel MM treatments into the healthcare system. Enhanced funding would not only support the adoption of novel MM treatments but also contribute substantially to improved overall quality of life and decrease in productivity loss for MM patients once they have access to new MM treatments. With rising health insurance costs due to an aging population, there is a need for the government to increase healthcare investment and explore diverse financial sources and strategies to enhance healthcare access for Korean citizens.

In addition to increased healthcare investment, there is a need for investments in infrastructure to facilitate patient access to novel treatments once they are available, especially with the emergence of innovations such as cell and gene therapy. Advanced therapies such as CAR-T therapy for MM, require logistical considerations, healthcare provider training and adequate healthcare facilities. The establishment of infrastructure such as haematology wards and ICU beds is critical to facilitate delivery of advanced treatments to MM patients effectively.[78] It will be timely to have this infrastructure in place now for MM patients to have swift access to these novel treatments once approved and recommended in the localized treatment guidelines.

2 Accelerated patient access to breakthrough treatments through ‘three tracks parallel process’

As part of healthcare policy reform, the government introduced a ‘three tracks parallel process’ to streamline drug regulation, reimbursement assessment, and pricing. While it is currently uncertain whether MM treatments would meet the necessary criteria, future MM treatments demonstrating clear improvements in clinical efficacy over existing therapies could be channelled through the ‘three tracks parallel process’ to expedite novel treatment reimbursement. This streamlined approach ensures that patients can access innovative therapies as soon as possible, significantly impacting their survival and disease progression.

A projection conducted by IQVIA lends strong support to this initiative, indicating that reimbursement of anti-CD38 monoclonal antibody and its corresponding increased usage in first-line treatment for both transplant-eligible (Figure 8) and transplant-ineligible (Figure 9) MM patients could potentially prevent a total of 968 deaths and 2,434 disease progressions for MM patients in Korea from 2024 to 2028 (Figure 10). This aligns with the trend observed in the United States where there has been a 23% decrease in mortality rates for MM from 1995 to 2018 since the introduction of novel MM treatments. In particular, incremental decrease in mortality rates were observed with each subsequent approval of novel agents for MM treatment.79 The prioritization of MM novel treatment through ‘three tracks parallel process’ would align with the overarching goal of the healthcare policy reformation – to enhance patient outcomes by facilitating timely access to novel treatments.

Figure 8. Projected clinical outcomes for transplant-eligible MM patients with and without access to immunotherapy treatment

