Details of amendments made by the ERG to the manufacturer's decision model submitted to the NICE Single Technology Appraisal of Pemetrexed as maintenance therapy for NSCLC in October2012

1) *Recalculation of mean pemetrexed acquisition cost per cycle*

This amendment is activated by a binary switch variable (Mod_1) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'Resource!N47' with the following:

=IF(Mod_1=0,SUM(N45:N46),1481.37)

The mean cost per dose was obtained as follows:

For Males create a table of 100mg dose units equivalent to steps of 0.2m^2 BSA. Use a cumulative normal distribution function to calculate the proportion of patients who can be treated up to the maximum dose available in that step. Determine the number of 100mg and 500mg vials required to deliver the dose for that step. Use a SUMPRODUCT function to calculate the mean number of 100mg and 500mg vials required by Males, and multiple these by the vial unit costs to obtain the overall mean cost for Males. Note that a dose cap of 1000mg is applied on clinical advice. The same procedure is used for Females and then a weighted average cost for all patients is calculated using the balance between Males and Females in the population.

The BSA distribution parameters are derived from the Sacco survey data excluding adjuvant and neoadjuvant patients, as follows:

Males - mean 1.88568, standard deviation 0.17933

Females - mean 1.65503, standard deviation 0.17249

Males: Females ratio based on PARAMOUNT trial (313:226)

2) *Removal of inappropriate continuity correction applied to pemetrexed acquisition costs*

This amendment is activated by a binary switch variable (Mod_2) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'Pem!DM11' with the following:

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=IF(Mod_2=0,AVERAGE(CW10,CW11),$D$4*BH10*PemCost
+$D$4*AVERAGE(BH10,BH11)*(propCTscans*pCTscans*cCTscan
+propconsults*pConsults*cConsult))
+IF(JMENcosts=1,AVERAGE(CX11,CX10)+AVERAGE(DD10,DD11))
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Copy this formula into cells 'Pem!DM12:DM366'

3) *Removal of differential use of second-line systemic therapies following disease progression*

The amendment is activated by a binary switch variable (Mod_3) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'Resource!N305' with the following:

=IF(Mod_3=0,IF(PSA=1,M305,F305),pBSCSyst)

Replace the formula in cell 'Resource!N306' with the following:

=IF(Mod_3=0,IF(PSA=1,M306,F306),pBSCSyst)

Replace the formula in cell 'Resource!F307' with the following:

=IF(Mod_3=0,F305/F304,1)

4) *Recalculation of mean docetaxel acquisition cost per cycle*

This amendment is activated by a 3-way switch variable (Mod_6) taking value 0 to use the original model logic, value 1 to apply the amendment using BNF prices and value 2 using eMIT prices.

Replace the formula in cell 'Resource!M376' with the following:

=CHOOSE(Mod_6+1,SUM(M373:M375),M375+800.06,M375+87.39)

The method of calculation is similar to that used for pemetrexed (see (1) above), with the following alterations:

- dosing steps are at 20mg intervals
- three vial sizes are used - 20mg, 80mg and 140mg
- the lowest generic BNF list prices are used (£154.61, £508.01 and £720.10 respectively)
- the best eMIT average contract prices are used (£11.13, £47.24 and £86.10 respectively)

5) *Use of the covariate adjusted EQ-5D model to determine utility values*

This amendment is applied by setting range 'QoLdata' to value 2.

6) *Use of the covariate adjusted PFS model*

This amendment is applied by setting range 'PFSdata' to value 2.

7) *Use of the covariate adjusted OS model*

This amendment is applied by setting range 'OSdata' to value 2.

8) *Inclusion of re-estimated costs of vitamin supplementation required for patients receiving pemetrexed*

This amendment is activated by a binary switch variable (Mod_10) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'Resource!V57' with the following:

=IF(Mod_10=0,SUM(V55:V56),1.778275)

This amendment is based on assigning protocol supplementation doses to each cycle, and applying this to the number of PARAMOUNT pemetrexed patients per cycle as shown in CSR addendum Table S124.4.8.

9) *Re-estimation of PFS follow-up costs*

This amendment proved difficult to implement within the main logic of the model. Therefore, the necessary alterations were implemented directly into cells in the Results spreadsheet. This involved calculating an estimated revised follow-up cost for both BSCand pemetrexed, and also the net discounted cost of PFS follow-up care in each arm.

The amendment is activated by a binary switch variable (Mod_11) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'Results!F50 with the following:

=IF(Mod_11=0,bscTFC,bscTFC-1550.64611+238.33899)

Replace the formula in cell 'Results!M50 with the following:

=IF(Mod_11=0,pemTFC,pemTFC-1606.71508+407.59520)

The calculation of follow-up costs is based on out-patient assessment every 4 cycles for pemetrexed patients, and at 3, 6, 12 and 18 months for BSC patients. The same number of CT scans are assumed in each arm, spread out pro-rata to the number of patients attending each assessment. Patient numbers used are taken from the PFS Kaplan-Meier estimates. The cost per OP appointment is £119.99, and the cost perCT scan is £142.92, and are discounted.

10) *Re-estimation of terminal care costs*

This amendment is activated by a binary switch variable (Mod_12) with value 1 to apply the amendment and value 0 to use the original model logic.

Replace the formula in cell 'JMEN_Resource!H45 with the following:

=IF(Mod_12=0,(E45/UKCPI_08)*UKCPI_11,3906.31)

This estimate is taken directly from an HTA report recently completed by the ERG for first-line chemotherapy for NSCLC, and encompasses costs of care for patients dying in hospital, in a hospice and at home, with all supportive community and voluntary services.

11) *Selecting alternate starting points for projection of OS*

This amendment is applied by setting ranges 'KMstopOSBSC' and 'KMstopPem' to the appropriate values:

For 15% survival use 41 & 47

For 20% survival use 36 & 44

For 25% survival use 41 & 47

12) *Substitution of ERG long-term model for OS projection*

This amendment is activated by a binary switch variable (Mod_13) with value 1 to apply the amendment and value 0 to use the original model logic.

The modification to the <u>BSC worksheet</u> requires the following changes:

- Set Cell AZ7 to " =0.00176541033416705 * 21 (This is the exponential risk parameter for a 21-day cycle)
- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ28
- Set Cell AZ29 to " =AZ28*EXP(-AZ7)" and copy this formula to range AZ30:AZ366

Replace the formula in cell AW11 as follows:

=IF(Mod_13=0, IF(Cycles<=IF(D4=0,KMstopOSBSC,KMstopOSPem), 1-AN11/AN10, IF(OSModel=1, AQ11, IF(OSModel=2,AR11 ,IF(OSModel=3,AS11 ,IF(OSModel=4,AT11, IF(OSModel=5,AU11,AV11)))))), 1-AX11/AX10)

Replace the formula in cell AX11 as follows:

=IF(Mod_13=0,(1-AW11)*AX10,AZ11)

Copy the range AW11:AX11, and paste the formula to the range AW12:AX366

The modification to the <u>Pem worksheet</u> requires similar changes:

- Set Cell AZ7 to "=0.00170103676595399 * 21
- Set Cell AZ10 to "= AN10", then copy this formula to the range AZ11:AZ17
- Set Cell AZ18 to " =AZ17*EXP(-AZ7)" and copy this formula to range AZ19:AZ366

All other changes are identical tothose in the BSC worksheet.