METHODS

Hazard Ratio NMA
- This was the method described for a Bayesian NMA by Woods et al. (2015).
- Models were fitted with fixed and random effects.
- Hazard ratios were applied to a model fitted to the reference treatment for the study that contained the main treatment under investigation to give predictions for the other treatments.
- Because of the presence of long-term survivors, hazard ratios were restricted to be greater than zero and were provided on a hazard ratio scale corrected from the general population.
- Model selection was based on deviance information criteria.

Reconstructed Patient-Level Data NMA
- This was the method described by Jansen (2011).
- Patient-level data were reconstructed as described by Bujkic et al. (2013).
- A variety of fixed and ordered or fractional polynomials with different power functions and models with two- and three-knot fractional polynomial and fixed slopes, and constant scale and variable slopes were considered.
- Second-order fractional polynomial models gives the best fit but flattened before reaching zero. For the first case study, hazard rates were estimated after follow-up through the use of a flexible spline-based model fitted to an external 5-year data set. After this point, hazard rates from a model fitted to general population data were used. For the second study, computer-simulated data were not available; instead the reference treatment predictions from the NMA were used to anchor the distributions.
- Model selection was based on deviance information criteria.

THE NETWORK OF EVIDENCE

Table 1: Possible Bias in the Networks of Evidence for the Two Case Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Endpoint</th>
<th>Number of Studies</th>
<th>Number of Studies Without Kaplan-Meier Estimates</th>
<th>Significant Nonproportional Hazard Rates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Case Study 1</td>
<td>Overall survival</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Case Study 2</td>
<td>Overall survival</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>

RESULTS

Case Study

Figures 3 and 4 present the results from the fractional polynomial NMA:
- Figure 3 shows the predicted overall survival by treatment.
- Figure 4 shows the predicted overall survival by treatment.
- Table 1 presents the number of studies in the network that did not report Kaplan-Meier estimates and the significant nonproportional hazard ratios.
- Figure 5 and 6 present the predicted overall survival by treatment.
- Figures 5 and 6 provide further evidence of nonproportional hazard ratios (some lines are not horizontal).
- Table 1 presents the number of studies in the network that did not report Kaplan-Meier estimates.
- Significant nonproportional hazard ratios are apparent in both case studies.

CONCLUSIONS

- Survival estimates from hazard ratio NMA are sensitive to which trial is selected to supply the reference treatment.
- Where networks of evidence contain a large number of studies, there is a high probability that one or more comparisons may contain nonproportional hazard ratios.
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- Hazard estimates from hazard ratio NMA are sensitive to which trial is selected to supply the reference treatment.
- When parts of the reference cohort offset Kaplan-Meier data, we can rely on the fractional polynomial results.
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- Significant nonproportional hazard ratios are apparent in both case studies.

REFERENCES