Methods for reanalyses of cost-effectiveness of TMZ based on subgroups

Method overview

The reanalysis was performed on subgroups for which only median overall survival was provided. We assumed that any extra life was accrued in the "Stable disease" state of the PenTAG model (i.e. extended progression free survival, PFS). Figure 1 shows how the extra time was allocated in the reanalysis for different subgroups.

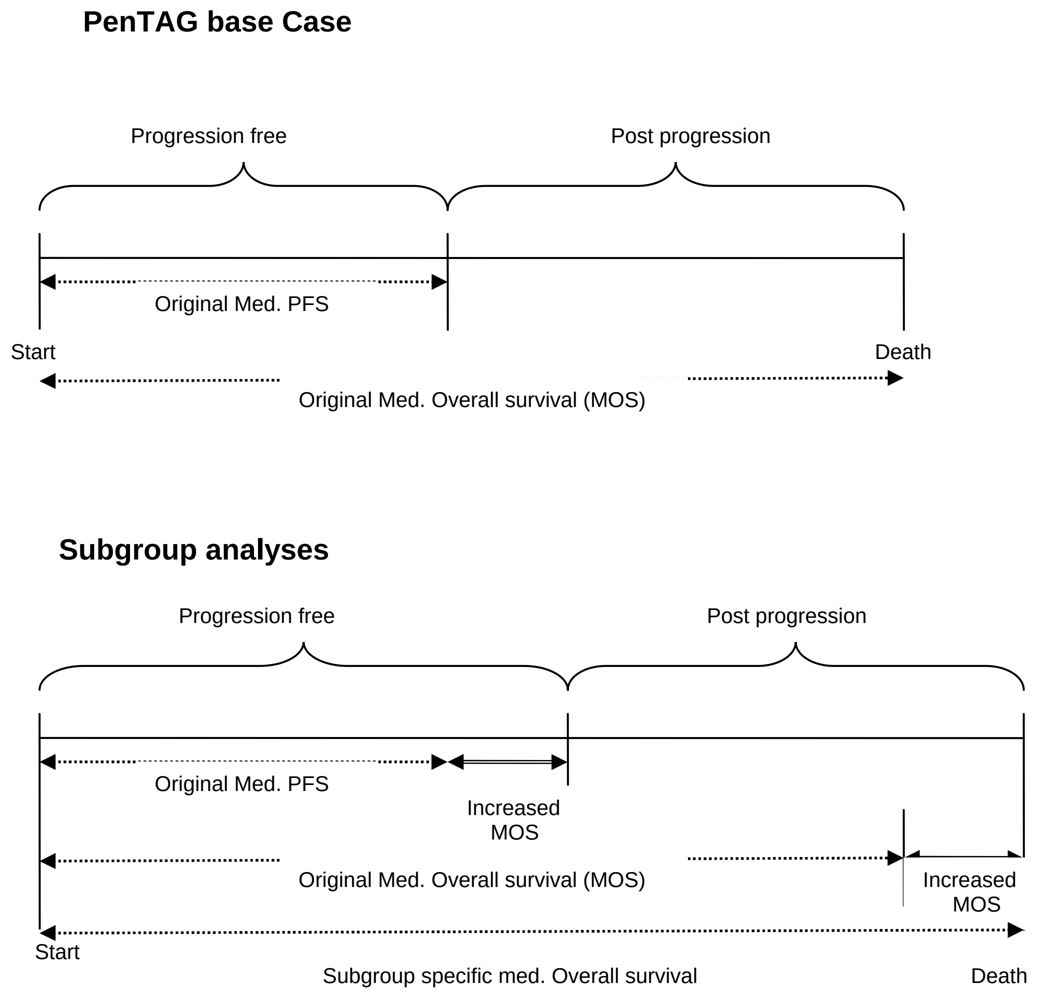

Figure 1

Mathematical theory used in subgroup analyses.

As was explained in the main report, both types of survival (progression free and overall) were modelled using Weibull curves. These curves are manipulated by two parameters (gamma and lamda) which control the shape and scale of the fitted curve.

Standard statistical theory states that for any given Weibull curve, the median survival is calculated using the formula:

$$Median\,survival = \left\{\frac{1}{\lambda} * \ln(2)\right\}^{1/\gamma}$$

Sensitivity analysis showed that the fitted curve was relatively robust to changes in the lamda parameter and sensitive to changes in the gamma parameter. Therefore, for the subgroup analyses we assumed that the lamda parameter was constant and that the gamma parameter changed as the median survival changed. Rewriting the above equation, gives the following equation used to calculate gamma for a particular median survival.

$$\gamma = \frac{(\ln(\ln(2)) - \ln(\lambda))}{\ln(Median\,survival)} \quad (1)$$

Algorithm used in the derivation of ICERs for each subgroup

For both treatment and control cohorts the following process was used.

i) Fix Lamda values for both progression free (PFS) and overall survival (MOS).

