Review

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From Toxicity to Immunity: Evaluating CAR-T and Conventional Therapies in Multiple Myeloma Through QALY Outcomes

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Review

From Toxicity to Immunity: Evaluating CAR-T and Conventional Therapies in Multiple Myeloma Through QALY Outcomes

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Abstract

Background: Over the past century, numerous pharmacological regimens have been developed for multiple myeloma (MM), yet relapse remains inevitable. Although these regimens prolong overall survival (OS), repetitive treatment cycles and cumulative toxicity progressively impair quality of life (QoL). This study aimed to compare conventional stepwise therapies with CAR-T cell therapy in terms of QoL, toxicity, cost, and ethical value. **Methods:** Kaplan-Meier survival curves were analyzed to estimate overall (OS) and progression-free survival (PFS). Based on these durations, treatment costs were calculated. A simple and transparent utility-based model was developed to enable clinicians, researchers, and health policy authorities to easily estimate quality-adjusted life years (QALY) and incremental cost-effectiveness ratios (ICER). **Results:** Among heavily pretreated patients, CAR-T therapy approximately doubled OS and PFS compared with other late-line regimens and provided markedly better quality of life with lower overall treatment burden. While daratumumab-based combinations improved survival and patient well-being, they were associated with very high treatment costs (~USD 1 million per patient). Carfilzomib-based regimens remained essential for managing high-risk disease despite their expense. In contrast, VMP represented a practical and accessible option, especially for transplant-ineligible or resource-limited patients. **Conclusion:** CAR-T therapy provided significant improvements in survival and quality of life compared with conventional regimens among patients who had received three or more prior lines of therapy. Its earlier use appears promising. However, the limited availability of CAR-T across only a few countries raises ethical concerns regarding treatment accessibility. Contrary to common assumptions, CAR-T can be less expensive than many traditional therapies, though its single-payment structure poses barriers for patients with limited financial means. Further analyses are needed to refine toxicity management and optimize its broader clinical application in multiple myeloma.

Keywords: multiple myeloma; CAR-T cell therapy; drug toxicity; quality-adjusted life years (QALY); cost-effectiveness; eastern cooperative oncology group (ECOG) performance status; Value-based medicine

Dedication

This work is dedicated to all patients and families living with multiple myeloma, whose resilience continues to inspire. Our goal is not only to advance science, but to restore dignity, equity, and hope in treatment. May these findings serve as a reminder that true progress is measured not solely in survival curves, but in the quality of lives preserved.

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1. Introduction

Multiple myeloma (MM) is a multisystemic malignancy characterized by the uncontrolled proliferation of plasma cells in the bone marrow, leading to disruption of bone, renal, and immune integrity. The monoclonal immunoglobulins produced by neoplastic plasma cells correlate with disease severity and alter the hematopoietic balance by disturbing the bone marrow microenvironment. Clinically, the disease defined by anemia, hypercalcemia, bone lesions, and renal impairment (CRAB criteria), presents with variable progression and therapeutic response due to its heterogeneous nature [1].

Over the past two decades, therapeutic strategies have evolved from conventional chemotherapy to proteasome inhibitors, immunomodulatory agents, monoclonal antibodies, and most recently, CAR-T cell therapies [2,3]. These advances have markedly extended survival, yet introduced new dimensions requiring assessment toxicity, quality of life, and cost. Today, therapeutic success is measured not only by survival outcomes but also by quality-of-life indicators, cost-effectiveness, and equitable access [4].

Despite numerous pharmacologic and technical interventions developed over the past two centuries, myeloma continues to relapse and develop resistance to therapy [5,6]. In recent years, CAR-T cell therapy has introduced a paradigm shift by re-engineering the patient's immune system to target malignant plasma cells. Although applied in advanced disease stages, CAR-T therapy has demonstrated significant improvements in overall survival (OS) and progression-free survival (PFS), stimulating trials that explore its potential in earlier treatment lines. Current research focuses on minimizing toxicity, shortening manufacturing time, and enhancing antigen-targeting capacity [7–13]. This study provides a comprehensive overview of the clinical, economic, and ethical dimensions of conventional and CAR-T therapies. It also introduces a simple pharmacoeconomic model based on ECOG performance scores, designed to allow clinicians, non-economist researchers, policymakers, and health authorities to easily evaluate cumulative toxicity across treatment lines. This approach serves not only as a numerical tool for cost-effectiveness but also as a patient-centered, ethically grounded, and translational framework for evaluating therapeutic value.

2. Myeloma Therapies

The treatment of multiple myeloma has undergone a long evolution, progressing from the rudimentary practices of the 1800s such as rhubarb, opium, and corset applications to today's sophisticated therapeutic approaches. Over time, the introduction of corticosteroids, alkylating agents, proteasome inhibitors (PIs), immunomodulatory drugs (IMiDs), and monoclonal antibodies (mAbs) has profoundly reshaped the therapeutic paradigm. In recent years, this transformation has accelerated with the advent of bispecific antibodies, antibody-drug conjugates (ADCs), and particularly, CAR-T cell therapies [3,14].

Contemporary myeloma therapy is individualized according to disease stage, cytogenetic risk profile, performance status, and comorbidities. Patients are typically stratified by transplant eligibility. In eligible candidates, high-dose melphalan followed by autologous stem cell transplantation (ASCT) remains the gold standard. Eligibility is determined not by chronological age but by biological fitness, performance status, and organ function. Patients with adequate cardiac, renal, hepatic, and pulmonary reserve (ECOG ≤2) are considered suitable for transplantation, whereas frail or organ-compromised individuals are treated with more tolerable regimens aimed at long-term disease control [15].

Standard therapeutic steps can be summarized as follows:

(1) Induction therapy: Combinations of proteasome inhibitors (bortezomib, carfilzomib), IMiDs (lenalidomide, thalidomide, pomalidomide), and dexamethasone. The addition of monoclonal antibodies such as daratumumab has enhanced efficacy.

(2)Transplantation: In eligible patients, ASCT achieves durable remission.

(3) Maintenance therapy: Typically involves lenalidomide to sustain disease suppression.

 doi:10.20944/preprints202509.2132.v2

(4) Relapsed/refractory stage: At this phase, next-generation PIs, IMiDs, monoclonal and bispecific antibodies, ADCs, and CAR-T cell therapies are employed [16] **(see Figure 1).**

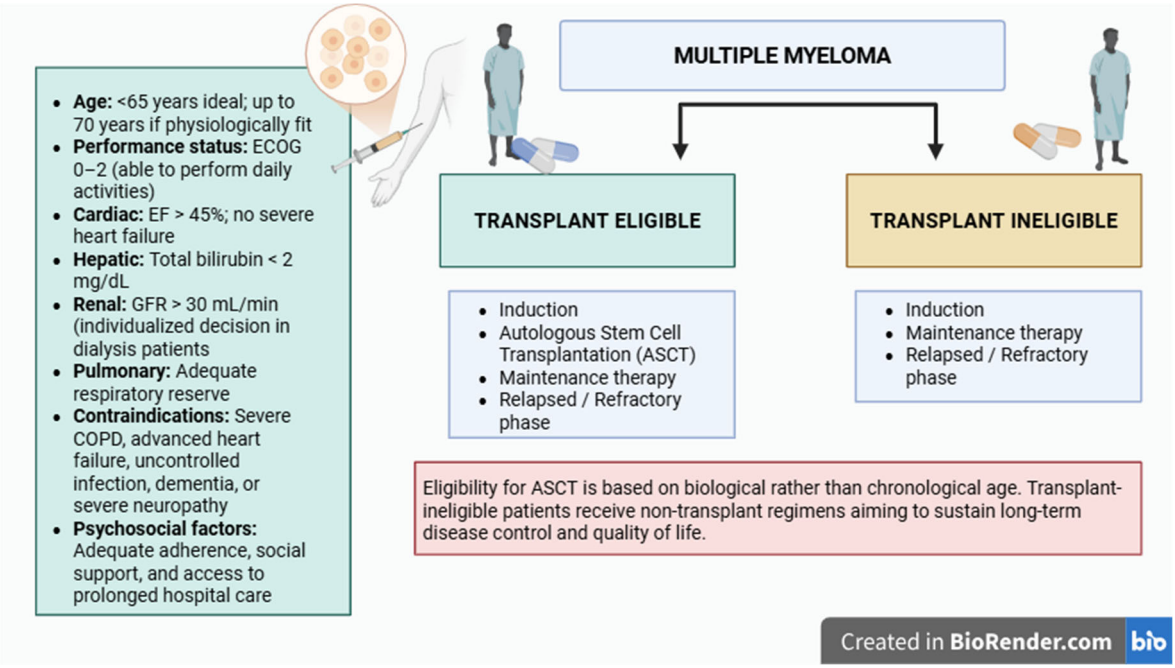

Figure 1. Simplified treatment algorithm for multiple myeloma according to transplant eligibility. Eligibility for ASCT is based on biological rather than chronological age. Transplant-ineligible patients receive non-transplant regimens aiming to sustain long-term disease control and quality of life (Created with BioRender.com).