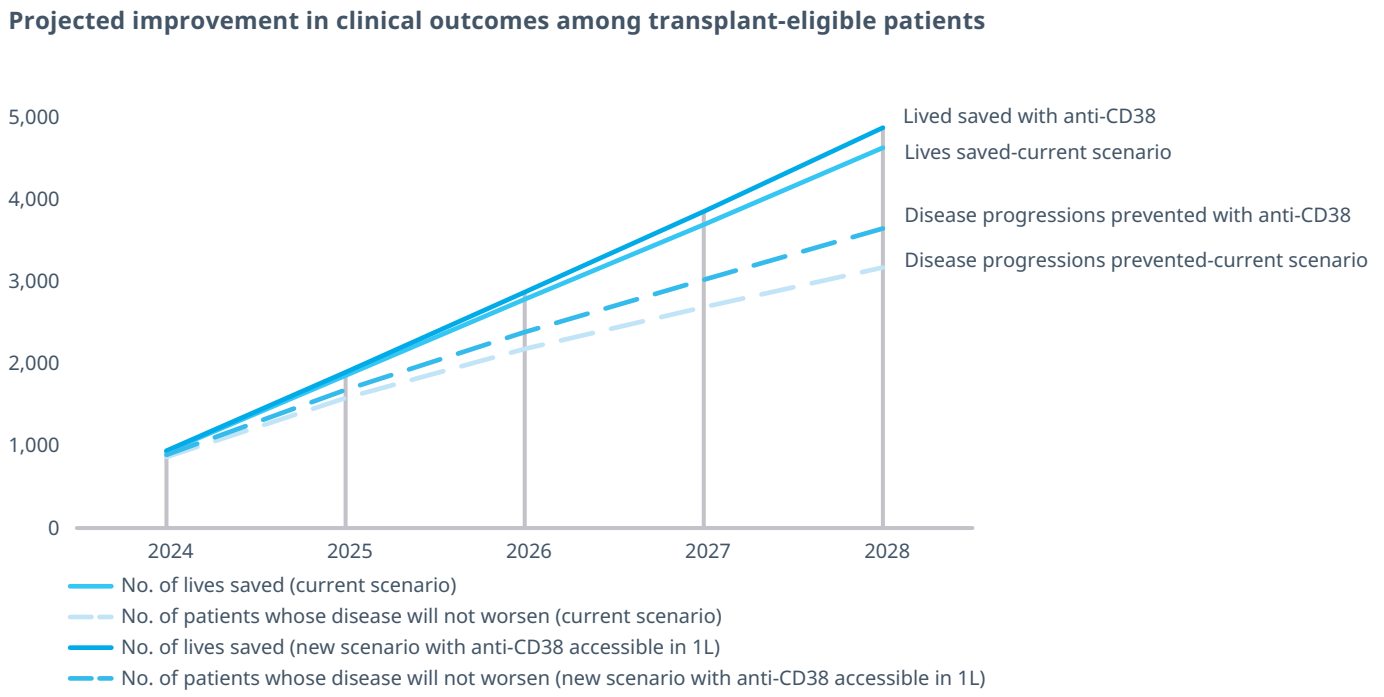


Figure 9. Projected clinical outcomes for transplant ineligible MM patients with and without access to immunotherapy treatment

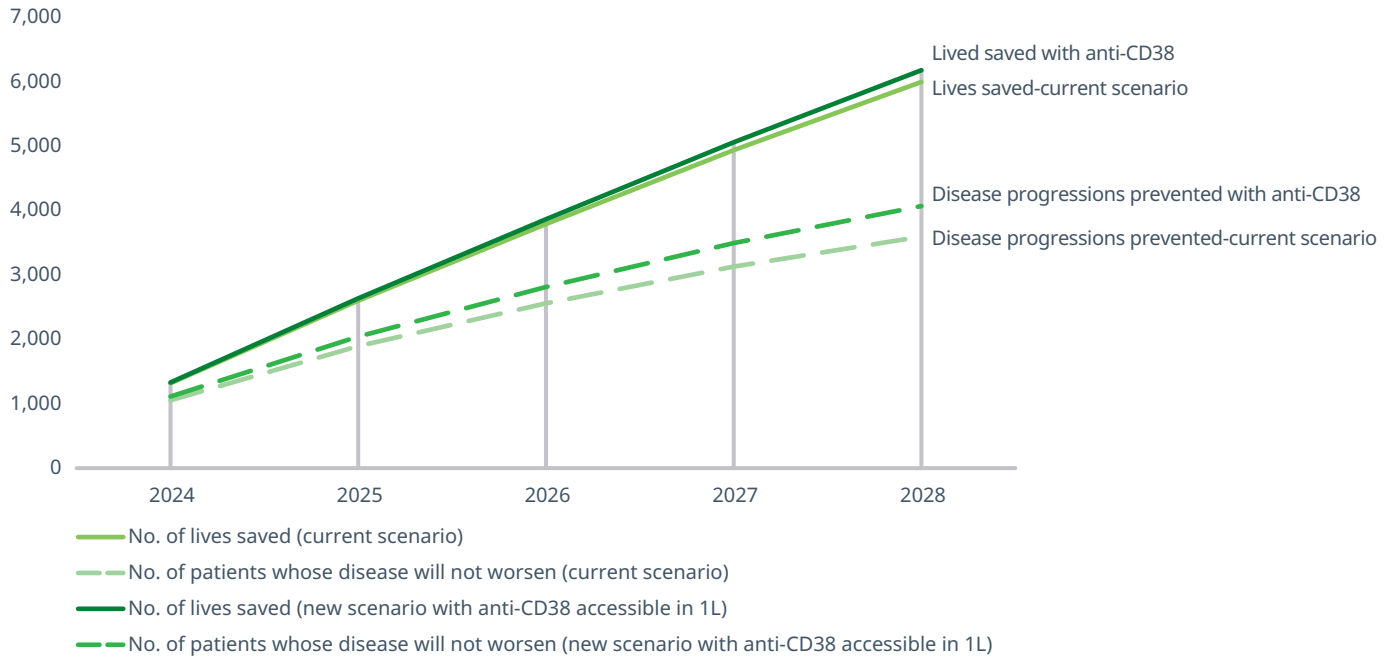


Figure 10. Anticipated improvements in treatment outcomes when MM patients have access to immunotherapy treatment in the first-line

