Supplemental Materials

Methods

Some of these treatments, i.e., ixazomib,\(^1\) were sufficiently new that long-term overall survival data had yet to be gathered at the time of the analysis. In the case of pomalidomide, the available trial evidence does not include a comparison to Vd or Rd.\(^2\) While the IxaRd triplet significantly improved PFS compared with Rd in the TOURMALINE (NCT-01564537) trial \(^3\), OS results were immature at the time of analysis and were therefore not calibrated into the model. Similarly, the OS results for the CASTOR trial (NCT-02136134)—which compared DaraVd versus Vd—\(^4\) were also immature and therefore omitted from our model.

Income estimation

Given the relatively small prevalence of multiple myeloma in the MEPS dataset, the average annual income for all survey respondents > 18 years of age who had a diagnosis of any type of cancer was used \(^5\). This was then weighted for our population based on the incidence age distribution for MM patients from the SEER data over this same time period. Further, survey weights and primary sampling units provided with the MEPS data were applied to account for the complex survey design \(^6\).

Adjustments

Because not every patient diagnosed with MM in SEER actually received treatment (e.g., some patients had smoldering or indolent myeloma) and SEER does not contain information on relapse, the survival in SEER may be higher than in a treated and/or RRMM population. Therefore, we implemented the following aging adjustment to estimate survival for the RRMM patient population:

1. Use a log-normal distribution with mean and standard deviation disease duration values based on the ASPIRE KRd arm patient population characteristics (mean 45.1 months, s.d. 35.22) to randomly sample and assign a simulated treatment duration values to patients in the SEER sample.

2. Age SEER patients:
   2.1. Increase patients’ age and year of diagnosis by their simulated disease duration,
   2.2. Create a variable that indicates the calendar year at the increased diagnosis year, i.e., the year they began treatment for RRMM,
   2.3. Decrease patient’s survival and censoring times by their (simulated) disease duration
   2.4. Remove patients with negative survival or censoring times from the analysis set and estimated survival.
3. Estimate survival model

Because SEER lacks information on which specific therapies patients utilize, we were only able to directly estimate the average impact of the introduction of bortezomib and lenalidomide on the entire RRMM population. To estimate the impact of bortezomib and lenalidomide on survival among treated patients, we used the Truven MarketScan® claims data to calculate the share of RRMM patients receiving treatment by these therapies. We inflated the survival gain in the overall SEER patient (intent to treat) population by this fraction, which we estimated to be approximately 50% of the RRMM patient population. The share of MM patients utilizing lenalidomide or bortezomib was estimated among those MM patients using either drug in the 12 months following the initiation of therapy.

Novel Survival Curve Calibration

Modelling the survival benefits attributable to novel therapies introduced in 2015 required predicted survival curves for patients diagnosed with RRMM in 2015. To estimate these curves, we used the hazard ratio estimates from the Cox proportional hazards model described above, and predicted the survival curve for the last year of the SEER data, 2013 based on the year fixed effects described above. This curve was used as a proxy for survival in 2015.

The survival benefits reported in recent clinical trials (i.e., POLLUX [NCT-02076009], ELOQUENT-2 [NCT-01239797], ASPIRE, and ENDEAVOR [NCT-01568666]) were applied to the SEER estimated 2015 survival curve. The SEER estimated coefficient (or log of the HR) on post-2012, $\ln(HR_{SEER})$, was inflated by the inflation factor, $\alpha$, to equal the coefficient on the treated arm observed in the relevant clinical trial, $\ln(HR_{CT})$. That is, we solved for $\alpha$ such that:

$$\alpha \times \ln(HR_{SEER}) = \ln(HR_{CT})$$

The survival calibration generated predicted survival curves for RRMM patients diagnosed in 2015 who were treated with (i) KRd, (ii) Kd, (iii) EloRd, and (iv) DaraRd. The incremental survival gain associated with the introduction of novel regimens is the difference between the aggregate survival estimate of (i), (ii), (iii), and (iv) and the survival curve associated with lenalidomide or bortezomib estimated in the survival analysis, respectively. These predicted survival curves were also compared to the estimated survival curve for the general population matched to the ENDEAVOR population.

Cohort Size Calculation

We assumed 90% of incident MM cases are active MM, and 10% are smouldering or inactive MM cases that eventually progress to active disease. The lenalidomide and bortezomib RRMM cohort estimates were further scaled by the approximate proportion of screened patients eligible for trial participation (80%) in the POLLUX (DRd), ASPIRE (KRd), and ELOQUENT-2 (EloRd) trials because this information was not available for the pivotal lenalidomide and bortezomib trials. Based on studies by MacEwan et al (2016) and Arikian et al (2015) we estimate that 49.6% of the incident MM patients—13,678 ($=0.496\times[0.9\times32,110]+[0.1\times0.1\times32,110]$) patients—in
any given year will progress to receive second-line treatment, i.e., become RRMM patients\textsuperscript{14,15,1}\textsuperscript{1}. The final annual incident RRMM cohort size for lenalidomide/bortezomib totalled 11,585 (=0.496×0.8×[(0.9×32,110) + (0.1×0.1×32,110)]). The carfilzomib, daratumumab, and elotuzumab RRMM cohort estimates were further scaled by the proportion of screened patients who were eligible for each trial, i.e., 83\% (ASPIRE), 85\% (ENDEAVOR), 81\% (POLLUX), and 85\% (ELOQUENT-2), respectively\textsuperscript{8,11,16,17}.

**Results**

\textsuperscript{1} In MacEwan et al. (2016) 1,797 of the 3,626 (49.6\%) MM patients who underwent first line treatment went on to receive second line treatment, i.e., relapsed, and in Arikian et al. (2015) the ratio of patients in second line treatment to patients in first line treatment was 0.479 (= 1361/2843) [44,45].
### Supplemental Table 1. Cox Proportional Hazards Survival Model Hazards Ratios

|                           | Odds ratio         |
|---------------------------|--------------------|
| **Year of Dx: 1999-2009** | 0.804              |
|                           | (0.758)            |
| **Year of Dx: 2004-2011** | 0.768***           |
|                           | (6.00e-08)         |
| **Year of Dx: 2012**      | 0.646              |
|                           | (0.540)            |
| **Age at Dx**             | 1.002              |
|                           | (0.719)            |
| **(Age at Dx)^2**         | 1.000***           |
|                           | (4.03e-09)         |
| **Female**                | 0.891***           |
|                           | (0)                |
| **Married**               | 0.957***           |
|                           | (0.00441)          |
| **Black**                 | 1.053***           |
|                           | (0.00588)          |
| **Asian, PI, or Alaska native** | 0.957   |
|                           | (0.172)            |
| **Hispanic**              | 1.030              |
|                           | (0.475)            |
| **Uninsured**             | 1.460***           |
|                           | (0.00139)          |
| **Medicaid**              | 1.348***           |
|                           | (1.86e-06)         |
| **Unknown insurance**     | 1.015              |
|                           | (0.665)            |
| **Cancer diagnosis sequence fixed effect** | Yes |
| **Year fixed effects**    | Yes                |
| **Observations**          | 32,269             |

Notes: p-values in parentheses; *** p<0.01, ** p<0.05, * p<0.1. Private/commercial insurance is the reference category for health insurance type. White is the reference race category.
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