

Patient population with multiple myeloma and transitions across different lines of therapy in the US: an epidemiologic model

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Abstract:	<p>Multiple myeloma (MM) is a progressive, malignant neoplasia with a worldwide, age-standardized annual incidence of 1.5 per 100,000 individuals and 5-year prevalence around 230,000 patients. Main favorable prognostic factors are younger age, low-moderate cytogenetic risk, and undergoing stem cell transplantation. Our aim was to estimate the size of the patient population with MM eligible to receive a new MM therapy at different lines of therapy in the US.</p> <p>Methods: We constructed a compartmental, differential equation model representing the flow of MM patients from diagnosis to death, via two possible treatment pathways and distinguished in four groups based on prognostic factors. Parameters were obtained from published references, available statistics, and assumptions. The model was used to estimate number of diagnosed MM patients and number of patient transitions from one line of therapy to the next over one-year. Model output included 95% credible intervals (CI) from probabilistic sensitivity analyses.</p> <p>Results: The base-case estimates were 80,219 patients living with MM, including 70,375 on treatment, 780 symptomatic untreated patients, and 9,064 asymptomatic untreated patients. Over a one-year period, the number of MM patients on treatment line 1 was estimated at 23,629 (CI 22,236-25,029), and the number of transitions from treatment line 1 to treatment line 2 estimated at 14,423.</p> <p>Conclusions:</p>

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	The size of the patient population with MM on different lines of therapy and in-patient subgroups of interest estimated from this epidemiologic model can be used to assess the number of patients who could benefit from new MM therapies and their corresponding budgetary impact.

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3 **Patient population with multiple myeloma and transitions across different lines of**
4 **therapy in the US: an epidemiologic model**
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6 **Running Head:** Multiple myeloma lines of therapy: an epidemiologic model
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16 **Keywords:** Epidemiology, multiple myeloma, prevalence, model, treatment line
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18 **Key Points:**

- 19
20 - The estimated number of patients with MM in the US provided by the epidemiology
21 model was consistent with the figure reported by SEER.
22 - The distribution of the patient population with MM on different lines of therapy and in
23 patient subgroups of interest can be estimated from the epidemiologic model.
24 - The size of the patient population with MM on different lines of therapy and in patient
25 subgroups can be used to assess the number of patients who could benefit from new
26 MM therapies, information required for budget impact analysis and to support the
27 planning of healthcare services.
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55 whole.
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ABSTRACT**Purpose:**

Multiple myeloma (MM) is a progressive, malignant neoplasia with a worldwide, age-standardized annual incidence of 1.5 per 100,000 individuals and 5-year prevalence around 230,000 patients. Main favorable prognostic factors are younger age, low-moderate cytogenetic risk, and undergoing stem cell transplantation. Our aim was to estimate the size of the patient population with MM eligible to receive a new MM therapy at different lines of therapy in the US.

Methods:

We constructed a compartmental, differential equation model representing the flow of MM patients from diagnosis to death, via two possible treatment pathways and distinguished in four groups based on prognostic factors. Parameters were obtained from published references, available statistics, and assumptions. The model was used to estimate number of diagnosed MM patients and number of patient transitions from one line of therapy to the next over one-year. Model output included 95% credible intervals (CI) from probabilistic sensitivity analyses.

Results:

The base-case estimates were 80,219 patients living with MM, including 70,375 on treatment, 780 symptomatic untreated patients, and 9,064 asymptomatic untreated patients. Over a one-year period, the number of MM patients on treatment line 1 was estimated at 23,629 (CI 22,236-25,029), and the number of transitions from treatment line 1 to treatment line 2 estimated at 14,423.

Conclusions:

The size of the patient population with MM on different lines of therapy and in-patient subgroups of interest estimated from this epidemiologic model can be used to assess the number of patients who could benefit from new MM therapies and their corresponding budgetary impact.

Word count: 250

INTRODUCTION

Multiple myeloma (MM) is a progressive, hematologic malignancy originating from plasma cells and with the most negative long-term prognosis among lymphoid malignancies.^{1,2} MM accounts for approximately 1% of all cancers and 10-12% of hematologic malignancies, with a worldwide age-standardized annual incidence of 1.5 per 100,000 or estimates of around 115,000 new cases per year, a rather small number compared to other cancers and chronic conditions.²⁻⁴ MM has an estimated worldwide 5-year prevalence of around 230,000 patients.⁴ Older age is associated with unfavorable outcomes,^{1,5} and there are no apparent prognostic differences associated with gender.¹ The presence of certain chromosomal abnormalities is also a negative prognostic factor.⁵⁻⁸

MM treatment is intended to control the symptomatic disease and minimize organ damage; however, relapse is likely. From high-dose therapy followed by autologous stem cell transplantation for candidates in good condition,^{7,9} to allogeneic stem cell transplantation (SCT) in young patients with high-risk disease,^{7,10} and to novel agents introduced in recent years,^{2,7,11,12} all are associated with prolonged survival of patients with this incurable disease.^{5,7,9,13-15} More than 10 drugs and a greater number of drug combinations offer therapeutic options to patients who have relapsed or are refractory to previous treatments and can result in patients receiving multiple lines of therapy.^{5,7} The prevalence of MM is likely to increase as a result of ageing societies and improved survival of patients. Multiple lines of therapy for an increasing number of patients with MM translate into increasing resource requirements at subsequent lines of therapy¹⁶ and competition among MM treatment alternatives on pharmacoeconomic grounds.¹⁷⁻¹⁹

Epidemiologic information including disease incidence, prevalence and mortality are inputs for burden of disease and cost-effectiveness analyses that aim to inform policy-making, planning and research prioritization in health care.²⁰ Previous studies have used mathematical modeling techniques to project the prevalence of chronic conditions such as diabetes and chronic kidney disease into the near or distant future.²¹⁻²³ In oncology, an epidemiologic model was used to estimate disease prevalence and the absolute number of patients at first-, second-, and third line of therapy for gastrointestinal stromal tumors,²⁴ providing useful information for budget impact analysis and healthcare services planning.²⁰

In the absence of current data on the number of patients with MM by line of therapy in the US, the objectives of this study were to estimate the current number of patients with MM who are potentially eligible to receive a new MM therapy at different lines of therapy in the US, and to estimate the corresponding number of patient transitions from one line of therapy to the next over a one-year period.