2.1. Induction Therapies

Induction therapy represents the first step in the management of multiple myeloma. Its primary goals are to reduce tumor burden, achieve deep remission, and prepare eligible patients for autologous stem cell transplantation (ASCT) [2,3].

Currently, the VRd regimen (bortezomib, lenalidomide, dexamethasone) is regarded as the gold standard for transplant-eligible patients in both Europe and the United States, achieving high response rates (≥VGPR above 70%) and prolonged progression-free survival (PFS) [17]. The KRd regimen (carfilzomib, lenalidomide, dexamethasone) offers deeper responses in patients with high-risk cytogenetic profiles [18].

The addition of CD38-targeted monoclonal antibodies has further enhanced induction efficacy. In the GRIFFIN trial, Dara-VRd significantly improved minimal residual disease (MRD) negativity and response depth compared with conventional VRd [19]. Similarly, Dara-KRd has shown promising results in high-risk patients [20].

For transplant-ineligible, elderly, or highly comorbid patients, more tolerable regimens such as D-Rd (daratumumab, lenalidomide, dexamethasone) and VRd-lite are preferred [21]. The D-VMP regimen (daratumumab, bortezomib, melphalan, prednisone) became the standard of care in this population following the ALCYONE trial, in which daratumumab addition significantly improved PFS and OS [17,22]. The Rd regimen (lenalidomide, dexamethasone) remains the mainstay for frail or very elderly patients [23,24].

Common adverse events include peripheral neuropathy related to bortezomib, cardiotoxicity associated with carfilzomib, and hematologic toxicity from lenalidomide. In contrast, daratumumab is generally well tolerated, with only mild infusion-related reactions such as fever, chills, or nasal congestion [25]. The incorporation of anti-CD38 antibodies enhances treatment depth without increasing toxicity, markedly improving MRD negativity rates and extending PFS **(see Table 1 and Appendix Table A1).**

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Table 1. Current Induction Regimens and Their Main Adverse Effects.

Regimen	Patient Group	Main Advantages	Main Toxicities
VRd	Transplant-eligible or ineligible (standard-risk)	High response rate, prolonged PFS	Peripheral neuropathy, hematologic toxicity
D-VRd	Transplant-eligible	Increased MRD negativity, well tolerated	Infusion reactions, hematologic toxicity
KRd	Younger, fit, high-risk cytogenetics	Deeper response, increased MRD negativity	Cardiotoxicity, hypertension
D-KRd	Transplant-eligible, high-risk	Deep and durable MRD negativity	Cardiac and hematologic toxicity
D-VMP	Transplant-ineligible, elderly	OS benefit, effective in elderly	Hematologic toxicity, infections
D-Rd	Transplant-ineligible, frail or elderly	Long OS, oral administration convenience	Immunosuppression, hematologic toxicity
Rd	Frail or relapsed patients	Oral administration, convenience	Myelosuppression, fatigue
VRd-Lite	Elderly, frail, or comorbid	Better tolerability	Potential lower efficacy

V: Velcade(Bortezomib), R: Revlimid(Lenalidomide), D:Darzalex(Daratumumab), K:Kyprolis(Carfilzomib), M:Melphalan, P: Prednisone, d: Dexamethasone. MRD: Minimal Residual Disease. OS=Overall Survival, PFS: Progression Free Survival.

2.2. Autologous Stem Cell Transplantation

Autologous stem cell transplantation (ASCT) is a therapeutic procedure in which the patient's own hematopoietic stem cells are reinfused following high-dose melphalan conditioning. For many years, ASCT has been regarded as the standard of care for transplant-eligible patients with multiple myeloma. The process includes several key steps: clinical preparation; stem-cell mobilization using cyclophosphamide and granulocyte colony-stimulating factor (G-CSF, e.g., filgrastim); $CD34^+$ cell collection by apheresis; cryopreservation of the harvested cells in 10% dimethyl sulfoxide (DMSO); high-dose melphalan conditioning chemotherapy; and subsequent reinfusion of the stem cells. Once reinfused, the stem cells home to the bone-marrow microenvironment, initiate proliferation, and restore hematopoietic and immune functions within approximately 2-4 weeks [26] (see Figure 2).

When combined with modern induction regimens such as VRd or Dara-VRd, ASCT further reduces tumor burden, deepens response, and significantly prolongs progression-free survival (PFS) [27,28]. However, the procedure is associated with substantial biological stress and transient toxicities. During mobilization and conditioning, increases in cytokines, oxidative stress, and mucosal injury are commonly observed [29,30].

Administration of G-CSF can trigger transient inflammatory responses; some studies have reported p53-mediated DNA damage and reduced engraftment efficiency [31,32]. Melphalan induces DNA damage and apoptosis in rapidly dividing cells, contributing to mucositis, pancytopenia, and infection risk, and has also been linked to long-term bone fragility and secondary malignancies [33–35]. DMSO, used during cryopreservation, may cause transient cardiovascular or gastrointestinal side effects during reinfusion [36].

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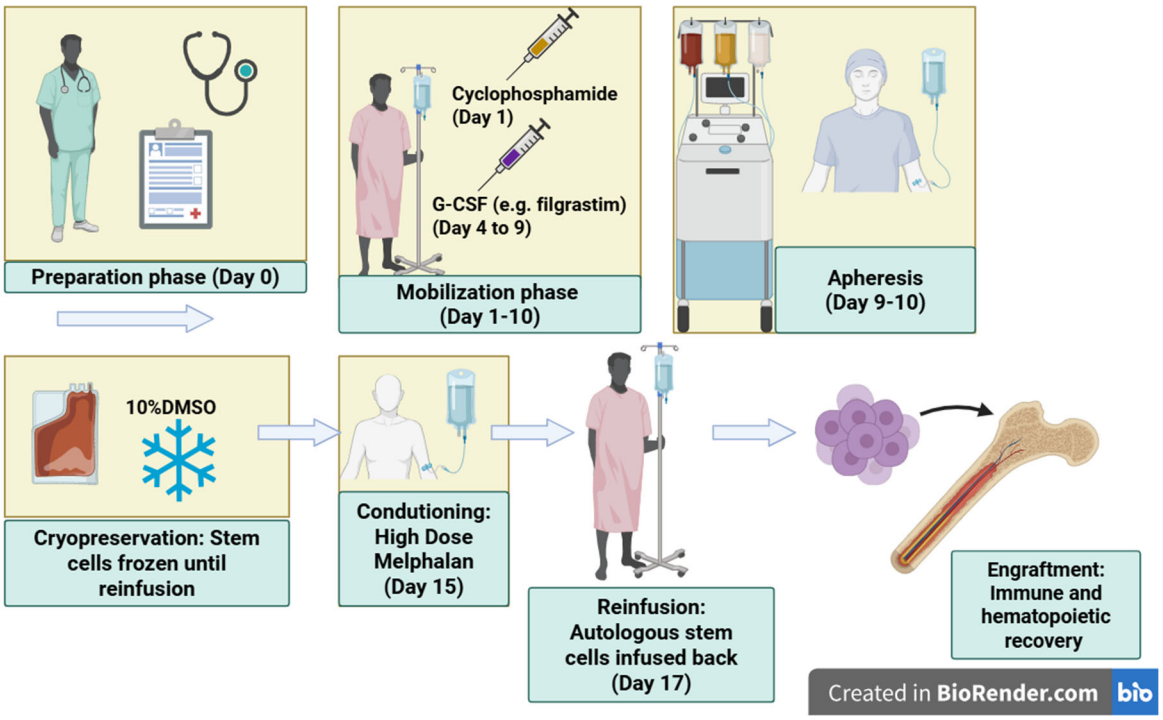

Figure 2. Schematic representation of the autologous stem cell transplantation (ASCT) process. The procedure comprises sequential stages: patient preparation, hematopoietic stem cell mobilization using cyclophosphamide (Day 1) and granulocyte colony-stimulating factor (G-CSF, Days 4-9), peripheral stem cell collection through apheresis (Days 9-10), and cryopreservation of harvested stem cells in 10% DMSO. Following a resting interval, high-dose melphalan conditioning (Day 15) eradicates residual myeloma cells and prepares the bone marrow niche for reinfusion. Autologous $CD34^+$ cells are then reinfused (Day 17). After transplantation, the patient is monitored in a protective environment to prevent infection during the neutropenic phase. Engraftment occurs as reinfused stem cells home to the marrow, proliferate, and reconstitute hematopoiesis and immune function within approximately 2-4 weeks (Created with BioRender.com).