Transplant eligible patients	Transplant ineligible patients
541 lives saved &	**427** lives saved &
1,135 patients' disease will not worsen	**1,299** patients' disease will not worsen

Cumulatively, from 2024-2028

The reimbursement of first-line immunotherapy for both transplant-eligible and transplant-ineligible MM patients in Korea can potentially prevent 968 deaths and 2,434 disease progressions among this patient population.

Source: IQVIA analysis

3 Provide greater clarity regarding reimbursement schemes and their relevance on MM

Although efforts are made to alleviate the financial burden of patients using non-reimbursed expensive treatments and facilitate access through the selective reimbursement scheme, there is currently no published guideline outlining the evaluation process nor defined criteria on drugs that qualify for this scheme. Consequently, a published guideline is essential to provide guidance on whether a treatment, especially costly MM drugs, can qualify for this scheme. This would enhance transparency and provide a structured approach for treatments to be included in the selective reimbursement scheme, thereby improving patient access to costly MM treatments.

"Applying flexible coinsurance rate instead of only 5% or 100% could enable more patients to be able to use the drug."

— Hematologist 4

4 Update ICER threshold to be aligned with current economic capacity

To ensure alignment with Korea's growing economic capacity, there is a pressing need to update the ICER threshold that is currently based on per-capita GDP from more than a decade ago. Furthermore, the unique nature and higher costs associated with oncology treatments, including those for MM, warrant a higher ICER threshold. Such an adjustment would allow for broader inclusion of costly cancer treatments, such as MM novel treatments, in reimbursement recommendations, leading to their inclusion in the positive list.

Although critical details still need to be elucidated to better understand the criteria considered for when a flexible ICER threshold is applied in evaluating new drugs, it is promising that HIRA has recently provided clarity in factors. Thus, it is anticipated that in the future a greater number of new drugs will be acknowledged for their innovative value, thereby improving patient access and outcomes. In addition to the flexible ICER threshold, raising the ICER threshold to be aligned with Korea's increased GDP holds the potential to significantly enhance MM patients' access to novel and potentially life-saving treatments, addressing the specific challenges posed by the high costs associated with cancer care.

5 Patient voices to be considered in decision-making

The current health technology assessment (HTA) mechanisms, through excluding patients' involvement in HTA process, fall short in fully recognizing the benefits of innovative treatments, such as improvements in patients' experience with reduction in patient burden, improvement in patient wellbeing and happiness. Countries such as Taiwan and Germany have also begun incorporating patient-reported experiences through involving patient representatives in HTA discussions.80–82 In Taiwan, patient advocacy groups are involved in several stages of the process, such as being members of expert committees, offering feedback, and consulting on draft recommendations. Online platform are used to allow patients, caregivers, and patient organizations to contribute information on various topics, including personal experiences with conditions and diseases; experiences with both traditional and new treatments; expectations for new treatments; effects on caregivers with and without new treatments; and other viewpoints.80 This is also a step towards incorporating patient experience and improvements in quality of life for reimbursement decision-making. By valuing insights and experiences from patients or patient advocacy groups, reimbursement evaluations can better capture the real-world impact of MM treatments. This patient-centric approach ensures that reimbursement decisions align with local MM patients' needs and preferences.

"Patients' opinions and their voices are as important as the opinions of the specialists in deciding whether to reimburse a drug."