METHODS

Model Overview

The size of the patient population with MM in the US across lines of therapy and the number of patient transitions from one line of therapy to the next was estimated using a compartmental model that represents the flow of patients with MM from disease occurrence to death, via two possible treatment pathways (SCT eligible; SCT non-eligible) (Figure 1). To account for the impact of different risk factors on disease progression,^{1,5-8} the model distinguished four groups of patients based on age at diagnosis and cytogenetic risk: older or younger than 65 years of age, and high or low/standard cytogenetic risk (Figure 1, as depicted by dotted lines).

All newly diagnosed patients with MM enter the model as symptomatic or asymptomatic. Asymptomatic patients are assumed to receive no treatment until symptom occurrence. Symptomatic patients can transition through two treatment pathways depending on whether they are eligible for an SCT or not. Patients in both pathways progress from one line of therapy to the next as they relapse. For patients eligible for a SCT, the first line of therapy represents induction, SCT and maintenance therapy post SCT. In each treatment line, patients are allowed to die from background mortality or mortality related to their condition. Eventually, all patients will die since the model assumes there is no cure for MM.

The model consists of a set of four differential equations which represent a mean approximation of the expected number of asymptomatic, symptomatic untreated, individuals who initiated on first line, and on subsequent treatment lines through time (Appendix A). The model parameters include estimates of MM incidence, mortality, and time to next treatment line (Table 1, Appendix A). The base case parameter values are shown in Table 1.

This model includes a number of assumptions necessary for its correct interpretation:

- Results for all lines beyond 17 are incorporated into the 17th line.
- Patients on the SCT pathway may have up to two SCTs along their line therapy trajectory.
- Asymptomatic MM (smoldering) is explicitly modeled, but no treatment is given.
- Patterns of co-morbidities (e.g., peripheral neuropathy) are not explicit.
- The model tracks time between starting one treatment line and starting the next. Treatment breaks and permanent discontinuations are not explicitly modelled.
- There is no stratification for academic versus community care (for settings where these different care types exist).
- Line of therapy is determined by disease progression, relapse, or drug toxicity resulting in a modification of the planned therapeutic approach.²⁵
- Being in the high-risk cytogenetic group does not affect SCT eligibility.

- Survival probabilities are characterized by an exponential function.
- The length of each treatment line is shorter than the previous one. Minimum length of a treatment line is approximately one week (1/50 year).
- Relative rate of patients transitioning from one line to another is constant across all lines.
- MM-related mortality while symptomatic before first line treatment initiation is slightly higher ($\approx 10\%$) than MM-related mortality while asymptomatic.
- MM attributable mortality declines in the first year because of plasma cell leukemia patient depletion from the cohort. It is relatively constant over the subsequent years ($\approx 10\%$ increase) but then increases, especially from the 6th line of therapy and beyond
- Forecasts are at the population level and not at the individual level.

Data Sources

To estimate the overall number of patients with MM, we used the incidence of MM obtained from Surveillance Epidemiology and End Results (SEER) Cancer Statistics²⁶ applied to the 2013 US population estimate from the US Census Bureau.²⁷ Mortality rates were obtained from 2007 US National Vital Statistics.²⁸ Other model parameters were obtained from targeted literature searches (Table 1). For each of these parameters, one or more references were identified from the literature. Internal validity of the parameter estimates obtained from the literature (or the degree to which the referenced studies are free from systematic error) is supported by the peer review process of such studies, consistency of results, and for some parameters, information provided from interviews with MM experts and market research surveys. External validity of the parameter estimates (or the degree to which those estimates can be applied to the overall population) is also expected, since the parameters' base-case values were chosen around mid-range values and the study results were consistent. Some references provided data in the format required by the model, while others required transformation. For example, survival figures expressed as percentage of surviving patients at a specific time after diagnosis or treatment initiation required transformation into yearly rates before they could be included in the model. No ethical committee approval was necessary for this study.

Sensitivity Analysis

Parametric uncertainty analyses were conducted through probabilistic sensitivity analysis (PSA). The PSA was performed on key selected model parameters²⁹ using Latin hypercube sampling (LHS).³⁰ This process involved two steps: first, parameters expected to influence model output were selected for inclusion in the PSA, and partial rank correlation coefficients (PRCCs) were then computed (Appendix B, Figure B-1) to illustrate the parameters that were the greatest sources of heterogeneity in model output.³¹ Secondly, the PSA consisted

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3 of varying the parameter values by sampling 1000 times from distributions specified by the
4 mean value (deterministic model input) and standard errors (Appendix B, Table B2).
5 Standard errors were selected to describe parameter variability observed in the data sources
6 and expected in the broad population of patients with MM. Distributions were determined by
7 the characteristics of the parameter and experience (e.g. beta distributions are usually
8 considered for binomial data; gamma or log normal for right skew parameters; log normal for
9 hazard ratios.³²)
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14 **Model Outcomes**

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16 Model outcomes include the size of the patient population with MM potentially eligible to
17 receive a MM therapy at different lines of therapy in the US, as well as the corresponding
18 number of patient transitions from one line of therapy to the next over a one-year period. The
19 model is designed to report outcomes at equilibrium, which is judged to have been achieved
20 when the model reaches a steady state, in that the number of patients in each line no longer
21 fluctuates and remains stable. All model outcomes are stratified by the eight subgroups of
22 interest resulting from the combination of SCT eligibility, age group, and cytogenetic risk
23 group. Model outcomes also include 95% credible intervals (analogous to a confidence
24 interval with estimates obtained from the sampling results) from the PSA for both the number
25 of patients and their transitions at different lines of therapy. Ninety five percent (95%)
26 credible intervals were defined by the upper and lower bounds of the distribution of model
27 outcomes from the PSA leaving 2.5% of the values below and above, respectively.
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35 **RESULTS**

36 **Prevalence of MM**

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38 Model results are presented in Table 2. An estimated 80,219 patients were living with
39 diagnosed MM in the US, of whom 70,375 patients were receiving treatment, 780 patients
40 were symptomatic untreated and 9,064 patients were asymptomatic who are untreated and
41 would be monitored for progression to symptomatic MM. Patient numbers stratified by SCT
42 eligibility, age group, and cytogenetic risk group are shown in Table 2. Additionally, the
43 model estimated that 19,330 patients with MM would die over a one-year period from
44 background mortality and mortality attributable to MM.
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50 **Patient Transitions from One Line of Therapy to the Next**

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52 Table 3 reports the number of patient transitions from one line of therapy to the next over a
53 one-year period, estimating that the total number of transitions experienced by the above
54 patient population would be 96,259. A total of 18,689 patients diagnosed with MM are
55 estimated to initiate first line therapy over a one-year period. Patients entering into treatment
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3 line 17 and beyond were estimated at 167. Results stratified by SCT eligibility, age group,
4 and cytogenetic risk group are also presented in Table 3.
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6 7 **PSA results**