Patients are closely monitored for infections during neutropenic and immunosuppressive phases, with appropriate supportive therapy provided. Despite these challenges, long-term survival outcomes following ASCT remain remarkable. Transplantation enhances the depth of hematologic remission and nearly doubles median overall survival [17,22,23,37].

Although transplantation-related toxicities may create clinical uncertainty [38] and novel agents are showing increasing efficacy in transplant-ineligible populations [17,23]. ASCT continues to offer unmatched benefits in survival, quality of life, and durable disease control when applied to appropriately selected patients.

2.3. Maintenance Therapies

The primary goal of maintenance therapy is to sustain remission achieved after first-line treatment or transplantation and to suppress residual malignant plasma cells. Currently, lenalidomide remains the standard maintenance agent, while bortezomib or monoclonal antibodies such as daratumumab represent effective options for high-risk patients [39].

Despite prolonged maintenance, the emergence of drug-resistant clones and an immunosuppressive bone marrow microenvironment often set the stage for inevitable relapse [5,6].

Upon relapse, treatment selection depends on the patient's overall condition, comorbidities, cytogenetic risk profile, and prior treatment response. In the relapsed/refractory (R/R) setting, second-line regimens are typically employed, which may involve introducing a new drug class or modifying the existing protocol [2].

 doi:10.20944/preprints202509.2132.v2

However, with successive relapses, therapeutic efficacy diminishes due to clonal evolution, cumulative toxicity, and emerging resistance mechanisms. At this stage, less effective agents are discontinued or replaced with alternatives, while each subsequent line of therapy becomes progressively more complex and less tolerable [40,41].

2.4. Relapsed/Refractory Phase

In the relapsed/refractory (R/R) phase, proteasome inhibitors (bortezomib, carfilzomib, ixazomib), immunomodulatory agents (lenalidomide, pomalidomide), CD38 monoclonal antibodies (daratumumab, isatuximab), SLAMF7-targeted antibodies (elotuzumab), and newer modalities such as bispecific antibodies and antibody-drug conjugates (ADCs) are used sequentially [2].

Each treatment line provides temporary disease control, yet relapse remains almost inevitable. This resistance process is linked to (1) the persistence of refractory clones, (2) the immunosuppressive myeloma microenvironment, and (3) the survival of stem-like cell populations [5,42,43]. Over time, clonal evolution, cumulative toxicity, and declining organ reserve progressively reduce therapeutic efficacy. Ineffective agents are therefore discontinued or replaced with drugs of different classes. Minimal residual disease (MRD) positivity and high-risk cytogenetic profiles are key indicators for early treatment modification [44,45].

Prolonged therapy imposes biological, psychological, and economic burdens on patients [46]. Exhaustion of hematopoietic reserve leads to progenitor suppression and pancytopenia [47]. Immunomodulatory and antibody-based therapies suppress T/NK-cell function, increasing the risk of hypogammaglobulinemia and opportunistic infections [48,49]. Moreover, microenvironmental disruption reduces stromal support, enhances osteoclast activity, and weakens the hematopoietic niche. Consequently, each new line of therapy not only reduces tumor burden but also erodes biological resilience, immune defense, and overall quality of life [26,50].

Advanced treatment lines impose substantial toxicity not only on the hematopoietic system but also on the liver, kidneys, and central nervous system. Hepatic enzyme induction, impaired renal elimination, and neuro-inflammatory changes further compromise treatment tolerance and drug metabolism. This multi-organ load is one of the major factors limiting the clinical benefit of combination regimens in late-line therapy [51–53].The resulting cycle of cumulative exhaustion progressively diminishes efficacy and renders the patient increasingly fragile (**see Figure 3**).

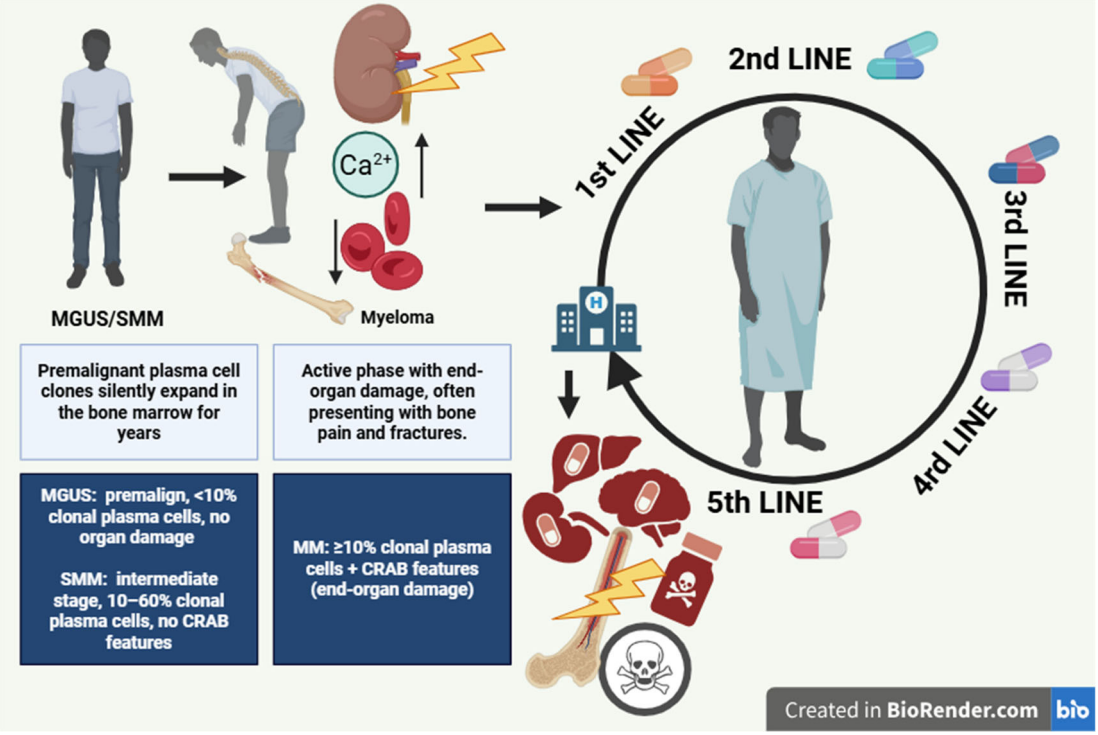

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Figure 3. Schematic representation of disease progression from premalignant stages (MGUS, SMM) to active multiple myeloma, and the cumulative impact of sequential therapy lines. Each treatment line contributes to cumulative toxicity, bone marrow damage, and declining patient tolerance, ultimately leading to poor outcomes (Created with BioRender.com).

Although multiple myeloma does not progress as aggressively as acute leukemias, its chronic and relentless nature gradually exhausts patients biologically, psychologically, and economically. Since the 19th century, therapeutic advances have dramatically extended survival, allowing many patients today to live five years or longer after diagnosis. Yet this progress comes at a cost: with each subsequent line of therapy, progression-free survival (PFS) shortens, cumulative toxicity increases, and survival curves narrow.

By occupying the bone marrow niche, myeloma not only disrupts hematopoiesis but also destabilizes systemic homeostasis. Anemia, immune deficiency, bone destruction, and organ dysfunction often reduce quality of life more than they contribute directly to mortality [46,54].

In this study, we comprehensively evaluated the clinical and economic impact of multiple myeloma treatment regimens by comparing estimated costs and mean overall survival (OS) values derived from published Kaplan-Meier curves. To quantitatively assess quality of life, quality-adjusted life years (QALYs) were calculated. These QALY values were not extracted directly from prior literature but were instead modeled using ECOG performance scores and survival data, in accordance with the study's central hypothesis **(see Table 2, Supplementary Table S1, Supplementary Table S2 and see section ''4.Quality-Adjusted Life Year (QALY) and ECOG-Based Modeling'')**.