— Hemato-oncologist 1

6 Develop MM treatment guidelines specific to local landscape

The establishment of comprehensive local MM treatment guidelines is crucial for ensuring standardized and effective care while enhancing patient access to suitable novel treatments. Japan has developed a guideline for the treatment and management of MM and this guideline cover diagnosis, treatment options, and follow-up care, and are based on the latest evidence and expert consensus.83 MM guidelines, founded on the latest clinical evidence and that are localized to Korean healthcare context, will serve as a fundamental resource for clinicians when making treatment recommendations, foster consistency in care delivery and ensure that MM patients have access to novel treatment options as they become available. The incorporation of the latest clinical evidence and alignment with the Korean healthcare context equips healthcare providers with a reliable reference, ultimately optimizing the overall quality of care and ensuring appropriate access to novel treatments for MM patients.

7 Patient voices to be considered in decision-making

While phase 3 trials provide rigorous evidence necessary for drug regulatory approval, it is recognized that patients in real-world practice are widely heterogenous and differ from trial populations. Approximately 40% of MM patients in real-world practice do not meet the criteria for inclusion in phase 3 studies, implying that existing clinical trial data may not be representative of a large proportion of real-world patients.84 Apart from the conventional definition of efficacy, treatment efficacy may not hold the same meaning to all patients. Other factors that affect a patient's quality of life, such as disease symptom control, treatment side effects and amount of supportive care needed may be considered pertinent to patients.

HIRA has established the Pharmaceutical Performance Evaluation Department responsible for post-launch evaluation of the performance and cost-effectiveness of high-priced drugs, including establishing and evaluating real-world evidence. To facilitate patient access, it would be advantageous for this department to integrate the assessment of real-world evidence into the new drug listing process in the foreseeable future.

To accurately assess the value of treatment to patients, it is necessary to identify and analyse all relevant real-world drivers that affect patients' experience of their MM treatment. The Korean Multiple Myeloma Working Party established a national database for MM — Korean Myeloma Registry — which serve as a valuable repository on real-world clinical outcomes such as response rates, PFS, adverse events, and quality of life.85,86 The comprehensive data available in this registry could be used to inform crucial aspects of healthcare, including treatment decisions, healthcare planning and budgeting and should therefore be shared and utilized during the reimbursement review process to the Pharmaceutical Performance Evaluation Department. This could potentially expedite the evaluation and positive reimbursement of treatments and in turn accelerate MM patients' access to novel treatments.

"Pharmaceutical companies should actively support research groups and societies."

— Hematologist 2

"Realistically, various companies are helping us, but we conduct a lot of research to make real-world evidence. Such things are conducted in organizations like MM research groups."

— Hematologist 3

8 Enhancing patient outcomes through support and education

The establishment of comprehensive local MM treatment guidelines is crucial for ensuring standardized and effective care while enhancing patient access to suitable novel treatments. Japan has developed a guideline for the treatment and management of MM and this guideline cover diagnosis, treatment options, and follow-up care, and are based on the latest evidence and expert consensus.83 MM guidelines, founded on the latest clinical evidence and that are localized to Korean healthcare context, will serve as a fundamental resource for clinicians when making treatment recommendations, foster consistency in care delivery and ensure that MM patients have access to novel treatment options as they become available. The incorporation of the latest clinical evidence and alignment with the Korean healthcare context equips healthcare providers with a reliable reference, ultimately optimizing the overall quality of care and ensuring appropriate access to novel treatments for MM patients.

Conclusion and call to action

Given the ageing demographics of the Korean patient population, the incidence of MM is set to continue increasing in the future. While the discovery of a cure for MM has yet to be achieved, patients have benefited from the creation of novel treatment classes over the past three decades that led to improvement in treatment outcomes. The availability of new treatments also allowed for a growing number of treatment combinations thus offering patients who no longer respond to earlier lines of therapy additional treatment options. Positive outcomes in future treatment will likely rely on identifying optimal combinations, sequencing and dose optimization of new agents.

We are currently at a critical juncture to improve outcomes of MM patients in Korea, with the emergence of novel treatments such as cell and gene therapy, along with ongoing healthcare policy reformations which aim to facilitate timely access to novel treatments. The crux remains to step up the current momentum in policy reforms and investments in healthcare infrastructure to ensure swift access to novel treatments once approved.