8 The results of the PSA are in Table 4, estimating 95% credible intervals (CI) for numbers of
9 MM patients and the numbers of patient transitions from one line of therapy to the next. The
10 results corresponding to the eight strata of interest defined by SCT eligibility, age group, and
11 cytogenetic risk group are shown in Appendix C. The PSA model runtime was around three
12 hours.
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15 16 17 **DISCUSSION**

18 The current estimated number of patients with MM in the US is 80,219, with 70,375 on
19 different lines of therapy. Over a one-year period, 19,330 deaths from all causes would be
20 expected as well as 14,423 transitions from line 1 into line 2. The estimated number of
21 patients initiating line 1 of therapy over one year is 18,689. Beyond line 17 of treatment, as
22 anticipated, the patient prevalence was close to 0, although the number of transitions over a
23 one year period could be larger as a consequence of the short time spent in those lines of
24 therapy when the condition is so advanced.
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27 The model estimates of the patient distribution across the different lines of therapy, from the
28 first to 17th line and beyond, at a snapshot in time, differed from the patient transition
29 breakdown over a one-year period. For early lines of therapy, lines 1 and 2, the number of
30 patient transitions over a one-year period was smaller than the number of patients at a point
31 in time, as a consequence of these patients spending long periods on treatment, or without
32 receiving treatment but free of disease progression and drug toxicity.²⁵ At subsequent lines
33 of therapy, the number of patient transitions decreased more slowly than the number of
34 patients reflecting that the average patient spends shorter periods on successive treatment
35 lines and eventually can transition through several lines of therapy over a one-year period.
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38 The estimated number of patients with MM in the US provided by the model, 80,219, was
39 consistent with the figure estimated by SEER for 2014 of 83,367 patients. Conversely, the
40 number of patients with MM who died of this disease over a one-year period was estimated
41 at 11,090 (SEER data from 2014),²⁶ while the model estimate was 16,670. This difference is
42 larger than expected because one would anticipate that the number of deaths over a one-
43 year period is somehow lower than the number of new patients being diagnosed, as a result
44 of the range of novel therapeutic alternatives providing increased patient survival over time.
45 The expected small difference between incident cases and patient mortality would translate
46 into a continuous steady increase of the prevalence of MM. The observed large difference in
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3 the SEER data between incident cases and patient mortality would result in the prevalence
4 of patients with MM increasing greatly over a short period. We hypothesize that the large
5 difference between the mortality estimates of the model and those of SEER could be
6 attributable to SEER reporting only mortality attributed to MM and not all mortality
7 experienced by patients with MM, and also to a proportion of deaths caused by MM not
8 being correctly classified as such (resulting in apparently increased background mortality
9 among patients with MM).

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14 We have not identified any other epidemiologic models reporting on patients with MM.
15 Nevertheless, there are several studies reporting on the use of epidemiologic models for
16 other oncologic conditions such as prostate cancer,^{33,34} breast cancer,³⁵ Hodgkin's
17 lymphoma,^{36,37} chronic myeloid leukemia,³⁸ and gastrointestinal stromal tumors.²⁴ The
18 rationale for developing such models is consistent with the objectives of the model presented
19 in this paper: while the epidemiology of these conditions is well documented, estimates of
20 patient numbers and their distribution across subgroups of interest are scarce in the
21 literature.^{24,33,35-37} Other research groups have developed similar models for such predictive
22 purposes.^{34,38}

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Estimates of numbers of patients in groups of interest produced by epidemiologic models
can inform budget impact analysis and support planning of healthcare services by limiting
the uncertainty associated with identifying patient numbers eligible for a given treatment.^{20,34}
This contribution can be especially relevant for conditions that have low frequency, and
hence are difficult to study, but could qualify for orphan designation and the corresponding
support for research and treatment development.^{24,39}

The model used has a complex structure and requires a large number of parameters. This is
the consequence of modelling a complex condition whose treatment is also complex. A
positive aspect is that the reported estimates provide a detailed picture of the patient
population with MM. On the other hand, complexity is a limitation when it comes to finding
supportive data for the parameters that inform the model. As a consequence, some
parameters are supported by only one or a few sources. This limitation is common to other
modeling studies.²⁴ Some prognostic factors of the condition such as tumor staging or renal
function⁵ were not included separately in the model. One limitation of the model to estimate
the real difference between incident cases and patient mortality is that, by definition, in the
model at equilibrium the number of incident patients with MM is the same as the number of
patients dying from MM and background mortality combined. Using this dynamic model to
look at projections for how the MM patient population will change over time would be of
interest but it is not within the scope of this project.

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3 Further research on the epidemiology of patients with MM will support more robust
4 parameter estimates that can be used in this and other models. Other parameters may
5 become pertinent to modeling prevalence of lines of therapy in patients with MM, which may
6 warrant additional research and model development. Different stratification variables, such
7 as disease stage or new risk classification, may prove important in further research.
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9 Additionally, future real world study results reporting on patient population and
10 subpopulations at different lines of therapy and transitioning across those lines will contribute
11 data to validate the model outcomes.
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16 In summary, the reported epidemiologic model estimates the size and the distribution of the
17 patient population with MM stratified by subgroups of interest and the patients transitioning
18 from one line of therapy to the next, corresponding to multiple disease relapses or treatment
19 intolerances, and increasing burden as the condition progresses. This information can be
20 used to assess the number of patients who could benefit from new MM therapies and their
21 corresponding budgetary impact.
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TABLES

Table 1. Model Base Case Parameter Values for the US

Parameter	Base Case	Units	Reference
Population			
Population size	316,128,839	persons	27
Background death rate of adults 40-64 years	0.008	proportion per year	28
Background death rate of adults ≥65 years	0.060	proportion per year	28
MM epidemiology			
Incidence of MM	0.000061	proportion per year	5,26
Proportion patients <65 years at MM diagnosis	38.00%	%	5,26
Proportion in high cytogenetic risk group at MM diagnosis	35.00%	%	5,6,9,40-46
Proportion symptomatic at MM diagnosis	87.50%	%	47-50
Median duration for progression from asymptomatic (smoldering) MM to symptomatic MM	58	months	47,48,50
MM-related death rate while asymptomatic (smoldering), <65 years, MM patients	0.0040	proportion per year	42,50
MM-related death rate while asymptomatic (smoldering), ≥65 years, MM patients	0.0400	proportion per year	42,50
MM-related death rate while symptomatic MM before treatment initiation, <65 years	0.0045	proportion per year	assumption
MM-related death rate while symptomatic MM before treatment initiation, ≥65 years	0.0450	proportion per year	assumption
Treatment initiation			
Time from diagnosis of symptomatic MM to treatment initiation	0.500	months	42,45
Proportion <65 years initiating SCT pathway	30.00%	%	51,52
Proportion ≥65 years initiating SCT pathway	10.00%	%	51,52
MM-related death rates on treatment pathway			
Patients <65 years, standard/low cytogenetic risk, non-SCT treatment pathway: treatment line 1	0.10	Proportion per year	11,53
MM-related death rate ratio: SCT compared to non-SCT	0.70	None (ratio)	9,54
MM-related death rate ratio: ≥65 year age group compared to <65 year age group	1.50	None (ratio)	9,49,52,55,56
MM-related death rate ratio: high cytogenetic risk group compared to standard/low cytogenetic risk group	2.25	None (ratio)	6,40,41,46,54,57-59