This approach allows comparison of treatment regimens not only in terms of clinical efficacy, but also through the lens of cost-effectiveness and ethical sustainability (see Supplementary Material for details). However, model-based QALY estimates presented here should not be directly compared with classical QALY values derived from prospective patient surveys. Although absolute QALY values are lower, the model provides internally consistent and reliable comparative insights across regimens **(see Methods and Supplementary Methods).**

Table 2. Estimated costs, mean overall survival (OS), and model-derived QALY values for major myeloma therapy regimens used in clinical practice.

Therapy	Setting/Lines	Mean OS*a	Mean PFS*a	Cost*b USD	QALY*c
Rd [23]	First Line/Frail	57 months	40 months	995,924 USD	3.6195
D-Rd [23]	First Line/TIE	70 months	54.1 months	1,924,803 USD	4.434
D-VRd [37,55]	First Line/TE	159.12 months	83.75 months	2,184,110 USD	9.9874
VRd [37,55]	First Line/TE	128.9 months	37.98 months	508,940 USD	7.145
KRd [56]	2-5th Line	56.9 months	23 months	795,518 USD	2.608
D-VMP [17,22]	First Line/TIE	87 months	66.7 months	766,416 USD	4.9778
VMP [17,22]	First Line/TIE	68 months	42.4 months	72,731 USD	3.0866
PVd [57]	2-4th+ Lines	43 months	24 months	633,028 USD	*d 0.7478
Vd [57]	2-4th+ Lines	38 months	18 months	70,333 USD	*d 0.6727
D-Kd [58,59]	2-4th Lines	61 months	37 months	2,153,071 USD	2.103

 doi:10.20944/preprints202509.2132.v2

D-Vd [58–61]	2-4+Lines	66 months	56 months	611,243 USD	1.9338
D-Pd [58,59,62]	2-4th Lines	73 months	32 months	1,176,157 USD	2.4164
Kd [58,59]	2-4th Lines	55 months	20 months	935,796 USD	1.7618
Elo-Rd [63]	2-4th Lines	47.1 months	31 months	995,764 USD	0.9655
Elo-Pd [64]	3-5th+ Lines	34 months	22 months	835,752 USD	0.8139
Elo-PVd [65]	2-10th Lines	35 months	18 months	700,628 USD	0.875
Isa-Kd [58,66]	2-4th Lines	54 months	34 months	1,700,907 USD	2.511
Isa-Pd [67]	3+ Lines	38 months	23.3 months	907,989 USD	0.95
CAR-T Legend-2 [68,69]	4+ Lines	54 months+	30 months	640,000 USD	1.7433
CARTITUDE-1 [69,70]	4+ Lines	85 months+	43.85 months	640,000 USD	2.7384
X-Vd [71]	2-4th Lines	34.98 months	18.5	839,679 USD	1.575

*a: Mean OS values were calculated by digitalizing Kaplan–Meier survival curves and estimating the area under the survival percentage curve. Values represent fully observed cohorts only; extrapolation for censored data was performed using a simple geometric projection model. *b Cost estimation reflects total drug acquisition and administration expenses up to treatment discontinuation, based on list prices obtained from Drugs.com. Supportive care and concomitant therapy costs were included within the same time horizon. *c QALY values were derived from mean OS and ECOG-based utility adjustments within the hypothesis framework of this study (see Methods and Supplementary Material for details). d QALY could not be modeled due to insufficient follow-up data. V: Velcade(Bortezomib), R: Revlimid(Lenalidomide), D:Darzalex(Daratumumab), K:Kyprolis(Carfilzomib), M:Melphalan, P: Prednisone(VMP), d: Dexamethasone., P:Pomalyst (Pomalidomide), X:Xpovio (Selinexor), Elo:Empliciti(Elotuzumab), Isa:Sarclisa(Isatuximab). OS=Overall Survival. PFS: Progression Free Survival. USD: United States Dollar. QALY: The quality-adjusted life-year.

3. CAR-T Therapies

A major milestone in multiple myeloma therapy was the identification of B-cell maturation antigen (BCMA) as a therapeutic target. To date, two autologous CAR-T cell products targeting BCMA have received regulatory approval.

Idecabtagene vicleucel (ide-cel, Abecma) was approved by the FDA in April 2021 following the KarMMa trials and demonstrated remarkable efficacy in heavily pretreated patients (≥3 prior lines including PI, IMiD, and anti-CD38). In this population, the overall response rate (ORR) reached 76% versus 32% with standard of care; ≥VGPR was 58% versus 14%; one-year progression-free survival (PFS) was 55% versus 30%; and minimal residual disease (MRD) negativity was approximately 20%. The most frequently reported toxicities included neutropenia, leukopenia, and cytokine release syndrome (CRS), with grade ≥3 CRS observed in roughly 14% of patients [13,72].

Ciltacabtagene autoleucel (cilta-cel, Carvykti), a second-generation BCMA-directed CAR-T construct with dual-epitope binding capacity, received FDA approval in February 2022. According to 2025 analyses, the median overall survival (OS) is approximately 56 months and median PFS about 18 months, with an MRD-negativity rate of 68%. Reported toxicities include low-grade CRS, immune effector cell-associated neurotoxicity syndrome (ICANS), cytopenias, and infections [70,73]

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3.1. Treatment Process and Clinical Application

The CAR-T therapy process involves the collection of a patient's T lymphocytes by apheresis, their genetic modification ex vivo, expansion in culture, and reinfusion as a single intravenous dose. Before infusion, lymphodepleting chemotherapy (fludarabine + cyclophosphamide) is administered to facilitate in vivo CAR-T expansion, reduce immune suppression within the tumor microenvironment, and enhance persistence. Manufacturing typically requires 2-4 weeks and includes the following main steps [74] **(see Figure 4)**:

- Activation: stimulation using anti-CD3/CD28 microbeads and cytokines such as IL-2, IL-7, and IL-15.
- Genetic modification: transduction of the CAR construct, most commonly via lentiviral vectors.
- Expansion: large-scale proliferation in controlled culture systems to generate millions of CAR-T cells.
- Quality control and cryopreservation: verification of cell viability, microbial safety, and CAR expression, followed by freezing and storage until infusion.

The prepared cells are thawed and administered as a single intravenous infusion. The most common adverse events are cytokine release syndrome (CRS) and neurotoxicity, both of which require management in experienced centers with intensive-care support.