Methods

LITERATURE REVIEW

To gain understanding of the current and future burden of MM, treatment landscape, existing policies and framework relevant to MM, a literature review of peer-reviewed publications, grey literature, including government reports, news articles and policy statements, and white papers was conducted. Additionally, we looked into the unmet needs faced by patients, barriers to access of novel treatment options, government initiatives aimed at facilitating access to advanced treatment options.

METHODOLOGY FOR PROJECTING DEATHS AND DISEASE PROGRESSIONS PREVENTED WHEN PATIENTS HAVE ACCESS TO ANTI-CD38 MONOCLONAL ANTIBODIES IN FIRST-LINE

We compared projected clinical outcomes (i.e., OS and PFS) among both transplant-eligible and transplant-ineligible patients over a 5-year horizon for (a) base case scenario which is the current situation, against (b) new scenario in which anti-CD38 containing regimens were more accessible in first-line. The objective was to determine how many patients would benefit with increased accessibility to anti-CD38 treatment regimens in the first-line.

Our projection included the following assumptions (i) MM patients joined the patient cohort at the start of each year, (ii) MM patients who joined the patient cohort in previous years would proceed to the next line of treatment in the subsequent year and would not remain on first-line treatment, (iii) all newly diagnosed MM patients would require treatment.

PATIENT POPULATION

The estimated population of MM patients in South Korea was derived based on the population in 2024 and projected growth in South Korea over the next four years. The incidence rate of MM in adults was estimated based on relevant published data, and expert opinions sought to determine the proportion of transplant-eligible and transplant-ineligible MM patients. The values and sources of the input parameters used are provided in Appendix table 1.

Appendix table 1. Population of MM patients in South Korea

PARAMETER	VALUE	SOURCE
Starting population size (Year 2024)	51,751,065	Reference 8
Population growth per year	- 0.14%	Reference 8
Average annual percent change incidence rate 2011-2021	6.0%	References 9-20
Crude incidence rate of MM per 100,000		
Year 1	4.6%	Projected
Year 2	4.9%	Projected
Year 3	5.2%	Projected
Year 4	5.5%	Projected
Year 5	5.9%	Projected
Transplant-eligible patients	40%	Expert opinion
Transplant-ineligible patients	60%	Expert opinion

CURRENT MM TREATMENT LANDSCAPE FOR TRANSPLANT-ELIGIBLE AND TRANSPLANT-INELIGIBLE PATIENTS

The MM treatment landscape in South Korea was derived by reviewing published treatment guidelines and reimbursement guidelines for MM management. Based on the literature review findings, we designed a discussion guide that was used to conduct a series of interviews with local clinical experts on MM management (described below). The information obtained from these interviews provided insights into the local MM treatment landscape. Estimated proportions of patients treated with respective treatment regimens for transplant-eligible and transplant-ineligible patients were obtained from these interviews. The mean estimated proportion of patients treated with respective treatment regimens were included in our projection model.

USAGE OF ANTI-CD38 TREATMENT REGIMENS IF REIMBURSED IN 1L AND MARKET EFFECT

Based on expert interviews, Appendix tables 2 and 3 shows the estimated distribution of treatment regimens used presently and if anti-CD38 antibodies were more accessible in the first-line for transplant-eligible and transplant-ineligible patients. We assumed that no other treatment options will be introduced in the 5 year-horizon in the current scenario thus proportions of patients treated with various MM treatment regimens would remain stable over the next 5 years. In the new scenario when anti-CD38 antibodies are more accessible in the first-line, we forecasted a constant uptake from base year (2024) to the 5th year (2028), based on inputs of local clinical experts.