Parameter	Base Case	Units	Reference
MM-related death rate ratio: 2nd line compared to 1st line treatment	1.00	None (ratio)	1,15,60
MM-related death rate ratio: 3rd line compared to 2nd line treatment	1.10	None (ratio)	1,15,60
MM-related death rate ratio: 4th line compared to 3rd line treatment	1.15	None (ratio)	1,15,60
MM-related death rate ratio: 5th line compared to 4th line treatment	1.20	None (ratio)	1,15,60
MM-related death rate ratio: 6th line compared to 5th line treatment	1.25	None (ratio)	1,15,60
MM-related death rate ratio: 7th line compared to 6th line treatment	1.40	None (ratio)	1,15,60
MM-related death rate ratio: 8th line compared to 7th line treatment (applicable to subsequent lines, up to 17, compared to the previous line)	1.50	None (ratio)	1,15,60
Time to next line of treatment			
Treatment duration on treatment line 1* (patients <65 years, standard/low cytogenetic risk, SCT pathway)	35.0	Months	5,40,42,46,49,58,59,61,62
Time to next line of treatment: n+1th line compared to nth line treatment	0.80	None (ratio)	41
Time to next line of treatment: ≥65 year age group compared to <65 year age group	0.75	None (ratio)	63,64
Time to next line of treatment: high cytogenetic risk group compared to standard/low cytogenetic risk group	0.45	None (ratio)	6,40,41,43,46,57,58
Treatment duration on treatment line 1* (patients <65 years, standard/low cytogenetic risk, non-SCT pathway)	27.0	Months	42,43,49,65,66

* Defined as time between initiating treatment line 1 and initiating treatment line 2.

Table 2. Estimated Total Number of Prevalent MM Cases in the US by Line of Therapy and Patient Subgroups of Interest

Treatment Line	Total	SCT Eligibility				SCT Non Eligibility			
		Low/Standard Cytogenetic Risk		High Cytogenetic Risk		Low/Standard Cytogenetic Risk		High Cytogenetic Risk	
		<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs
Line 1	23,629	3,375	1,196	825	306	6,000	8,351	1,465	2,111
Line 2	15,350	2,287	742	562	198	4,017	5,201	985	1,358
Line 3	10,249	1,584	477	390	132	2,746	3,346	676	898
Line 4	6,966	1,114	314	274	89	1,901	2,201	469	604
Line 5	4,786	790	210	193	61	1,325	1,469	328	410
Line 6	3,301	561	142	136	42	925	987	229	279
Line 7	2,252	394	95	95	28	637	657	158	188
Line 8	1,501	271	62	65	19	428	427	106	123
Line 9	971	181	40	43	12	279	269	69	78
Line 10	605	116	25	27	7	175	164	43	48
Line 11	363	72	15	17	4	106	95	26	28
Line 12	206	43	8	10	2	61	52	15	15
Line 13	111	24	5	5	1	33	27	8	8
Line 14	54	12	2	3	0	17	13	4	3
Line 15	23	6	1	1	0	8	5	1	1
Line 16	7	2	0	0	0	3	2	0	0
Line 17 and greater	2	1	0	0	0	1	0	0	0
Total patients on treatment	70,375	10,833	3,333	2,646	901	18,662	23,266	4,582	6,152

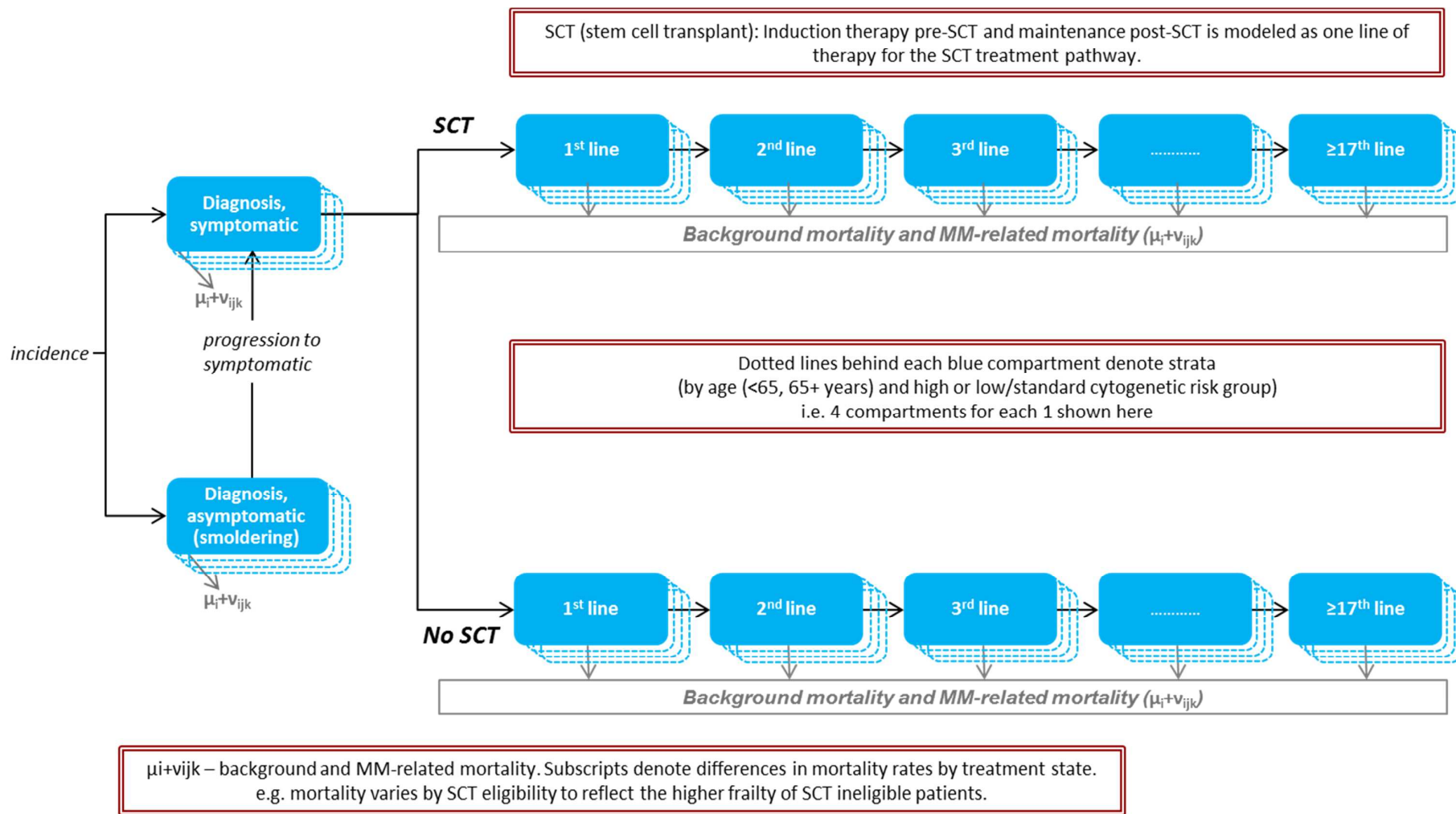
Table 3. Number of MM Patient Transitions in the US by Line of Therapy and Patient Subgroups of Interest