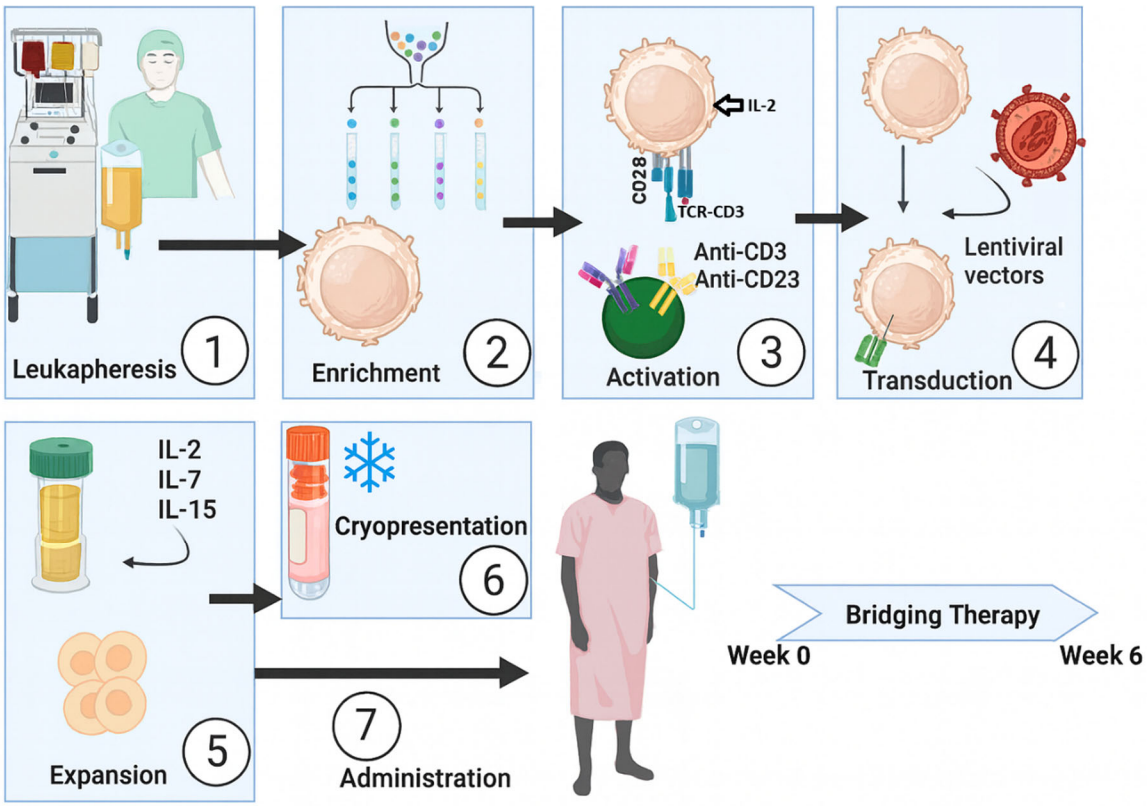

Figure 4. Schematic representation of the CAR-T cell manufacturing process. Autologous T cells are harvested from the patient via leukapheresis, then enriched and activated through CD3/CD28 co-stimulation with cytokine support (IL-2, IL-7, IL-15). The CAR construct is introduced using lentiviral vectors, followed by large-scale expansion, quality control, and cryopreservation. After bridging therapy and lymphodepleting chemotherapy, the engineered CAR-T cells are thawed and administered intravenously (Created with BioRender.com).

3.2. Clinical Efficacy, Innovations, and Limitations of CAR-T Cell Therapy

CAR-T cell therapy achieves high response rates (≥70%) and prolonged remissions in patients with relapsed/refractory multiple myeloma (RRMM). Clinical trials such as CARTITUDE-4 have

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demonstrated that CAR-T therapy can be used as early as the second line, aiming to improve both survival and quality of life with earlier intervention [12].

Its single-dose, potentially curative nature positions CAR-T as one of the most promising modalities in modern oncology. However, high cost, lengthy manufacturing, and the need for intensive toxicity management currently limit its widespread application. The comparative analysis in this study highlights that ciltacabtagene autoleucel (cilta-cel) offers unexpectedly favorable outcomes in terms of both economic sustainability and biological toxicity profile [74].

Cilta-cel's single-infusion design reduces cumulative toxicity associated with multiple treatment lines and improves not only survival but also quality-of-life metrics (QALY) [59]. Although upfront costs are high, the long-term reduction in complications, lower hospitalization rates, and extended treatment-free intervals make CAR-T therapy a relatively cost-effective investment [74] (see Supplementary Material for details).

Recent advances have focused on moving CAR-T therapy into earlier lines of treatment, shortening manufacturing time, and enhancing antigen-binding efficiency ("docking efficiency"). Traditional autologous CAR-T production takes several weeks, during which many patients may experience disease progression before infusion. To address this, rapid manufacturing platforms such as FasT CAR-T have been developed. For instance, BCMA/CD19 dual-target GC012F CAR-T cells can be generated within 48-72 hours [7]. Similarly, the NEX-T process integrates non-viral gene-transfer systems (e.g., Sleeping Beauty transposons) and automated quality-control algorithms, potentially reducing production time to just a few days [8,9]. In addition, "off-the-shelf" allogeneic CAR-T products aim to eliminate wait times and improve accessibility [10].

At the molecular level, optimization of antigen-binding domains including linker length and conformational stability has improved docking efficiency. Dual-target constructs (e.g., BCMA + GPRC5D or BCMA + CD38) show promise in preventing antigen escape [11]. Early-line clinical testing (before third-line therapy) suggests these approaches may preserve immune-cell function and extend durable remission [12,13].However, as manufacturing time decreases, careful evaluation of cell quality, CRS incidence, and long-term efficacy remains critical.

Despite impressive response rates, CAR-T therapy faces major limitations due to severe toxicities and restricted T-cell persistence. The most frequent and potentially life-threatening adverse event is cytokine release syndrome (CRS), triggered by excessive release of pro-inflammatory cytokines such as IL-6, IFN-γ, and TNF-α, leading to systemic inflammation, fever, hypotension, hypoxia, and multi-organ dysfunction [75]. CRS typically occurs within the first few days post-infusion and is managed with tocilizumab or corticosteroids.

A second key toxicity is immune effector cell-associated neurotoxicity syndrome (ICANS), commonly observed with CD19- and BCMA-directed CAR-T therapies. Symptoms include confusion, aphasia, tremor, or seizures, linked to endothelial activation and disruption of the blood-brain barrier [76]. Prolonged neutropenia and hypogammaglobulinemia further increase the risk of secondary infections and delay immune reconstitution [75].

Despite these remarkable outcomes, limited accessibility remains a major challenge. Ide-cel is currently available only in the United States, France, Switzerland, Japan, and Germany, while cilta-cel is approved solely in the United States and Germany. Manufacturing delays, logistical barriers, and strict eligibility criteria continue to restrict broader use. The autologous nature of most CAR-T products limits functional capacity in older or heavily pretreated patients, reducing T-cell persistence [77,78]. Additional barriers include antigen loss, immunosuppressive microenvironmental effects (e.g., TGF-β, IL-10, accumulation of MDSCs), and high production costs. In allogeneic ("off-the-shelf") CAR-T approaches, safety concerns such as graft-versus-host disease (GVHD) and immune rejection remain unresolved [79].

To overcome these challenges, next-generation strategies such as armored CAR-T, self-destruct switches, and regulated CAR systems are being developed to enhance persistence and minimize toxicity.

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3.3. CAR-T Cell Trials

The first-generation BCMA-targeted CAR-T therapy, idecabtagene vicleucel (ide-cel; bb2121), represents the pioneering autologous CAR-T construct evaluated in the KarMMa trials. Its single-epitope binding design limited both antigen affinity and cellular persistence. In vivo proliferation peaked early, leading to rapid but short-lived responses [80,81]. Consequently, KarMMa-1 reported a median progression-free survival (PFS) of 8.8 months and a median overall survival (OS) of 19.4 months values substantially lower than those achieved by later dual-epitope designs [81].

By contrast, ciltacabtagene autoleucel (cilta-cel; LCAR-B38M), a second-generation BCMA-directed CAR-T product developed through the LEGEND-2 and CARTITUDE programs, demonstrated markedly improved outcomes [11,68]. Its dual-epitope binding configuration enhances antigen affinity, strengthens T-cell proliferation, and promotes durable immunologic memory [70].

Among clinical trials evaluating CAR-T efficacy, LEGEND-2 and CARTITUDE-1 provide the most comprehensive long-term data. CARTITUDE-1 confirmed that deep and durable responses can be achieved even in heavily pretreated patients. After 61 months of follow-up, median OS reached 60.7 months, while the mean OS (area-under-curve analysis) was estimated at ~85 months [70].

LEGEND-2 (NCT03090659), the first-in-human, open-label phase 1 study of the dual-epitope construct LCAR-B38M, enrolled 74 patients with RRMM previously treated with at least three therapy lines including proteasome inhibitors and immunomodulatory agents. Following lymphodepletion with fludarabine and cyclophosphamide, patients received 0.5-1.0 × 10^6 CAR^+ T cells/kg as single or split doses. Response rates were high: overall response rate (ORR) 88-90%, complete response (CR) 74%, and MRD negativity ~68% [68]. Median PFS was 20 months and median OS 36 months. CRS occurred in most patients but was predominantly grade 1-2 and manageable; neurotoxicity was rare. This study provided the first clinical evidence that BCMA-directed CAR-T therapy could induce deep and durable remissions.

Following these successes, CARTITUDE-2, a multicenter phase 2 trial, explored CAR-T efficacy across diverse patient subgroups: **Cohort A:** triple-class-refractory patients (≥3 prior lines), **Cohort B:** lenalidomide-refractory patients with 1-3 prior lines [82], **Cohort C:** patients at first relapse [83], **Cohort D:** transplant-ineligible, lenalidomide-refractory patients [84], **Cohort E:** high-risk or MRD-positive early-stage disease [73].

