Overall survival for cetuximab plus irinotecan: stage 1

We have identified four methods to estimate overall survival for cetuximab plus irinotecan, each of which has strengths and weaknesses.

Method A

This method is very similar to method A for the estimation of progression-free survival in *Appendix 14*. We first estimate the median overall survival for patients with *KRAS* WT status on cetuximab monotherapy in the BOND RCT[49] as:

median overall survival of 9.5 months for patients with *KRAS* WT status taking cetuximab + best supportive care in the RCT of cetuximab + best supportive care vs best supportive care[45]
× median overall survival of 6.9 months for all patients (*KRAS* WT and mutant status) taking cetuximab + best supportive care in the BOND RCT[49]
/ median overall survival of 6.1 months for all patients (*KRAS* WT and mutant status) taking cetuximab + best supportive care in the RCT of cetuximab + best supportive care vs best supportive care[37]
= 10.7 months [Equation 22]

Next, we estimate the median overall survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan as:

median overall survival of 8.6 months for all patients (*KRAS* WT and mutant status) taking cetuximab + irinotecan in the BOND RCT[49]
× [estimated median overall survival of 10.7 months for patients with *KRAS* WT status taking cetuximab + best supportive care in the BOND RCT
/ median overall survival of 6.9 months for all patients (*KRAS* WT and mutant status) taking cetuximab + best supportive care in the BOND RCT][49]
= 13.4 months [Equation 23]

Next, we adjust our estimate of the median overall survival of 13.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan for the purposes of the indirect comparison, as follows:

Estimated modelled median overall survival for patients with *KRAS* WT status taking cetuximab + irinotecan
= estimated median overall survival of 13.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab + irinotecan
× (modelled median overall survival of 9.0 months for *KRAS* WT people taking cetuximab + best supportive care
/ estimated median overall survival of 10.7 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab + best supportive care)
= 11.3 months [Equation 24]

However, the problem with this step in the calculation is that there was extensive crossover: approximately 50% of patients randomised to cetuximab plus best supportive care crossed over to cetuximab plus irinotecan on disease progression in the BOND RCT. This then unfairly dilutes the overall survival advantage of cetuximab plus irinotecan relative to cetuximab plus best supportive care. Therefore, 11.3 months is probably an underestimate of the median overall survival of patients with *KRAS* WT status on cetuximab plus irinotecan.

Method B

This is very similar to the method used by Merck Serono. Merck Serono estimated overall survival for patients with *KRAS* WT status on cetuximab plus irinotecan by adjusting overall survival for patients with *KRAS* WT status on cetuximab plus best supportive care (taken from the cetuximab plus best supportive care vs best supportive care RCT) by the hazard ratio for overall survival for patients with *KRAS* WT status between those on cetuximab plus irinotecan and those on cetuximab plus best supportive care taken from other sources. Alternatively, Merck Serono quotes a hazard ratio of 0.53 for patients with *KRAS* WT status between cetuximab plus irinotecan and cetuximab plus best supportive care from De Roock and colleagues[48] (p. 72, Merck Serono's submission[69]). The assumption when using hazard ratios from De Roock and colleagues[48] is that very few of the patients on cetuximab plus best supportive care later received cetuximab plus irinotecan on disease progression. Unfortunately, such information is not reported, but Merck Serono states that it estimated the hazard ratio by reading off survival data from the overall survival curves published in De Roock and colleagues.[48]

In method B, we use a very similar method as Merck Serono to estimate overall survival for cetuximab plus irinotecan for patients with *KRAS* WT status for the purposes of the indirect comparison. We estimate the median overall survival for patients with *KRAS* WT status for cetuximab plus irinotecan as:

median overall survival for cetuximab + best supportive care from our model
× (median overall survival for patients with *KRAS* WT status on cetuximab + irinotecan from De Roock and colleagues[48]
/ median overall survival for patients with *KRAS* WT status on cetuximab + best supportive care from De Roock and colleagues[48])
= 9.0 × (10.3/6.2) = 15.0 months [Equation 25]

This method uses the median overall survival for patients with *KRAS* WT status on cetuximab plus best supportive care from De Roock and colleagues,[48] which is uncertain because of the very small sample size (18 patients). Also, this method relies on similarity in baseline characteristics between treatments in De Roock and colleagues[48] given that that the data are retrospective, not randomised. The method also assumes little crossover from cetuximab plus best supportive care to cetuximab plus irinotecan. The estimate of the median overall survival of 15.0 months for *KRAS* WT patients on cetuximab plus irinotecan is therefore very uncertain.

Method C

Here, we estimate that the modelled median overall survival for patients with *KRAS* WT status taking cetuximab plus irinotecan:

= estimated median overall survival of 13.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab + irinotecan (see *Method A*)
× [modelled median progression-free survival of 7.1 months for patients with *KRAS* WT status taking cetuximab + irinotecan (see *Appendix 14*, stage 2 calculations)
/estimated median progression-free survival of 5.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab + irinotecan (see *Appendix 14*, stage 1 calculations)]
= 17.7 months [Equation 26]

This method has the advantage that it does not rely on the highly uncertain data from De Roock and colleagues;[48] however, the disadvantage is that all three quantities in the calculation above are themselves estimates.

Method D

Here, we simply set our estimate of the median overall survival for patients with *KRAS* WT status on cetuximab plus irinotecan in our model equal to that from the BOND RCT, which we estimate in method A as 13.4 months. This has the advantage of simplicity, and the estimate is not affected by confounding due to crossover. However, it has the disadvantage that randomisation is broken, and no adjustment is made for the indirect comparison with other treatments.

In summary, the median overall survival for patients with *KRAS* WT status on cetuximab plus irinotecan for our model is:

- > 11.3 months from method A
- 15.0 months from method B
- 17.7 months from method C
- 13.4 months from method D.

Considering all methods we chose method B because it is closest to the average of all methods, and because it gives a similar mean overall survival for patients with *KRAS* WT status on cetuximab plus irinotecan (see the following section) as estimated by Merck Serono, who used a slightly different method.

Overall survival for cetuximab plus irinotecan: stage 2

This stage is identical to stage 3 in the estimation of progression-free survival (see *Appendix 14*). Given that we have specified the median overall survival for cetuximab plus irinotecan and we assume the same shape parameter, γ, for cetuximab plus irinotecan as for cetuximab plus best supportive care, this then specifies the scale parameter, λ, of the Weibull. This then gives the estimated mean overall survival for cetuximab plus irinotecan of 16.6 months, which is very similar to Merck Serono's estimate of 16.3 months.