New Treatment Regimens		SCT Eligibility				SCT Non Eligibility			
		Low/standard cytogenetic risk		High cytogenetic risk		Low/standard cytogenetic risk		High cytogenetic risk	
		<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs	<65 yrs	≥65 yrs
Line 1	18,689	1,418	742	763	399	3,309	6,680	1,781	3,597
Line 2	14,423	1,155	545	627	309	2,661	4,928	1,440	2,758
Line 3	11,677	979	422	533	250	2,227	3,837	1,210	2,219
Line 4	9,715	848	339	463	208	1,902	3,085	1,038	1,832
Line 5	8,225	746	278	406	176	1,646	2,535	900	1,538
Line 6	7,038	662	233	358	150	1,433	2,113	786	1,303
Line 7	6,047	589	196	316	129	1,250	1,773	686	1,108
Line 8	5,131	518	164	275	109	1,075	1,472	590	928
Line 9	4,241	444	134	234	90	900	1,192	493	754
Line 10	3,396	370	107	193	72	730	934	399	591
Line 11	2,616	298	82	153	55	571	704	310	443
Line 12	1,920	230	60	116	40	427	505	229	313
Line 13	1,334	169	42	84	28	303	342	160	206
Line 14	862	117	28	57	17	202	215	103	123
Line 15	511	76	17	35	10	125	124	60	64
Line 16	267	45	9	19	5	70	63	30	26
Line 17 and greater	167	40	5	12	1	52	37	14	6
Total transitions	96,259	8,704	3,403	4,644	2,048	18,883	30,539	10,229	17,809

Table 4. Median and Credible Intervals of the Number of MM Patients and Number of Patient Transitions by Line of Therapy in the US

Treatment Lines	Number of MM Patients			Number of Patient Therapy Line Transitions		
	Median	95% Credible Interval		Median	95% Credible Interval	
		Lower	Upper		Lower	Upper
Line 1	23,584	22,236	25,029	18,696	18,558	18,817
Line 2	15,346	13,845	16,760	14,415	13,489	15,176
Line 3	10,234	8,908	11,515	11,658	10,348	12,811
Line 4	6,955	5,847	8,053	9,699	8,223	11,085
Line 5	4,778	3,893	5,685	8,214	6,670	9,744
Line 6	3,298	2,609	4,038	7,028	5,483	8,630
Line 7	2,252	1,723	2,850	6,042	4,531	7,669
Line 8	1,502	1,106	1,975	5,131	3,695	6,766
Line 9	975	687	1,338	4,244	2,919	5,872
Line 10	612	409	886	3,403	2,223	4,964
Line 11	369	232	568	2,629	1,612	4,075
Line 12	213	125	353	1,937	1,107	3,273
Line 13	116	63	210	1,350	714	2,487
Line 14	59	30	119	878	428	1,788
Line 15	28	13	63	525	236	1,212
Line 16	12	5	32	279	120	719
Line 17 and greater	9	5	22	192	77	523

Figure 1. Model to Assess Prevalence of Patients with MM at Different Treatment Lines



Appendix A: Model Parameters and Equations

Table A - 1. Model Parameters

	Description
β_u	Incidence of MM (all stages) for demographic group u (proportion/year)
P	Proportion of MM patients that is symptomatic at diagnosis*
K	Progression rate of asymptomatic MM to symptomatic*
α	Progression rate of symptomatic MM to treatment* (per year)
μ_u	Background death rate for demographic group u (per year)
θ_u	MM-related death rate for demographic group u as yet untreated, asymptomatic (per year)
φ_u	MM-related death rate for demographic group u as yet untreated, symptomatic MM (per year)
ψ_{uz}	Proportion symptomatic initiating first line of treatment within demographic group u who are assigned to each treatment pathway ¹ z
ν_{uzw}	MM-related death rate for demographic group u on treatment pathway z and line of therapy w (per year)
$1/\gamma_{uzw}$	Time to next line of treatment for patients in demographic group u on treatment pathway z and line of therapy w (years)

MM = multiple myeloma

*Assumption that this parameter has the same value regardless of risk and age group.

†Demographic groups= <65 years and low/standard cytogenetic group; ≥65 years and low/standard cytogenetic group; <65 years and high cytogenetic group; ≥65 years and high cytogenetic group;

¹Treatment pathways= at least one SCT is performed; no SCT is performed

Model Equations

The model initiates upon diagnosis with MM. Individuals flow between states in the model.

Patients may be diagnosed with asymptomatic (A_u) or symptomatic (S_u) MM, where u is demographic group (currently four groups according to age group and cytogenetic risk

group). Asymptomatics (A_u) receive new cases with proportion $(1 - P)$ of the total

incidence β_u . Individuals become symptomatic at rate K . Symptomatics (S_u) receive a

proportion P of the incident cases directly and initiate treatment at a rate α with proportions

ψ_{uz} in each of the two treatment pathways. Asymptomatics experience MM-related

mortality at rate θ_u whilst symptomatics experience MM-related mortality at rate φ_u .