In CARTITUDE-4, cilta-cel demonstrated statistical superiority over standard regimens in early-relapse settings in terms of progression-free survival [85]. The ongoing CARTITUDE-5 and CARTITUDE-6 studies [86,87] are now evaluating whether CAR-T therapy can replace the conventional ASCT + maintenance paradigm as a first-line treatment option, independent of transplant eligibility. Together, these consecutive trials establish CAR-T therapy not merely as a "last resort," but as an emerging early-line, immune-rejuvenating strategy in multiple myeloma **(see Table 3).**

Table 3. Clinical Summary of Cilta-cel and Ide-cel Based CAR-T Trials.

Study Name	Phase / Design	Patient Profile	Treatment Line	Regimen / Comparator	Key Message
LEGEND-2 (NCT03090659) [68]	Phase 1, open-label, single-arm	≥3 prior lines (PI + IMiD-treated RRMM)	4+ line	LCAR-B38M single infusion	First-in-human BCMA-CAR-T; deep and durable responses

 doi:10.20944/preprints202509.2132.v2

CARTITUDE-1 (NCT03548207) [70]	Phase 1b/2, multicenter	≥3 prior lines (PI + IMiD + anti-CD38)	4+ line	Cilta-cel single infusion	Global validation; high depth and long PFS
CARTITUDE-2 (NCT04133636)	Phase 2, multi-cohort	Cohorts A-E: RRMM, len-refractory, 1-3 prior lines	2nd–3rd line	Cilta-cel single infusion	High efficacy maintained in early-line settings
CARTITUDE-4 (NCT04181827) [85]	Phase 3, global	1–3 prior lines, len-refractory	2nd–3rd line	Cilta-cel vs PVd / DPd	Phase 3 confirmation of superiority vs SOC
CARTITUDE-5 (NCT04923893) [86]	Phase 3 (ongoing)	Newly diagnosed, transplant ineligable	1st line	VRd+Cilta-cel vs VRd+Rd maintenance	CAR-T as potential maintenance alternative in frontline
CARTITUDE-6 (NCT05257083) [87]	Phase 3, comparative	Newly diagnosed, transplant-eligible	1st line	D-VRd+Cilta-cel + Lenalidomide vs D-VRd+ASCT+DVRd+Lenalidomide	Immune-regenerative CAR-T as ASCT replacement
KarMMa-1 (NCT03361748) [13]	Phase 2, single-arm	≥3 prior lines RRMM	4+ line	Ide-cel (bb2121)	First approved BCMA-CAR-T (US)
KarMMa-3 (NCT03651128) [88]	Phase 3, randomized	2nd–4th line	-	Ide-cel vs SOC	Ide-cel effective but with shallower depth of response

BCMA: B-cell maturation antigen; SOC: Standard of Care; NDMM: Newly Diagnosed Multiple Myeloma; RRMM: Relapsed Refractory Multiple Myeloma; CAR: Chimeric antigen receptor; PFS: Progression Free Survival.

4. Quality-Adjusted Life Year (QALY) and ECOG-Based Modeling

The Quality-Adjusted Life Year (QALY) is an integrative measure that captures both the quantity and quality of life. One QALY represents one year lived in perfect health; for an individual experiencing 50% health quality, one year corresponds to 0.5 QALY. This concept allows treatment outcomes to be compared not only by survival duration but also by their impact on quality of life. In multiple myeloma, cumulative toxicity and treatment-related complications affect patients as profoundly as survival itself. Physical limitations, fatigue, immune suppression, and infection risk directly influence therapeutic success. Modern oncology therefore emphasizes combined metrics of

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longevity and quality most notably, the QALY as standard of value-based care. Quality of life is commonly assessed using validated questionnaires such as EORTC QLQ-C30, EQ-5D, or FACT-MM. The resulting utility scores, ranging from 0 to 1, are multiplied by the number of life-years gained to calculate QALY values [89]:

$$\textbf{QALY}=\text{Utility}\times\text{Life Years}$$

In parallel, the ECOG Performance Status (0-4) provides a clinician-rated, objective measure of functional capacity and independence: 0 = fully active; 1 = mild restriction; 2 = capable of limited activity; 3 = restricted to self-care; 4 = completely disabled; 5 = death.

Multiple studies have demonstrated a strong correlation between ECOG scores and HRQoL or EQ-5D utility values [89–93]. However, this relationship has rarely been formalized into a simple, quantitative model.

In this study, based on [94] the following ECOG-to-utility conversion was applied: ECOG 0 = 0.85, 1 = 0.75, 2 = 0.65, 3 = 0.55, 4 = 0.45. Each one-point increase in ECOG corresponds to an average utility decrement of 0.05–0.10, representing a clinically meaningful change (MID).

This method directly links performance status to quality of life and enables standardized, transparent, and practical QALY estimation even in the absence of patient-reported data. Supplementary materials detail how this ECOG-based model was adapted to specific treatment arms and integrated with cost data. Furthermore, the model incorporates Incremental Cost-Effectiveness Ratio (ICER) analysis, which quantifies the additional cost required to gain one extra QALY compared with an alternative treatment:

- Low ICER → higher cost-effectiveness
- High ICER → lower value or higher cost per QALY [95]

This framework assesses not only the economic burden of therapy but also the value gained per unit of quality-adjusted survival. In our analysis, CAR-T therapies particularly those from CARTITUDE-1 showed lower ICER values than most conventional regimens. This finding suggests that CAR-T represents not a “high-cost innovation,” but a high-value therapy whose long-term gains in quality of life justify its initial expense. Ultimately, this study proposes a simple, mathematically consistent, and ethically grounded model that enables clinicians, policymakers, and researchers to evaluate myeloma therapies not only in clinical and economic terms but also through a humanistic and justice-oriented lens.

5. Methods (Summary)

This analysis was designed to evaluate multiple myeloma treatment regimens within a comparative, model-based framework from a healthcare system perspective. The methodological approach focused on estimating cost, overall survival (OS), and quality-adjusted life years (QALY) across sequential lines of therapy. All values were derived from published clinical trial data using Kaplan-Meier survival curves and corresponding cost-effectiveness parameters.

QALY estimates were calculated by weighting survival duration with utility values derived from ECOG performance scores. The utility coefficients were obtained according to the model described in the hypothesis section (ECOG 0 = 0.85; 1 = 0.75; 2 = 0.65; 3 = 0.55; 4 = 0.45). In studies where ECOG data were not reported, estimated utilities were derived by optimizing toxicity (TEAE) and mortality data. Since all regimens were analyzed within the same methodological framework, results are proportionally comparable across treatment lines **(Supplementary Material Table S1).**

Mean overall survival (OS) values were computed by calculating the area under the Kaplan-Meier curve (AUC). Graphical data were digitized using WebPlotDigitizer software, and geometric integration was used to estimate the area beneath survival curves. Similarly, progression-free survival (PFS) values were extracted using the same method. Missing curve segments were interpolated geometrically based on slope trajectory and directional trends.

Cost estimation was performed according to the primary endpoint reported in each trial, which was PFS in all cases. Drug costs were calculated based on dosage, administration frequency, and

 doi:10.20944/preprints202509.2132.v2

treatment duration, using unit prices adapted from recent literature and national reimbursement databases (see Supplementary Material, Table S2). A detailed description of the model structure, parameter sources, dose calculations, and sensitivity analyses is provided in **the Supplementary Material - Methods** section.

6. Discussion and Conclusion

The primary aim of this study was to evaluate the advantages of CAR-T cell therapies over conventional regimens in terms of toxicity, progression-free survival (PFS), and overall survival (OS). Within this scope, QALY calculations and other pharmacoeconomic analyses were developed to interpret this major paradigm shift in hematology through an ethical and value-based framework. The study contrasts traditional approaches characterized by repeated chemotherapy cycles, high costs, and continuous hospital dependency with the transformative potential of CAR-T therapy: a single infusion that offers prolonged survival, reduced toxicity, and sustained remission. The goal, therefore, was not only to demonstrate clinical superiority but also to examine the ethical and human dimensions of modern therapeutic strategies. QALY-based cost analyses were used as a numerical representation of this ethical framework, seeking a clinical and philosophical answer to the question: "Is progress measured by the length of life, or by the quality of living?"

Most existing pharmacoeconomic studies in the literature rely on predefined QALY values and Markov-based cost-effectiveness models [59]. However, such models are often complex, making them difficult for clinicians and biomedical researchers to apply or interpret. In this context, our analysis provides a simpler but systematic framework that allows direct comparison of toxicity and survival outcomes without requiring complex modeling. Moreover, the cumulative toxicity observed with conventional therapies and the biological-economic transformation brought by CAR-T cells highlight an urgent need to reassess therapeutic priorities in hematology. This study responds to that need by evaluating treatment lines in terms of toxicity, survival, and quality of life, proposing an ethical, clinically meaningful, and practical framework for decision-making.