For overall median survival:

ii) Input overall median survival for a given subgroup in equation (1) and calculate corresponding gamma value.

iii) Fit Weibull curve for overall survival using this value

For progression free survival

iv) Calculate the difference in median survival between original PenTAG model and particular subgroup (incorporated as increase in PFS)

v) Calculate corresponding gamma value using equation (1).

vi) Fit Weibull curve for overall survival using this value.

Implementation in Excel model.

Table 2 shows the ICERs derived for each of the subgroup analyses, together with the estimated increase in survival and the lamda and gamma values used in the curve fitting process derived using the above algorithm. The values presented have been rounded for clarity of presentation and as a result there may by slight deviations from the output ICERS if these are re-run. These results can be simulated by replacing the gamma values for PFS and median overall survival (MOS) in the “parameters” sheet of the PenTAG model. These are to be found in the cells shown in Table 1.

Table 1: Cells in PenTAG model for changing gamma inputs for progression free and overall survival

cell number	PFS Gamma	MOS gamma
Control	E231	E225
treatment	E243	E237

Table 2: Lamda and gamma values used in the subgroup analyses

	Model inputs (months)		Weibull Parameters				
	Cohort	Increase in Med. Overall survival	PFS Lamda	PFS Gamma	MOS Lamda	MOS gamma	ICER
PenTAG Base Case	Control	-	0.01337	1.31083	0.00057	1.79414	
	Treatment	-	0.00889	1.25111	0.0006	1.68798	**45,778**
Age <50	Control	1.1	0.01337	1.20573	0.00057	1.75511	
	Treatment	2.8	0.00889	1.16522	0.0006	1.631299	**37,881**
Resection surgery	Control	0.8	0.01337	1.22459	0.00057	1.76514	
	Treatment	1.2	0.00889	1.22426	0.0006	1.668531	**52,558**
WHO performance status 0	Control	1.2	0.01337	1.19977	0.00057	1.75185	
	Treatment	2.8	0.00889	1.16522	0.0006	1.631299	**38,886**
WHO performance status 1	Control	-0.2	0.01337	1.30095	0.00057	1.80126	
	Treatment	-0.6	0.00889	1.317297	0.0006	1.71769	**67,430**

Methods for reanalyses of cost-effectiveness of carmustine implants based on subgroups

The industry submissions for BCNU wafers presented information on median overall survival AND median progression free survival. A different approach to that used for TMZ for apportioning increased survival could therefore be used as it was possible to fit curves for both types of survival separately.

The method used to generate the lamda and gamma values used to drive the Weibull curve for overall survival is exactly the same as outlined in the temozolomide analysis. In the PenTAG TAR, survival in patients using BCNU-W was informed by the Westphal and colleagues trial which did not publish a Kaplan-Meier curve for progression free survival; we therefore assumed an exponential model for PFS. Survival data modelled in such a way is only dependant one parameter, lamda, and not on two as was the case with a Weibull model. Standard Theory states that, for a given median survival value, the corresponding value of Lamda can be calculated using the formula:

$$\lambda = \ln(2) \big/ Median\,Survival$$

Table 1 below shows the original reanalysis produced by PenTAG and Table 2 shows the lamda and gamma values used to derive these results. The values presented for both inputs and outputs have been rounded so small differences from the published ICERS are again to be expected.

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

	Model inputs (months)				Model outputs		
Model arm	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**

Table 2: Lamda and Gamma values used in BCNU-W Reanalysis 1.

Model inputs (months)		Parameters used in Survival analysis				
Cohort	Med. Overall survival (Months)	MOS Lamda	MOS gamma	Med PFS (Months)	PFS Lamda	ICER
Original PenTAG model						
Control	11.6	0.00018	2.078381	5.9	0.02711	
Treatment	13.9	0.00044	1.794639	5.9	0.02711	**56,954**

PFS determined by Radiological imaging						
Control Treatment	12.6 14.75	0.00018 0.00044	2.064416 1.77061	5.9 6.1	0.02711 0.026222	**47,444**
PFS determined by mean time to KPS decline						
Control Treatment	12.6 14.75	0.00018 0.00044	2.064416 1.77061	8.6 10.4	0.018599 0.01538	**36,676**
PFS determined by the Mean (of mean) times to neuro-performance decline						
Control Treatment	12.6 14.75	0.00018 0.00044	2.064416 1.77061	8.4 10.5	0.019042 0.015234	**35,598**