CARMUSTINE WAFERS

PLEASE NOTE THAT SCOPE FOR REANALYSIS IS LIMITED BECAUSE ONLY DATA ON MEDIAN SURVIVAL IS AVAILABLE.
We have adjusted our fitted survival curve through altering one of the parameters that produce the Weibull curve.

Reanalysis based on Link comments on ACD Appendix 2

(note imbalance in grade 3 tumours for this subgroup - 13.8% of BCNU-W pts and 3.8% in placebo – Table 2, p.27)

The Link submission for different durations of PFS gives mean times. This has been converted to median times to assist comparison with original PenTAG model. Derived values are shown *in italics*.

BCNU-W Reanalysis 1 based on all patients receiving total resection

Model arm	Model inputs (months)				Model outputs		
	Overall Median survival	Overall mean survival	Mean PFS	Median PFS	Differential Costs	Differential QALYs	ICER
Original model							
Placebo	11.6	*16.73*		5.9			
Treatment	13.9	*20.05*		5.9	6,104,273	107	**56,954**
PFS determined by Radiological imaging							
Placebo	12.6	*18.17*	8.5	*5.9*			
Treatment	14.75	*21.28*	8.8	*6.1*	6,391,583	135	**47,444**
PFS determined by mean time to KPS decline							
Placebo	12.6	*18.03*	12.4	*8.6*			
Treatment	14.75	*21.06*	15.0	*10.4*	5,712,415	156	**36,676**
PFS determined by the Mean (of mean) times to neuro-performance decline							
Placebo	12.6	*18.03*	12.09	*8.4*			
Treatment	14.75	*21.06*	15.15	*10.5*	5,621,585	158	**35,598**

BCNU-W Reanalysis 2 based on patients with GBM receiving total resection group

Model arm	Model inputs (months)				Model outputs		
	Overall Median survival	Overall mean survival	Mean PFS	Median PFS	Differential Costs	Differential QALYs	ICER
Original model							
Placebo	11.6	*16.73*		5.9	-	-	
Treatment	13.9	*20.05*		5.9	6,104,273	107	**56,954**
PFS determined by Radiological imaging							
Placebo	12.5	*18.17*	8.5	*5.9*	-	-	
Treatment	14.6	*21.28*	8.8	*6.1*	6,345,958	132	**47,997**
PFS determined by mean time to KPS decline							
Placebo	12.5	*18.03*	12.4	*8.6*	-	-	
Treatment	14.6	*21.06*	15.0	*10.4*	5,676,000	153	**37,143**
PFS determined by the Mean (of mean) times to neuro-performance decline							
Placebo	12.5	*18.03*	12.09	*8.4*	-	-	
Treatment	14.6	*21.06*	15.15	*10.5*	5,586,245	155	**36,053**

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TEMOZOLOMIDE

Response to Section 4.2.9 (p.5) of comments on the draft ACD:

1. <u>Drug acquisition costs of TMZ</u>: The model in fact correctly factors in the cost of 42 days of concurrent (concomitant) therapy with TMZ. The reference to 7 weeks belongs to a label only – the number it refers to is correctly applied to the model for the 6 weeks of radiotherapy.

2. <u>Cost associated with treatment at first relapse:</u> See the attached sheet which was provided to NICE at the first ACM.

3. <u>Failure to conduct relevant subgroup analysis:</u> We conducted extensive sensitivity analyses which show the extent of improved survival that would be required in order for TMZ to be considered cost-effective. However, we have undertaken additional scenario analysis based on subgroups.

4. <u>Overestimation of cost of adjuvant chemotherapy</u>. Again the actual model results are closer to those reported by Stupp et al - median number of cycles received is 4:

81% start adjuvant TMZ (i.e. have at least one cycle)
71.% have the 2nd cycle
63% the 3rd
54% the 4th
47% the 5th and
40% the 6th.

As reported by Stupp et al Table 2:

78% start adj. Chemo with TMZ
47% have the full 6 cycles
Median: 3 cycles

Reanalysis based on Schering comments on the ACD

We have re-run the model using the subgroups provided by Schering.

We have also re-run the model for these subgroups assuming that the scenario described in the attached sheet, whereby patients having received first line TMZ treatment are both less likely to receive chemotherapy at progression and those that do are less likely to receive TMZ (see attached sheet for details).

For both these analyses, we have assumed that any additional survival extends PFS rather than the post-progressive period.

TMZ Reanalysis 1 using subgroups (same post-progression drug costs as base case)

		Model inputs (months)		Model Outputs		
	Cohort	Increase in Med. Overall survival	Differential Costs	Differential QALYs	ICER
PenTAG Base case	Control	-			
	Treatment	-	8,555,601	187	**45,778**
Age <50	Control	1.1			
	Treatment	2.8	9,757,868	258	**37,881**
Resection surgery	Control	0.8			
	Treatment	1.2	9,050,135	172	**52,558**
WHO performance status 0	Control	1.2			
	Treatment	2.8	9,734,744	250	**38,886**
WHO performance status 1	Control	-0.2			
	Treatment	-0.8	8,213,683	122	**67,430**

TMZ Reanalysis 2 using subgroups and differential post-progression drug costs.

		Model inputs (months)		Model Outputs		
	Cohort	Increase in Med. Overall survival	Differential Costs	Differential QALYs	ICER
PenTAG Base case	Control	0			
	Treatment	0	6,383,847	187	**34,158**
Age <50	Control	1.1			
	Treatment	2.8	7,649,637	258	**29,696**
Resection surgery	Control	0.8			
	Treatment	1.2	6,926,110	172	**40,223**
WHO performance status 0	Control	1.2			
	Treatment	2.8	7,614,823	250	**30,402**
WHO performance status 1	Control	-0.2			
	Treatment	-0.8	6,140,685	122	**50,412**