During the analysis, significant data gaps and transparency issues were encountered across clinical trials. Research reports should be written not only for clinicians but also for investigators from other disciplines. Yet, many pivotal phase studies compromise scientific clarity through excessive technical terminology, incomplete or unclear data presentation (particularly omission of death counts), and TEAE graphics that fail to reflect the patient's actual clinical condition. These limitations blur the boundaries between methodological reliability and ethical accountability. Broadly defined treatment categories such as "2nd–10th line" often encompass heterogeneous patient populations that differ greatly in biological and functional capacity. A patient in the second line of therapy and one in the tenth line are clinically incomparable. Such grouping may distort both positive and negative interpretations of efficacy and safety. Therefore, publishers, reviewers, and researchers share an ethical obligation to report baseline and final patient status using functional indices (e.g., ECOG, quality-of-life scales) and to provide arm-specific mortality data transparently. Clear definition of heterogeneity, and, when necessary, separate analyses by treatment line, is essential not only for methodological accuracy but also for a patient-centered ethical evaluation.

In the transplant-ineligible group, the VMP regimen remains the most cost-effective option, offering a favorable balance between total cost and utility/QALY gains. Despite the abundance of new agents, the continued clinical efficacy of agents such as melphalan and prednisone drugs whose origins trace back to the post-World War II era demonstrates that progress in medicine is not always defined by innovation, but often by continuity and resilience [96]. Analysis of induction-phase regimens (VRd, D-VRd, D-VMP, VMP, D-Rd, and Rd) revealed the highest QALY and utility values at this early treatment stage (Table 2; Supplementary Table S2). This raises a broader question: should we favor well-known, lower-cost regimens with predictable toxicity and management profiles, or prioritize new, high-cost combinations whose long-term outcomes remain uncertain? Perhaps the time has come for a paradigm shift toward individualized treatments that strengthen the patient's own immune system, integrating nutritional and lifestyle-based support with modern

 doi:10.20944/preprints202509.2132.v2

immunotherapies. Such a holistic approach may represent a more scientifically sound and ethically sustainable direction for the future [97,98].

In transplant-eligible patients, both survival and quality-of-life metrics were significantly superior. Adding daratumumab to VRd, which yielded an average QALY of 7.145, extended survival by more than 2.5 years though at approximately four times the cost. The most striking benefit of daratumumab was observed in progression-free survival (PFS): median PFS increased from 38 months with VRd to 84 months with D-VRd. Similar improvements were observed when daratumumab was added to VMP or Rd regimens, leading to sustained gains in both survival and quality of life [99].

Analysis of carfilzomib-based regimens (e.g., KRd, D-Kd) showed overall-survival advantages often exceeding 50 months, although progression-free survival (PFS) durations were shorter. This finding confirms that carfilzomib provides a mortality-reducing and quality-of-life-enhancing effect, particularly in high-risk patient groups [100]. Despite its short-term toxicity risks, carfilzomib continues to hold a valuable place within risk-adaptive therapeutic strategies.

Among late-line therapies, evaluated regimens include Elo-Rd, Elo-Pd, Elo-PVd, Isa-Pd, XVd, and CAR-T cell treatments such as those from the CARTITUDE-1 and LEGEND-2 trials **(Appendix B, Figure A1).** When daratumumab intolerance or resistance occurs, elotuzumab-based regimens become clinically relevant due to their low toxicity profile and unique SLAMF7-targeting mechanism [101]. In patients refractory to both lenalidomide and daratumumab, Elo-Pd remains a feasible alternative. Because most of these patients have previously received proteasome inhibitors, combinations such as Elo-PVd which include bortezomib are typically used in later treatment lines **(Appendix B Figure A1).**

Although late-line regimens such as PVd, Pd, and XVd achieve median overall survival (OS) approaching 40 months, the reliability of these data remains limited. The referenced studies involve highly heterogeneous patient populations, and the clinical characteristics of survivors are often underreported. In heavily pre-treated patients exposed to cumulative toxicity, the true clinical meaning of these survival durations is uncertain. The derived utility values were nearly ten-fold lower than those observed in the induction phase, with a mean progression-free survival (PFS) of only about 20 months. Treatment costs averaged roughly USD 800 000 per patient. Regimens such as Elo-Rd and Isa-Pd yielded QALY scores approaching 1.0, yet these modest gains came at an additional cost of about USD 100 000. Among them, Elo-Rd offered roughly one extra year of survival compared with other late-line options; however, this difference may partly reflect patient heterogeneity or residual lenalidomide sensitivity [102]. Within this landscape, the most remarkable finding was the CAR-T cell therapy results. Despite excluding patients from second- or third-line cohorts, cilta-cel demonstrated an estimated mean OS exceeding 85 months, PFS around 44 months, and a substantially lower annual cost (Table 2; Supplementary Table S2). In the ongoing CARTITUDE-1 [70], the mean OS exceeded 85 months, and the calculated QALY reached 2.744 approximately three times higher than conventional late-line regimens. These findings suggest that CAR-T therapy redefines the end-stage paradigm not only biologically, but also economically and ethically. To evaluate how much it costs to provide one additional year of quality-adjusted life, we performed an Incremental Cost-Effectiveness Ratio (ICER) analysis (Figure 5). This approach quantifies the comparative cost of achieving one year in which the patient perceives themselves as “healthy,” integrating clinical, economic, and ethical dimensions into a unified assessment of therapeutic value.

 doi:10.20944/preprints202509.2132.v2

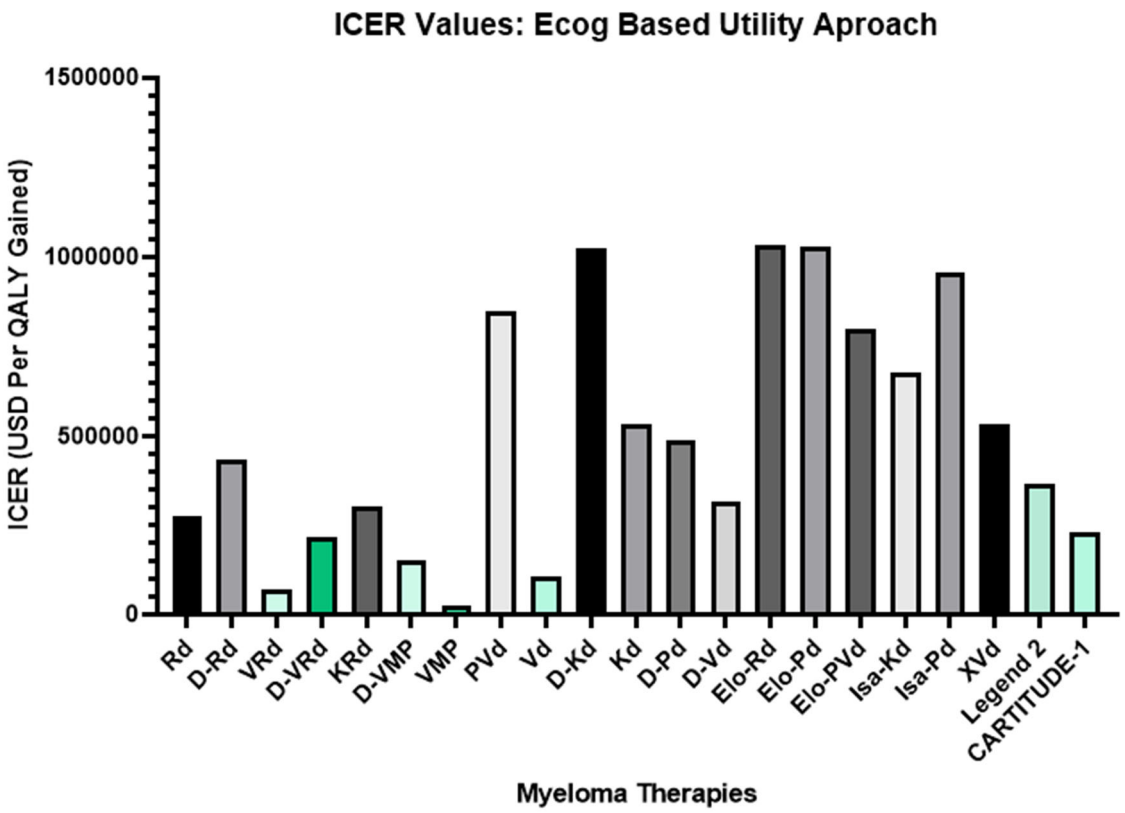

Figure 5. ICER distribution across myeloma therapies based on ECOG-adjusted utility approach. Each bar represents the incremental cost-effectiveness ratio (ICER) expressed as cost per QALY gained. Green tones illustrate relative cost-effectiveness proximity among regimens, highlighting CAR-T (CARTITUDE-1) within the lowest ICER range, comparable to D-VRd and other advanced monoclonal antibody combinations.