Appendix table 2. Estimated proportion of transplant-eligible patients treated in 1L with respective treatment regimens currently and if anti-CD38 regimens were accessible

TREATMENT REGIMENS USED IN 1L FOR TRANSPLANT-ELIGIBLE PATIENTS	CURRENT SCENARIO	SCENARIO WITH ANTI-CD38 REGIMENS ACCESSIBLE IN 1L	SOURCE
	YEAR 1 TO YEAR 5	YEAR 1 TO YEAR 5	
DVTd	18%	60%	Expert opinions
VTd	0%	0%	
VRd	82%	40%	

Appendix table 3. Estimated proportion of transplant-ineligible patients treated in 1L with respective treatment regimens currently and if anti-CD38 regimens were accessible

TREATMENT REGIMENS USED IN 1L FOR TRANSPLANT-INELIGIBLE PATIENTS	CURRENT SCENARIO	SCENARIO WITH ANTI-CD38 REGIMENS ACCESSIBLE IN 1L	SOURCE
	YEAR 1 TO YEAR 5	YEAR 1 TO YEAR 5	
VRd	78%	20%	Expert opinions
Rd	15%	8%	
VMP	2%	0%	
DVMP	2%	3%	
DRd	3%	69%	

CLINICAL OUTCOMES OF NEWLY-DIAGNOSED MM PATIENTS WITH RESPECTIVE TREATMENT REGIMENS

Overall survival and PFS data from various publications were used to estimate the number of patients who will benefit from the use of anti-CD38 treatment regimens in first-line. The clinical outcomes data used in the projection are summarized in Appendix Tables 4, 5, 6 and 7.

Appendix table 4. Overall survival outcome – transplant-eligible patients

TREATMENT	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	HAZARD RATIO	SOURCE
DVTd	98.57%	96.94%	94.67%	91.56%	91.56%	DVTd vs VTd: 0.54	Reference 41
VTd	97.84%	93.79%	90.05%	84.53%	82.58%		
VRd	95.46%	90.46%	83.80%	75.24%	75.24%	DVTd vs VRd: 0.31	Reference 88

Appendix table 5. Overall survival outcome – transplant-ineligible patients

TREATMENT	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	HAZARD RATIO	SOURCE
VRd	94.61%	88.01%	84.05%	75.81%	68.60%	VRd vs Rd: 0.77	Reference 35
Rd	93.90%	84.96%	75.10%	65.14%	56.10%		
VMP	96.72%	91.72%	85.92%	79.68%	73.61%	VMP vs Rd: 1.30	Reference 44
DVMP	98.02%	94.95%	91.30%	87.26%	83.21%	DVMP vs Rd: 0.78	Reference 44
DRd	95.93%	89.80%	82.78%	75.36%	68.28%	DRd vs Rd: 0.68	Reference 44

Appendix table 6. PFS outcome – transplant-eligible patients

TREATMENT	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	HAZARD RATIO	SOURCE
DVTd	95.94%	88.38%	79.32%	68.75%	60.87%	DVTd vs VTd: 0.58	Reference 41
VTd	93.64%	78.54%	64.08%	53.35%	47.53%		
VRd	91.56%	76.89%	61.08%	45.06%	34.78%	DVTd vs VRd: 0.47	Reference 87

Appendix table 7. PFS outcome – transplant-ineligible patients

TREATMENT	YEAR 1	YEAR 2	YEAR 3	YEAR 4	YEAR 5	HAZARD RATIO	SOURCE
VRd	78.99%	63.64%	54.00%	45.26%	37.21%	VRd vs Rd: 0.74	Reference 35
Rd	74.55%	56.44%	43.85%	35.30%	26.46%		
VMP	78.60%	62.56%	50.86%	42.58%	33.61%	VMP vs Rd: 0.82	Reference 88
DVMP	90.38%	82.12%	75.28%	69.86%	63.26%	DVMP vs VMP: 0.42	Reference 45
DRd	85.08%	73.01%	63.55%	56.40%	48.13%	DRd vs Rd: 0.55	Reference 89

EXPERT INTERVIEWS

Insights from the literature review were validated through virtual semi-structured interviews (~60 minutes) conducted with Professors of hematology or hemato-oncology. 4 interviews with hemato-oncologists and hematologists were conducted from May to June 2024. Discussion guide used for interview were developed surrounding key themes — current treatment landscape and frequently used treatment options, current unmet needs in managing MM, perspective of novel treatment options for MM if reimbursed in first line, recommendations to improve access to novel MM treatments – to fill any gaps in knowledge from the literature review. Experts' consent was requested at the start of the interview for their participation, as well as for their permission for the interview to be recorded.

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