Each treatment state is represented by T_{uzw} , where u is demographic group, z is treatment pathway (currently: 1 = at least one SCT is performed; 2 = no SCT is performed), and w is line of therapy). Treated cases progress through 17 lines of treatment (index w from 1 to 17) at rate γ_{uzw} and experience MM-related mortality at rate ν_{uzw} . Asymptomatic, symptomatic, and treated individuals are all subject to background death rate μ_u .

Line of therapy is understood as one or more cycles of a planned treatment program (single agent, combination therapy, or sequence of treatments administered as planned). A new line of therapy is assumed to start when a planned treatment program is modified to include other drugs as a result of disease progression, relapse or toxicity, or when a planned period off-treatment is interrupted because additional treatment for MM is required.²⁵

For patients undergoing SCTs, first-line treatment usually represents the package of treatments that are required for an SCT procedure (i.e., includes induction therapy as well as SCT). A second SCT is recorded as second-line treatment. In some cases, a first SCT could also take place at a line of therapy greater than line 1.

Asymptomatic MM:

$$\frac{dA_u}{dt} = \beta_u (1 - P) - A_u(K + \mu_u + \theta_u)$$

Where $u = 1...4$

Symptomatic MM, untreated:

$$\frac{dS_u}{dt} = \beta_u P + A_u K - S_u (\alpha + \mu_u + \phi_u)$$

Where $u = 1...4$

MM treatment stages

First-line treatment:

$$\frac{dT_{uzw}}{dt} = S_u \alpha \psi_{uz} - T_{uzw} (\mu_u + \nu_{uzw} + \gamma_{uzw})$$

Where $u = 1...4$; $z = 1, 2$; $w = 1$

Subsequent treatment lines ($w > 1$):

$$\frac{dT_{uzw}}{dt} = T_{uzw-1}\gamma_{uzw-1} - T_{uzw}(\mu_u + \nu_{uzw} + \gamma_{uzw})$$

Where $u = 1...4$; $z = 1,2$; $w = 2...20$

The values of MM-related death rates and MM time to next treatment (TTNT) durations for each MM treatment state are related to a baseline MM-related death rate and two baseline time to next line of treatment values:

- The baseline MM-related death rate is for MM patients on the first line of treatment, on the non-SCT pathway, < 65 years of age and in the low/standard cytogenetic risk group.
- MM-related death rates for all other treated MM health states are derived from the baseline rate using the following death rate relative risks (RR):
 - RR for patients ≥ 65 years compared to < 65 years
 - RR for patients in the high cytogenetic risk group compared to the low/standard-risk group
 - RR for patients on the SCT pathway compared to those on the non-SCT pathway
 - RR for patients on the $n+1^{\text{th}}$ line of treatment compared to those on the n^{th} line of treatment
- The baseline TTNT values are for MM patients on the first line of treatment, < 65 years of age and in the low cytogenetic risk group. There is one baseline value for patients on the SCT treatment pathway and another value for patients on the non-SCT pathway.
- TTNT values for all other treated MM health states are derived from the baseline values using the following TTNT RRs:
 - RR for patients ≥ 65 years compared to < 65 years
 - RR for patients in the high cytogenetic risk group compared to the low/standard-risk group
 - RR for patients on the $n+1^{\text{th}}$ line of treatment compared to those on the n^{th} line of treatment

Appendix B: Probabilistic Sensitivity Analysis

Based on model influence diagram face validity discussions, the parameters expected to influence model output selected for inclusion in the PSA were:

Population inputs:

1. Proportion patients < 65 years at MM diagnosis (**prop_young in Figure B-1 below**)
2. Proportion in low/standard cytogenetic risk group at MM diagnosis (**prop_lowrisk**)
3. Proportion symptomatic at MM diagnosis (**prop_sympt**)

Treatment inputs:

4. Proportion < 65 years initiating SCT pathway (**prop_less65_SCT**)
5. Baseline MM-related death rate; patients < 65 years, low/standard cytogenetic risk, non-SCT treatment pathway: treatment line 1 (**baseline MM death rate**)
6. MM-related death rate ratio: ≥ 65 year age group compared to < 65 year age group (**RR_mort_oldage**)
7. MM-related death rate ratio: high cytogenetic risk group compared to low/standard cytogenetic risk group (**RR_mort_highrisk**)

We used the LHS method³⁰. Running the model with model parameters for the baseline country produced the PRCCs shown in **Figure B-1**. The magnitude of each PRCC quantifies the importance of each parameter, with the sign of the PRCC value indicating the specific qualitative relationship between the input and the output variable: positive values of PRCC imply that increasing the value of the input variable will lead to an increase in the output variable (number of forecasted patients with MM). As a general rule, parameters with the largest influence are defined as those with a PRCC greater than 0.4 or less than -0.4.

Figure B-1 shows that the parameters with the greatest influence on the model outcomes for the baseline country are all the MM-related death rates ratios [5-7 from list above], with the relationship being negative. Additionally, the proportion of patients in low cytogenetic risk group [2] and the proportion symptomatic [3] are shown to have a great positive influence on model outcomes. The observed low PRCCs for the proportion of young patients [1] and the proportion of young patients initiating SCT [4] imply that their influence on the model outcomes is expected to be low.

Figure B-2. Partial Rank Correlation Coefficients for Key Model Parameters

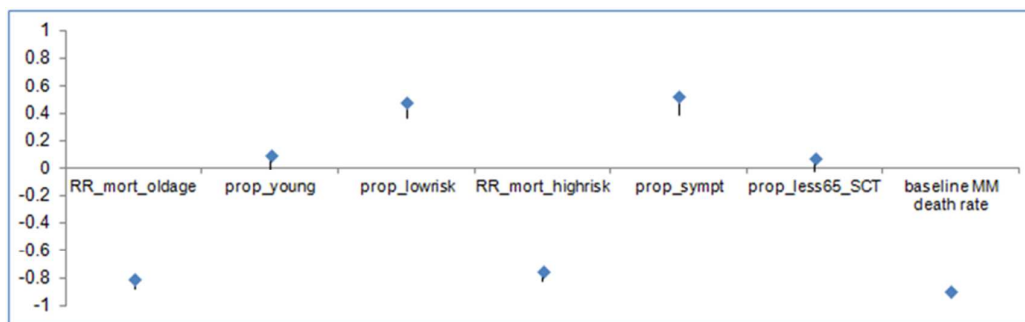


Table B - 2. Probabilistic Sensitivity Analysis Parameters

Parameter (unit)	Base Case	Standard Error	Distribution
Proportion patients <65 years at MM diagnosis	38.00%	1.80%	Beta
Proportion in high cytogenetic risk group at MM diagnosis	35.00%	2.50%	Beta
Proportion symptomatic at MM diagnosis	87.50%	1.50%	Beta
Proportion <65 years initiating SCT pathway	85.00%	2.5%	Beta
Proportion patients <65 years, standard/low cytogenetic risk, non-SCT treatment pathway: treatment line 1	0.100	0.010	Gamma
MM-related death rate ratio: ≥65 year age group compared to <65 year age group	1.50	0.15	Lognormal
MM-related death rate ratio: high cytogenetic risk group compared to standard/low cytogenetic risk group	2.25	0.25	Lognormal

Appendix C: PSA Results for Subgroups of Interest

Table C - 1. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, Low/Moderate Cytogenetic Risk and Eligible for SCT.

