Required survival gains for My-5FU to be cost effective in mCRC

Assuming a mean number of My-5FU tests of 3.23 at an average cost of £61.03 this results in an average test cost of £197 per patient. An additional £37 is required to cover consultant time associated with dose adjustments. Starting from an assumption of no clinical difference between My-5FU and BSA dosing, this requires that My-5FU generate an additional 0.01 QALYs.

The main quality of life estimates are from Farrkila et al and from Best et al.

If there are gains to overall survival and all these gains are experienced at the progression free survival quality of life, the relevant quality of life values are 0.820 from Farrkila et al and 0.515 from Best et al. If these survival gains are mainly experienced post progression, the relevant quality of life values are 0.643 from Farkkila et al and 0.213 from Best et al.

If there are gains to progression free survival but no gains to overall survival, these gains should be valued at the quality of life increment for progression free survival over survival with progression: 0.177 from Farrkila et al and 0.302 from Best et al.

The gains in discounted survival and progression free survival that are required to achieve a cost effectiveness estimate of £20,000 per QALY are outlined below. Note that these do not take into account any additional costs associated with increased overall survival, but given the magnitude of the required values this is probably a relatively minor concern at least for the values associated with the Farkkila et al quality of life values.

Table 01: Required additional discounted survival in days at a WTP of £20,000 per QALY

	Farrkila et al	Best et al
Required additional OS		
Spent in PFS	5.2	8.3
Spent in SWP	6.6	20.0
Required additional PFS if no OS gain	24.1	14.1

This compares with the main undiscounted survival estimates presented within the DAR as below.

Table 02: Undiscounted survival estimates within the DAR: FOLFOX studies

	Source	Scale	Shape	Mean (mths)
Base Case				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Capitain et al., 2012: from median	λ=0.00398	γ=1.66906	24.49
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Capitain et al., 2012: from median	λ=0.05060	γ=1.13668	13.19
Scenario analysis 01				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Gamelin et al., 2008 0.829255 HR	..	..	30.17
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Capitain et al., 2012: from median	λ=0.05060	γ=1.13668	13.19
Scenario analysis 02				
OS My5-FU	Capitain et al., 2012	λ=0.00233	γ=1.66906	33.76
OS BSA	Pooled 5 BSA studies	λ=0.00942	γ=1.50343	20.09
PFS My5-FU	Capitain et al., 2012	λ=0.02438	γ=1.13668	25.06
PFS BSA	Pooled 3 BSA studies	λ=0.03194	γ=1.40082	10.65

Table 03: Undiscounted survival estimates within the DAR: 5-FU + FA Studies

	Source	Scale	Shape	Mean (mths)
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
PFS BSA	Pooled 3 BSA studies	λ=0.05541	γ=1.35834	7.71
Scenario analysis 01				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 2008: resp. dur. A	λ=0.02047	γ=1.82786	7.46
PFS BSA	Gamelin et al., 2008: resp. dur. A	λ=0.05378	γ=1.54066	6.00
Scenario analysis 02				
OS My5-FU	Gamelin et al., 2008	λ=0.00270	γ=1.82786	22.59
OS BSA	Gamelin et al., 2008	λ=0.00865	γ=1.54066	19.65
PFS My5-FU	Gamelin et al., 2008: resp. dur. B	λ=0.00798	γ=1.82786	12.49
PFS BSA	Gamelin et al., 2008: resp. dur. B	λ=0.03280	γ=1.54066	8.27

Turning to the threshold hazard ratios, these can be derived from the electronic model by initially assuming clinical equivalence between My-5FU and BSA dosing. The relevant hazard ratio for either

overall survival or progression free survival that result in a cost effectiveness estimate of £20,000 per QALY can then be derived.

Note that due to the model structure, applying a hazard ratio to overall survival but retaining a unitary hazard ratio for progression free survival implies that the additional overall survival is mainly experienced at the survival with progression quality of life value. The exception to this is where the progression free survival curve cuts the overall survival curve. Where this occurs the additional survival is thereafter experienced at the progression free survival quality of life. This consideration applies to the tail of the FOLFOX analysis.

Based upon the BSA dosing curves for FOLFOX derived from Capitain et al and excluding 2nd line treatment for the reasons already given in the DAR, the following hazard ratios are required.

Table 04: Required hazard ratios for FOLFOX study based analyses

	Farrkila	Best
HR OS	0.98	0.87
HR PFS	1.00	1.00
ICER	£21,015	£20,830
HR OS	1.00	1.00
HR PFS	0.91	0.95
ICER	£20,071	£19,397

Based upon the BSA dosing curves for 5FU + FA derived from Gamelin et al for overall survival and the pooled 3 studies for progression free survival and excluding 2nd line treatment for the reasons already given in the DAR, the following hazard ratios are required.

Table 05: Required hazard ratios for 5FU + FA study based analyses

	Farrkila	Best
HR OS	0.97	0.85
HR PFS	1.00	1.00
ICER	£16,794	£20,542
HR OS	1.00	1.00
HR PFS	0.76	0.88
ICER	£20,811	£19,935