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Impact of Treatment Sequencing with CAR T-cell Therapies and Bispecific Antibodies on Long-term Survival in 4L+ RRMM in the US: A Simulation Model

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INTRODUCTION

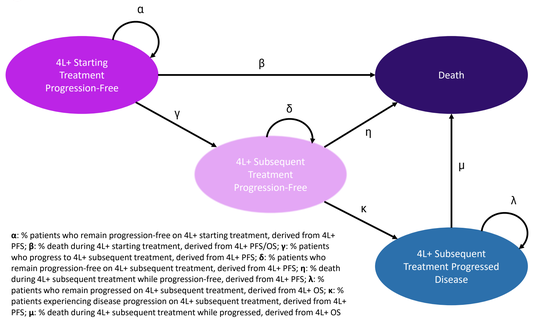
- Chimeric antigen receptor (CAR) T-cell therapies and bispecific antibodies (BsAb) are increasingly used in treating relapsed/refractory multiple myeloma (RRMM) in the fourth line setting and beyond (4L+).
- Treatment sequencing with CAR T-BsAb has both clinical and economic impact.
- The primary objective of this study was to estimate progression-free survival (PFS) and overall survival (OS) based on treatment sequence in 4L+ RRMM (starting treatment followed by subsequent treatment), comparing 4L+ CAR T followed by BsAb vs. 4L+ BsAb followed by CAR T, to inform optimal therapy.
- The secondary objective was to estimate the total costs over the median PFS (mPFS) and the median OS (mOS) periods for each treatment sequence.

METHODS

Model Overview

- A US-based Markov model with time-dependent transitions and pre-defined treatment sequence rules was used to estimate long-term survival outcomes for 4L+ RRMM through 2030 by treatment sequence, using available evidence on incidence, treatment patterns, and clinical efficacy (Figure 1).

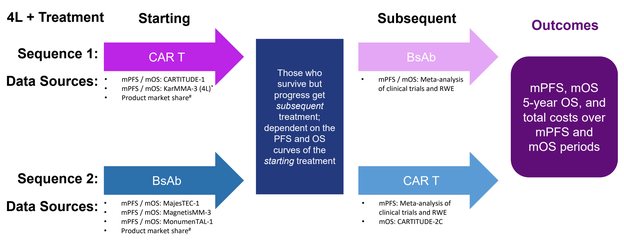
Figure 1. Markov Model Structure



α: % patients who remain progression-free on 4L+ starting treatment, derived from 4L+ PFS; **β**: % death during 4L+ starting treatment, derived from 4L+ PFS/OS; **γ**: % patients who progress to 4L+ subsequent treatment, derived from 4L+ PFS; **δ**: % patients who remain progression-free on 4L+ subsequent treatment, derived from 4L+ PFS; **η**: % death during 4L+ subsequent treatment while progression-free, derived from 4L+ PFS; **λ**: % patients who remain progressed on 4L+ subsequent treatment, derived from 4L+ OS; **κ**: % patients experiencing disease progression on 4L+ subsequent treatment, derived from 4L+ PFS; **μ**: % death during 4L+ subsequent treatment while progressed, derived from 4L+ OS

- In each model cycle, patients could remain progression-free (PF) or in progressed disease (PD) based on PFS and OS of the starting treatment (CAR T or BsAb), upon which a subsequent treatment was initiated (BsAb and CAR T, respectively), and patients began to follow the PFS and OS curves of the subsequent treatment (Figure 2).

Figure 2. Model Schematic for Patient Flow[1-5]



BsAb, bispecific antibodies; CAR T, chimeric antigen receptor T; mOS, median overall survival; mPFS, median progression-free survival; RWE, real world evidence
*4L subgroup of KarMMa-3 #Market share inputs for CAR T and BsAb products were based on internal market research assumptions

- Treatments modeled included cilta-cel, ide-cel, elranatamab, teclistamab, and talquetamab. The distribution of each drug was based on internal market share assumptions.
- mPFS and mOS inputs of the starting treatment were based on those reported in clinical trials with the longest follow-up. In situations where these outcomes were not directly reported, survival curves were identified and digitized to extrapolate mOS and mPFS, and used to derive survival curves used in the model to simulate the cohort over time. For subsequent treatment, real-world evidence (RWE) was used where trial data was not available.