Treatment Lines	Number of Patients			Number of Patient Transitions		
	Median	95% Credible Interval		Median	95% Credible Interval	
		Lower	Upper		Lower	Upper
Line 1	3,357	2,792	4,030	1,414	1,177	1,693
Line 2	2,270	1,882	2,773	1,150	956	1,380
Line 3	1,570	1,284	1,929	972	806	1,187
Line 4	1,099	887	1,363	840	687	1,032
Line 5	774	618	976	734	593	911
Line 6	548	431	702	646	515	814
Line 7	384	297	503	570	449	732
Line 8	263	200	351	499	386	653
Line 9	175	129	240	425	324	568
Line 10	113	81	159	353	261	485
Line 11	70	49	102	283	204	398
Line 12	42	28	64	218	151	320
Line 13	24	15	39	160	107	247
Line 14	13	8	22	111	70	182
Line 15	7	4	12	72	43	128
Line 16	3	2	6	43	24	83
Line 17 and greater	5	4	7	43	21	95

Table C - 2. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥ 65 Years, Low/Moderate Cytogenetic Risk and Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	Median	95% Credible Interval		Median	95% Credible Interval	
		Lower	Upper		Lower	Upper
Line 1	1,195	1,080	1,316	744	682	798
Line 2	740	643	846	545	492	600
Line 3	475	396	561	421	366	482
Line 4	314	248	383	338	282	400
Line 5	210	159	265	279	221	341
Line 6	142	102	186	233	176	294
Line 7	95	65	129	197	141	257
Line 8	63	40	90	165	112	223
Line 9	41	24	61	135	86	193
Line 10	25	14	41	108	63	163
Line 11	15	8	27	83	45	135
Line 12	9	4	17	62	30	108
Line 13	5	2	10	43	19	83
Line 14	3	1	6	29	11	61
Line 15	2	1	4	17	6	42
Line 16	1	1	2	10	3	26
Line 17 and greater	4	4	4	4	3	11

Table C - 3. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, High Cytogenetic Risk and Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	822	631	1,033	759	608	940
Line 2	561	409	723	624	479	785
Line 3	388	265	528	532	389	687
Line 4	271	175	386	461	314	627
Line 5	192	116	282	402	260	572
Line 6	136	76	208	355	214	522
Line 7	95	49	153	315	176	480
Line 8	66	30	111	274	141	440
Line 9	44	18	79	235	108	398
Line 10	28	11	56	194	80	352
Line 11	18	6	38	154	57	306
Line 12	11	3	25	117	38	258
Line 13	6	2	17	85	23	209
Line 14	3	1	11	58	13	165
Line 15	2	1	6	37	7	123
Line 16	1	1	4	21	3	85
Line 17 and greater	4	4	5	8	3	42

Table C - 4. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥ 65 Years, High Cytogenetic Risk and Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	305	252	362	400	344	457
Line 2	199	148	247	308	254	366
Line 3	133	89	174	251	186	312
Line 4	90	55	124	209	140	274
Line 5	62	34	90	177	108	243
Line 6	43	22	66	151	84	220
Line 7	29	14	47	130	67	200
Line 8	20	8	34	110	51	179
Line 9	13	5	24	91	37	160
Line 10	8	3	17	73	26	140
Line 11	5	2	12	56	17	119
Line 12	3	1	8	41	10	98
Line 13	2	1	5	28	6	78
Line 14	1	1	3	18	3	59
Line 15	1	1	2	10	2	41
Line 16	1	1	2	5	1	26
Line 17 and greater	2	2	2	3	2	16

Table C - 5. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, Low/Moderate Cytogenetic Risk and Not Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	6,011	5,350	6,686	3,309	2,967	3,675
Line 2	4,024	3,519	4,526	2,667	2,373	2,966
Line 3	2,757	2,373	3,136	2,232	1,951	2,510
Line 4	1,906	1,614	2,211	1,911	1,644	2,173
Line 5	1,330	1,106	1,567	1,651	1,398	1,915
Line 6	929	760	1,118	1,439	1,196	1,696
Line 7	641	512	792	1,256	1,027	1,512
Line 8	430	335	549	1,081	864	1,336
Line 9	281	211	371	905	704	1,154
Line 10	176	129	242	735	553	971
Line 11	107	74	154	574	418	789
Line 12	62	41	93	431	299	622
Line 13	34	21	55	307	204	464
Line 14	18	10	30	205	128	331
Line 15	9	5	16	128	75	221
Line 16	4	2	8	72	39	137
Line 17 and greater	5	4	8	61	29	133

Table C - 6. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥ 65 Years, Low/Moderate Cytogenetic Risk and Not Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	8,341	7,522	9,219	6,689	6,133	7,180
Line 2	5,182	4,464	5,969	4,919	4,435	5,436
Line 3	3,338	2,723	4,001	3,820	3,290	4,400
Line 4	2,202	1,702	2,735	3,074	2,508	3,684
Line 5	1,472	1,078	1,897	2,533	1,958	3,146
Line 6	989	687	1,324	2,114	1,549	2,726
Line 7	660	430	924	1,773	1,231	2,375
Line 8	432	259	636	1,475	962	2,065
Line 9	273	152	429	1,199	720	1,766
Line 10	167	84	282	941	522	1,478
Line 11	97	44	180	709	358	1,201
Line 12	54	22	111	508	229	940
Line 13	29	10	65	344	136	703
Line 14	14	4	37	216	74	495
Line 15	7	2	19	122	36	323
Line 16	3	1	9	61	15	188
Line 17 and greater	3	3	7	33	7	130

