## Progression-free survival for cetuximab plus irinotecan: stage 1

We suggest four possible methods for estimating median progression-free survival for patients with *KRAS* WT status on cetuximab plus irinotecan in the BOND RCT.[49] All methods split out the median progression-free survival of 4.1 months for all patients combined (KRAS WT and KRAS mutant status) on cetuximab plus irinotecan in the BOND RCT to obtain the corresponding figure for patients with *KRAS* WT status only.

### *Method A*

We first estimate the median progression-free survival for patients in the BOND RCT with *KRAS* WT status on cetuximab plus best supportive care as:

median progression-free survival of 3.7 months for *KRAS* WT patients taking cetuximab + best supportive care in the RCT of cetuximab + best supportive care vs best supportive care[45]
× median progression-free survival of 1.5 months for all patients (*KRAS* WT and mutant status) taking cetuximab + best supportive care in the BOND RCT[49]
/ median progression-free survival of 1.9 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]
= 2.9 months [Equation 19]

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

median progression-free survival of 4.1 months for all patients (*KRAS* WT and mutant status) taking cetuximab + irinotecan in the BOND RCT[49]
× [estimated median progression-free survival of 2.9 months for patients with *KRAS* WT status taking cetuximab + best supportive care in the BOND RCT
/ median progression-free survival of 1.5 months for all patients (*KRAS* WT and mutant status) taking cetuximab + best supportive care in the BOND RCT][49]
= 8.0 months [Equation 20]

### *Method B*

Alternatively, we can estimate the median progression-free survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan, denoted by *M*, as follows. First, we note that the median progression-free survival for patients with *KRAS* mutant status taking cetuximab plus irinotecan is approximately 12 weeks, and the median progression-free survival for patients with *KRAS* WT status taking cetuximab plus irinotecan is approximately 34 weeks

from the study by De Roock and colleagues.[48] Then, given that 59.3% of patients were *KRAS* WT status (the rest *KRAS* mutant status) in De Roock and colleagues:[48]

$$59.3\%M + (100\% - 59.3\%)\frac{12}{34}M$$

= median progression-free survival of 4.1 months for all patients (*KRAS* WT and mutant status) taking cetuximab plus irinotecan in the BOND RCT.

Solving, we find $M = 5.6$ months, which is considerably lower than the 8.0 months estimated by method A.

### Method C

This method is identical to method B except that we use data from Lievre and colleagues[86] instead of data from De Roock and colleagues.[48] In Lievre and colleagues[86] the median progression-free survival for patients with *KRAS* mutant status taking cetuximab plus irinotecan is approximately 9 weeks; the median progression-free survival for patients with *KRAS* WT status taking cetuximab plus irinotecan is approximately 32 weeks; and 68% of patients were *KRAS* WT status. Solving again for *M*, the estimated median progression-free survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan is 5.3 months.

### Method D

This method is identical to methods B and C except that we use data from De Roock and colleagues.[83] In this study, the median progression-free survival for patients with *KRAS* mutant status taking cetuximab plus irinotecan is approximately 12 weeks; the median progression-free survival for patients with *KRAS* WT status is approximately 24 weeks; and 58% of patients were *KRAS* WT status. Solving for *M*, the estimated median progression-free survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan is 5.2 months. One possible problem with the data from De Roock and colleagues[83] is that patients were treated with cetuximab plus chemotherapy, in which the 'chemotherapy' is not specified. We require the chemotherapy to be irinotecan, but this is not clear. However, the data set has the advantage that it covers many patients.

It is very difficult to choose a preferred method for estimating the median progression-free survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan because all methods rely on assumptions, and all have strengths and weaknesses. Method A assumes that the proportionate difference in progression-free survival for patients on cetuximab plus irinotecan between patients with *KRAS* mutant and those with *KRAS* WT status is similar to the proportionate difference in progression-free survival for patients on cetuximab between patients with *KRAS* mutant and those with *KRAS* WT status. However, it has the advantage that it relies solely on randomised data. Methods B–D assume similarity in the baseline characteristics of the patients on cetuximab plus irinotecan between patients with *KRAS* mutant and those with *KRAS* WT status, given that the De Roock and colleagues,[48] De Roock and colleagues[83] and Lievre and colleagues[86] studies were observational, not randomised. However, methods B–D give very similar estimates of the median progression-free survival (5.6, 5.3 and 5.2 months respectively), and these are different to the estimate of 8.0 months from method A. Given the consistency in the estimates using methods B–D, we take the average of these values and hence estimate the median progression-free survival in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan as 5.4 months.

## Progression-free survival for cetuximab plus irinotecan: stage 2

Next, we adjust our estimate of the median progression-free survival of 5.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab plus irinotecan for the purposes of the indirect comparison with other treatments, as follows:

Estimated modelled median progression-free survival for patients with *KRAS* WT status taking cetuximab + irinotecan
= estimated median progression-free survival of 5.4 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab +irinotecan (calculated in stage 1)
× modelled median progression-free survival of 3.9 months for patients with *KRAS* WT status taking cetuximab + best supportive care (estimated from lambda and gamma of Weibull)
/estimated median progression-free survival of 2.9 months in the BOND RCT for patients with *KRAS* WT status taking cetuximab + best supportive care (estimated in *Method A*)
= 7.1 months [Equation 21]

## Progression-free survival for cetuximab plus irinotecan: stage 3

Finally, given that we have specified the median progression-free survival for cetuximab plus irinotecan (7.1 months), and that we assume the same Weibull shape parameter, $\gamma$, for cetuximab plus irinotecan as for cetuximab plus best supportive care, this then specifies the scale parameter, $\lambda$, of the Weibull for cetuximab plus irinotecan, given that the median $t^*$ of the Weibull is given by $0.5 = \exp(-\lambda t^*)$. This then gives an estimated mean progression-free survival for cetuximab plus irinotecan of 8.8 months, which is similar to Merck Serono's estimated mean of 7.8 months.