METHODS *(CONTINUED)*

Inputs

- All model inputs are shown in Table 1.
- The median age at diagnosis of 69 years was used as the starting age for the simulation, with an incidence of 4L RRMM estimated to be 3,739 in 2025, representing ~11% of all new cases (3,739 / 35,780).[7]
- Background population-based US annual mortality rates were also included.
- mPFS and mOS for each treatment sequence was based on clinical trial data and a meta-analysis of clinical trial and RWE studies reporting efficacy for 4L+ CAR Ts followed by BsAbs, and for 4L+ BsAbs followed by CAR Ts.
- Costs were based on literature estimates reporting per-patient-per-month (PPPM) costs per PF and PD health states for CAR T vs. BsAbs.
  - These PPPM costs were used to estimate the total cost over median PFS and median OS of each sequence.
  - CAR T administration costs (including pre- and peri-infusion along with short term adverse event management costs) were applied as a one-time cost since CAR T is administered once, unlike BsAbs which are administered over time on a weekly or biweekly schedule.

Table 1. Model Inputs

Patient Characteristics		
Starting age (years)	69	
% Male	55.5	
Survival Inputs		
Starting Treatment	From clinical trials[1-5]	
Subsequent Treatment	**Outcome (since subsequent treatment initiation)**	**Estimate (95% CI)***
4L+ BsAb (after CAR-T)	mPFS[3,5,8–10]	11.6 (9.7-14.5)
	mOS[3,8,10,11]	22.2 (19.4-25.9)
4L+ CAR T (after BsAb)	mPFS[6,12,13]	2.8 (2.4-3.4)
	mOS[6]	13.2 (0.6-25.8)
Cost Inputs, PPPM	**CAR T**	**BsAb**
Progression-Free	$519[14]	$36,522[15]
Progressed Disease#	$18,863[14]	$18,863[14]
One-Time Treatment Cost†	$588,701[14]	*NA*‡

BsAb, bispecific antibody; CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival; PPPM, per patient per month; RWE, real world evidence. Market share inputs were based on internal market research assumptions. Costs are shown inflated to 2025 USD.
*From meta-analysis of RWE and clinical trials except 4L+ CAR T (after BsAb) mOS which was derived from a single study. #Assuming treatment with conventional medication classes. †Pre- and peri-infusion along with short-term adverse event management cost for CAR T was applied upfront as a one-time cost. ‡Since administered weekly/biweekly

Outcomes

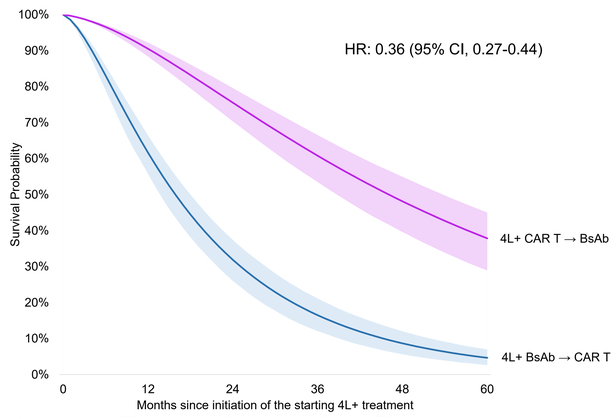
- The study estimated 5-year OS, mPFS, mOS, hazard ratios (HRs), and total costs over the mPFS and mOS periods for each treatment sequence.

Sensitivity and Scenario Analysis

- A probabilistic sensitivity analysis with 1,000 simulations was conducted to generate 95% credible range estimates for each model outcome.
- Two scenario analyses using alternate health states costs were also conducted:
  - Using a per-month PF state in BsAb cost of $44,107[16], keeping other costs constant.
  - Using a conservative average sales price (ASP) for CAR T of $565,869 as per the Q4 2025 Centers for Medicare and Medicaid Services ASP Files,[17] keeping other costs constant.