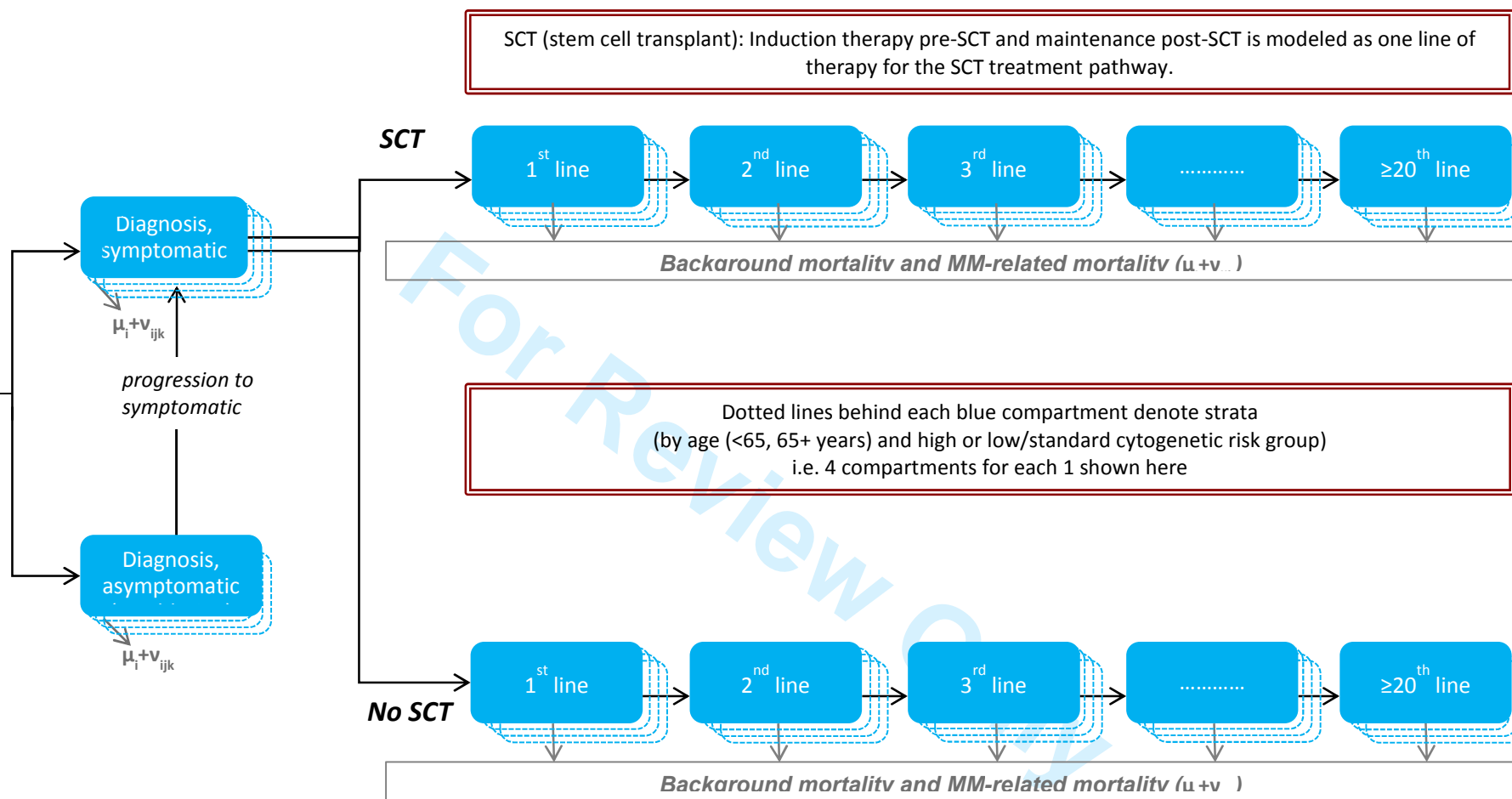
Table C - 7. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients <65 Years, High Cytogenetic Risk and Not Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	1,460	1,194	1,733	1,779	1,514	2,059
Line 2	979	747	1,220	1,436	1,174	1,705
Line 3	674	476	877	1,203	919	1,500
Line 4	470	305	641	1,035	731	1,347
Line 5	329	201	467	902	586	1,230
Line 6	230	131	345	788	482	1,118
Line 7	159	82	252	688	391	1,030
Line 8	107	49	183	591	305	938
Line 9	70	29	130	496	228	845
Line 10	45	16	91	402	162	748
Line 11	27	8	62	314	108	644
Line 12	16	4	41	232	67	540
Line 13	9	2	26	163	39	430
Line 14	5	1	16	107	20	330
Line 15	2	1	10	64	9	238
Line 16	1	1	6	34	4	153
Line 17 and greater	3	3	6	6	2	43

Table C - 8. Median and Credible Intervals of the Number of Patients and Number of Patient Transitions, by Line of Therapy: Patients ≥ 65 Years, High Cytogenetic Risk and Not Eligible for SCT

Treatment Lines	Number of Patients			Number of Patient Transitions		
	95% Credible Interval			95% Credible Interval		
	Median	Lower	Upper	Median	Lower	Upper
Line 1	2,106	1,718	2,512	3,597	3,090	4,111
Line 2	1,360	989	1,709	2,747	2,241	3,277
Line 3	902	580	1,205	2,217	1,612	2,787
Line 4	606	355	857	1,836	1,181	2,454
Line 5	413	219	619	1,540	903	2,177
Line 6	281	136	448	1,308	693	1,963
Line 7	189	82	324	1,109	537	1,770
Line 8	125	47	231	926	401	1,590
Line 9	80	26	163	754	284	1,397
Line 10	49	13	111	591	189	1,210
Line 11	29	7	75	442	117	1,005
Line 12	16	3	50	312	67	814
Line 13	9	2	32	204	34	629
Line 14	4	1	20	119	15	452
Line 15	2	1	12	60	6	292
Line 16	1	1	6	22	2	152
Line 17 and greater	1	1	2	4	1	39

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μ_i+v_{ijk} – background and MM-related mortality. Subscripts denote differences in mortality rates by treatment state. e.g., mortality varies by SCT eligibility to reflect the higher frailty of SCT ineligible patients.



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26 Representatives of Onyx Pharmaceuticals, an Amgen subsidiary, participated in this project
27 providing scientific advise, reviewing the model and commenting on the manuscript.
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34 Patient population with multiple myeloma and transitions across different lines of therapy in the US:
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Evie Merinopoulou has been an employee of Evidera and served as paid consultant to Onyx Pharmaceuticals for the work in this study.

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This work was funded by Onyx Pharmaceuticals. Leighton P was employed by Evidera and served as consultant to Onyx Pharmaceuticals.

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8. Manuscript title (first six words are sufficient)

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