In the late-line analysis, the calculated ICER values indicate that, despite its seemingly high upfront cost, CAR-T therapy stands among the most value-based interventions in multiple myeloma. Its single-infusion design, minimal hospitalization time, and lack of cumulative toxicity management substantially reduce total healthcare expenditures. In contrast, conventional treatments administered "piece by piece" across multiple cycles create far greater long-term economic and biological burdens. Therefore, CAR-T should not be viewed as an "expensive innovation," but rather as a high-value and sustainable solution. When cost optimization, insurance coverage, and public reimbursement mechanisms are implemented, its financial impact may become lighter than that of conventional regimens over time. Current evidence shows that CAR-T therapy provides remarkable improvements in survival and quality of life, even in heavily pretreated patients. Although results from early-line trials (such as the CARTITUDE and KarMMa series) are still maturing, preliminary findings suggest that CAR-T could be administered earlier, with lower toxicity and longer-lasting remission. This potential points toward a new therapeutic paradigm in myeloma one focused not on multiple sequential treatments, but on single-intervention, durable control. In this sense, CAR-T may represent not only an early intervention candidate, but also the first genuinely personalized therapy capable of achieving lasting remission with one infusion.

From an ethical standpoint, a therapy initially limited by high cost but ultimately capable of providing more life years, less toxicity, and lower overall expenses demands a re-examination of what constitutes justice and value in modern medicine. Today, CAR-T cell therapy remains accessible only in a few countries and primarily to patients who can afford its one-time infusion price. This disparity raises critical questions about how biotechnological innovation can be balanced with equity and accessibility. In a patient-centered and socially sustainable healthcare model, CAR-T should be recognized not only as a scientific breakthrough, but also as a transformative model redefining

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ethical, economic, and human values in medicine. Expanding its accessibility will not only improve clinical outcomes, but also strengthen equality, humanism, and the principle of "kill the tumor, not the human.

See Supplementary Material for details.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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Availability of data and materials: All data used in this study were obtained from publicly available clinical trial publications and databases, which are cited in the manuscript.

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Consent for publication: Not applicable.

Appendix A

Table A1. Modern Therapies in Multiple Myeloma: Clinical Role.

Therapy / Class	Year (Approval / Milestone)	Mechanism / Target	Current Use in MM	Key Toxicities
Autologous Stem Cell Transplant (ASCT)	1983 (MM application)	Hematopoietic rescue	Standard in eligible patients	Myelosuppression, infection risk
Bortezomib (first PI) [103,104]	2003	Reversible 20S proteasome inhibitor	Backbone of induction (VRd etc.)	Peripheral neuropathy
Carfilzomib (2nd-gen PI) [104]	2012	Irreversible PI	Relapsed/refractory, combo regimens	Cardiac toxicity
Ixazomib (oral PI) [104]	2015	Oral PI	Maintenance, frail patients	GI, mild cytopenias
Lenalidomide (IMiD) [102]	2005	IMiD, cytokine modulation, T-cell activation	Frontline & maintenance backbone	Cytopenias, thrombosis
Pomalidomide (IMiD) [105]	2013	Next-gen IMiD	Relapsed/refractory settings	Cytopenias, infections
Daratumumab (anti-CD38 mAb) [1,107]	2015	ADCC, CDC, ADCP, direct apoptosis	Widely used frontline & RRMM	Neutropenia, infusion reactions
Isatuximab (anti-CD38 mAb) [1,106]	2020	Distinct CD38 epitope, direct apoptosis	Combo with Pd in RRMM	Neutropenia, infections

 doi:10.20944/preprints202509.2132.v2

Selinexor (XPO1 inhibitor) [1,106]	2019	Nuclear export inhibition, p53 reactivation	Triple-class refractory	GI toxicity, cytopenias
Venetoclax (BCL-2 inhibitor) [1,106]	Investigation	BCL-2 inhibition	Targeted subgroup (t(11;14))	Tumor lysis, cytopenias
Melflufen (peptide-drug conjugate) [1,106]	2021 (revoked FDA approval)	Alkylating payload via peptide conjugate	EMA-approved, not FDA	Cytopenias, survival concern
HDAC inhibitors (e.g., panobinostat) [1,106]	2015 (panobinostat FDA)	Histone deacetylase inhibition	Adjunct in refractory disease	GI, fatigue, cytopenias
Checkpoint inhibitors (PD-1/PD-L1) [1,106]	Trials (halted in MM)	Immune checkpoint blockade	Investigational only	Immune toxicities
Bispecific Abs / CAR-T / NK [1,106]	2020s	Redirected T/NK cytotoxicity	Rapidly emerging	CRS, neurotoxicity, cytopenias

Appendix B

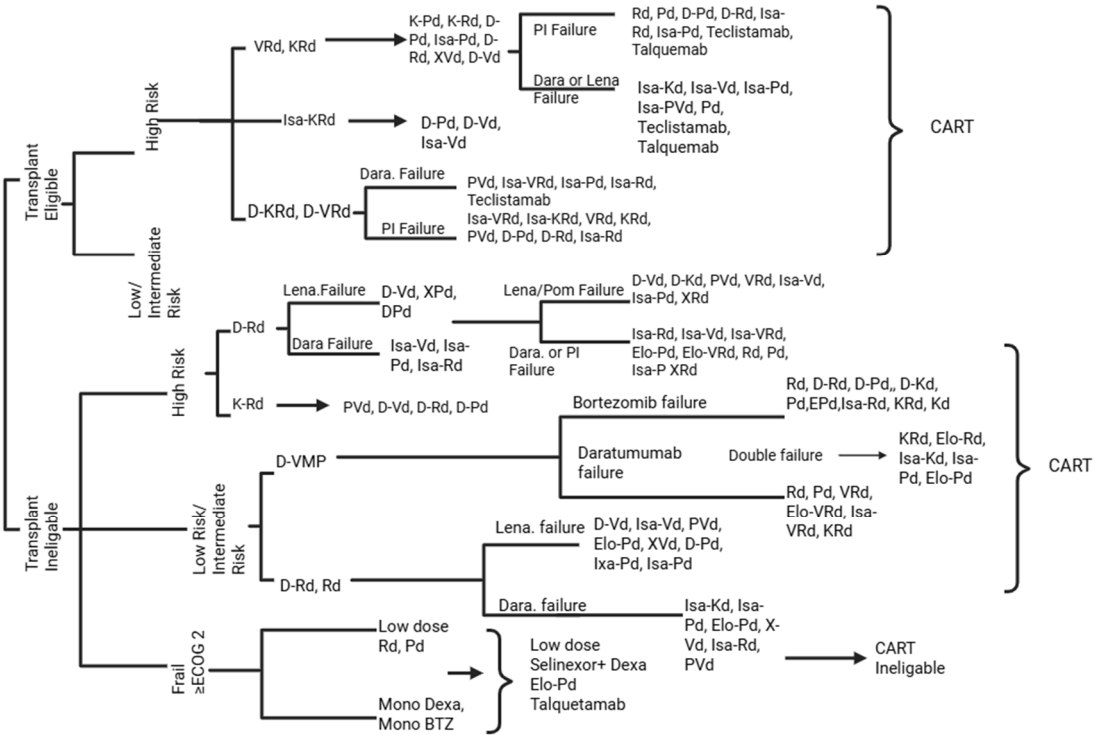

Figure A1. Proposed treatment pathway for multiple myeloma based on the author's synthesis of recent clinical studies (2018-2025), reflecting risk stratification, treatment eligibility, and therapeutic failure sequences. This algorithm was constructed by integrating data from the clinical trials and publications cited in the main text. It represents an interpretative synthesis rather than an adaptation of any single guideline. All references used to generate this figure are included in the manuscript's reference list.

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