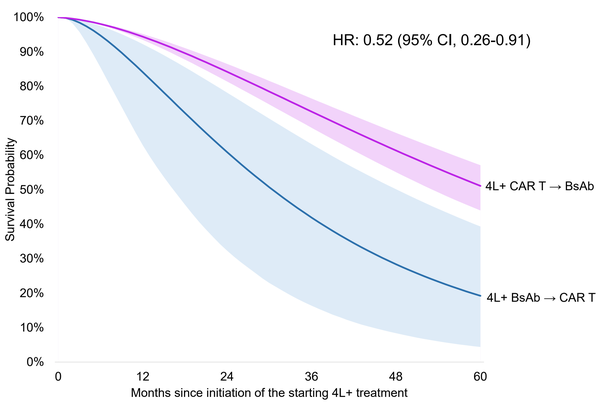
RESULTS

Figure 3a. Estimated 5-year PFS: Sequencing 4L+ CAR T before BsAb vs. BsAb before CAR T



BsAb, bispecific antibodies; CAR T, chimeric antigen receptor T; CI, confidence interval; HR, hazard ratio; PFS, progression-free survival
NOTE: Shaded regions depict 95% confidence interval limits

Figure 3b. Estimated 5-year OS: Sequencing 4L+ CAR Ts before BsAb vs. BsAb before CAR Ts



BsAb, bispecific antibodies; CAR T, chimeric antigen receptor T;CI, confidence interval; HR, hazard ratio; OS, overall survival
NOTE: Shaded regions depict 95% confidence intervals

Table 2. Results of Sequencing Cost Outcomes

Outcome	**CAR T → BsAb**	**BsAb → CAR T**
mPFS, months (95% CI)	46.4 (38.3-54.5)	16.8 (13.2-18.6)
Total Cost Over mPFS	$934,628	$1,222,713
Cost Per-Patient-Per-mPFS Month*	$20,143	$72,781
mOS, months (95% CI)	61.5 (53.8-69.9)	32.0 (13.2-44.5)
Total Cost Over mOS	$1,019,513	$1,450,958
Cost Per-Patient-Per-mOS Month*	$16,577	$45,342

BsAb, bispecific antibodies; CAR T, chimeric antigen receptor T; CI, confidence interval; mOS, median overall survival; mPFS, median progression-free survival
*Obtained by amortizing the total cost of mPFS/mOS over the entire mPFS/mOS period

Results

- Treatment sequencing analysis estimated that using 4L+ CAR T before BsAb resulted in significantly longer survival: mPFS of 46.4m (95% CI 38.3–54.5) and mOS of 61.5m (95% CI 53.8–69.9) compared to the 4L+ BsAb before CAR T sequence (mPFS: 16.8m, 95% CI 13.2–18.6; mOS: 32.0m, 95% CI 13.2–44.5) (Figure 3a-b).
  - This survival advantage of sequencing CAR T before BsAb was supported also by HRs of 0.36 (95% CI 0.27–0.44) for PFS and 0.52 (95% CI 0.26–0.91) for OS vs. BsAb before CAR T.
  - The 5-year OS estimates were also substantially higher for 4L+ CAR T before BsAb (51.9%, 95% CI 44.8–57.8) vs. BsAb before CAR T (19.9%, 95% CI 4.6–40.1).
- Over the mPFS and mOS periods, 4L+ CAR T before BsAb had substantially lower overall costs (cost savings of $288,085 and $431,445, respectively) and per-patient-per-month total costs vs. BsAb before CAR T (Table 2).
  - With sensitivity analyses, overall cost savings with 4L+ CAR T before BsAb increased to $351,038 and $494,398 over mPFS and mOS, respectively.

CONCLUSIONS

- **In this simulation model, using 4L+ CAR T before BsAb reduced risk of progression or death by 64%, and death by 48% over 5 years vs. BsAb before CAR T, as shown by the HRs.**
- **Sequencing CAR T before BsAb led to substantial projected cost savings over the mOS period ($430,000-$500,000) in 4L+ RRMM.**
- **These findings support the use of CAR T before BsAb among patients with 4L+ RRMM to improve long-term patient outcomes with substantial cost savings.**

Limitations

- Though we prioritized studies with similar designs and patient characteristics, efficacy estimates came from trial and RWE populations without baseline adjustment, which may introduce residual confounding.
- More trial data on treatment sequencing is needed to validate these results.

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Disclosures

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