Details of amendments made by ERG to BMS Ipilimumab Malignant Melanoma treatment model
14 September, 2011

All modifications are activated by simple numerical switches (ModA – ModE, taking value 0 for ‘inactive’, and 1 for ‘active’). For Mod_A the value 1 implements ERG’s original change, and 2 also applies change to ip_survat5 and comp_survat5.

**Modification_A: Background mortality logic error**

On Sheet 'PF_Ipilimumab'

Name cell M1870 as 'newip_survat5'

Change cell N45 from

=IF(B45>=5,N44*(1-VLOOKUP(p_starting_age+B45-1,mort_table,5,FALSE)),1)

to

=IF(IF(Mod_A=0,B45>=5,B45>5),N44*(1-VLOOKUP(p_starting_age+B45-1,mort_table,5,FALSE)),1)

Copy this revised formula to the rest of the range N45: N3891

Change cell P45 from

=IF(AND(B45>=5,mort_only="Yes"), ip_survat5*N45,IF(OS_curvetype_Ip="Actual Data to 1.5 years",M45*IF(adj_mort="Yes",N45,1),G45))

To

=IF(AND(IF(Mod_A=0,B45>=5,B45>5),mort_only="Yes"),
IF(Mod_A<2,ip_survat5,newip_survat5)*N45, IF(OS_curvetype_Ip="Actual Data to 1.5 years",M45*IF(adj_mort="Yes",N45,1),G45))

Copy this revised formula to the rest of the range P45:P3891

On Sheet 'PF_Comparator'

Name cell M1870 as 'newcomp_survat5'

Repeat the same substitutions to cells in ranges N45:N3891, and P45:P3891
Modification_B: AE costs logic error

On Sheet 'PF_Ipilimumab'

Change the start of the formula in cell AG45 from

=IF(A45=1, SUMPRODUCT(p_ae_ip,p_ae_cost,p_ae_dur),0)* ......

to

=IF(A45=1,IF(Mod_B=0,SUMPRODUCT(p_ae_ip,p_ae_cost,p_ae_dur),SUMPRODUCT(p_ae_ip,p_ae_cost)),0)* ........

Copy this revised formula to the rest of the range AG45: AG3891
**Modification_C: Age-adjustment to utility values**

**On Sheet 'Utilities'**

Cell T63 = -0.004114

Cells S66:S109 enter numbers 1-44 (Years)

Cell T66 = p_u_stable

Cell U66 = p_u_progressive

Cell T67 = $T$66+$T$63*($S$67-1)  
Cell U67 = $U$66+$T$63*($S$67-1)

Copy Range T67:U67 to Rows 68-109

Name range S66:U109 as "ERG_utils"

**On Sheet 'PF_Ipilimumab'**

Change the start of the formula in cell AJ45 from

=Q45*(IF(util_bydrug="Yes", u_stable_ipi, p_u_stable)) + ......

to

=Q45*(IF(util_bydrug="Yes", u_stable_ipi, IF(Mod_C=0, p_u_stable, VLOOKUP(B45,ERG_utils,2)))+......

Change the start of the formula in cell AK45 from

=Q45*(IF(util_bydrug="Yes", u_prog_ipi, p_u_progressive)) + ......

to

=Q45*(IF(util_bydrug="Yes", u_prog_ipi, IF(Mod_C=0, p_u_progressive, VLOOKUP(B45,ERG_utils,3)))+......

Copy cells AJ45:AK45 to the rest of the range AJ45: AJ3891

**On Sheet 'PF_Comparator'**

Repeat the above modifications for range CB45:CC3891 of the 'PF_Comparator' worksheet.
**Modification_D: Ipilimumab cost**

The cost of ipilimumab was adjusted by applying a multiplier to the formula in range p_cost_ip (cell Parameters!L239) as follows:

\[
= \text{IF}(J239=0, E239, \text{IF}(J239=1, H239, \text{IF}(J239=2, I239, K239))) \times \text{IF}(\text{Mod}_D=0, 1, \text{Results}_\text{Standard}!$T$38)
\]

The value of the multiplier is \(0.989302383083229\)

This was based on a separate calculation as follows:

From MDX010-20 baseline body weight data for all patients (Table B5 of manufacturers clarification response):

<table>
<thead>
<tr>
<th></th>
<th>Mean (kg)</th>
<th>SD</th>
<th>LogNormal (\mu)</th>
<th>LogNormal (\sigma)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males</td>
<td>86.62</td>
<td>16.95</td>
<td>4.423954</td>
<td>0.193847</td>
</tr>
<tr>
<td>Females</td>
<td>70.66</td>
<td>16.01</td>
<td>4.207816</td>
<td>0.223748</td>
</tr>
</tbody>
</table>

Where by method of moments

\[
\sigma = [ \ln( 1 + \text{SD}^2 / \text{mean}^2 ) ]^{0.5}
\]

\[
\mu = \ln( \text{mean} ) - \sigma^2
\]

<table>
<thead>
<tr>
<th>50mg vials</th>
<th>Weight limit (kg)</th>
<th>Males Cum.freq (Log Normal)</th>
<th>Frequency in band</th>
<th>Females Cum.freq (Log Normal)</th>
<th>Frequency in band</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>16.66667</td>
<td>0.000000000</td>
<td>0.000000000</td>
<td>0.000000000</td>
<td>0.000000000</td>
</tr>
<tr>
<td>2</td>
<td>33.33333</td>
<td>0.000001108</td>
<td>0.000001108</td>
<td>0.000861787</td>
<td>0.000861787</td>
</tr>
<tr>
<td>3</td>
<td>50.0</td>
<td>0.004134259</td>
<td>0.004133150</td>
<td>0.093085320</td>
<td>0.092223533</td>
</tr>
<tr>
<td>4</td>
<td>66.66667</td>
<td>0.123669764</td>
<td>0.119535505</td>
<td>0.485540701</td>
<td>0.392455381</td>
</tr>
<tr>
<td>5</td>
<td>83.33333</td>
<td>0.497724912</td>
<td>0.374051494</td>
<td>0.831735426</td>
<td>0.346194725</td>
</tr>
<tr>
<td>6</td>
<td>100.0</td>
<td>0.825064913</td>
<td>0.327340001</td>
<td>0.962125087</td>
<td>0.130389661</td>
</tr>
<tr>
<td>7</td>
<td>116.66667</td>
<td>0.958190198</td>
<td>0.133125286</td>
<td>0.993146367</td>
<td>0.031021280</td>
</tr>
<tr>
<td>8</td>
<td>133.33333</td>
<td>0.992216442</td>
<td>0.034026243</td>
<td>0.998899352</td>
<td>0.005752985</td>
</tr>
<tr>
<td>9</td>
<td>150.0</td>
<td>0.998763059</td>
<td>0.006546617</td>
<td>0.999833418</td>
<td>0.000934066</td>
</tr>
<tr>
<td>10</td>
<td>166.66667</td>
<td>0.999821538</td>
<td>0.001058479</td>
<td>0.999975352</td>
<td>0.000141934</td>
</tr>
<tr>
<td>11</td>
<td>183.33333</td>
<td>0.999975644</td>
<td>0.000154106</td>
<td>0.999996353</td>
<td>0.000021001</td>
</tr>
<tr>
<td>12</td>
<td>200.0</td>
<td>0.999996768</td>
<td>0.000021124</td>
<td>0.999999453</td>
<td>0.000003100</td>
</tr>
</tbody>
</table>

Mean vials per dose: 5.60040 4.63479
Cost per vial: £3,750 £3,750
Cost per dose: £21,001.50 £17,380.48

Gender proportions: 54.54% 45.46%
Weighted average cost per dose: £19,355.4009
4 cycles: £77,421.60
Model estimate: £78,258.79
Ratio: 0.989392383

Gender proportions from 'E+W deaths from malignant melanoma 2008' in 'ONS Mortality Statistics: Cause England and Wales 2008 London TSO 2010'
Modification E: Exploratory survival analysis

A large lookup table was created of ERG survival estimates.

This consists of 5 columns:

1) Time in days matching the values used in the model (0-1827 in increments of 1 day, then 1834-10955 in increments of 7 days)

2) PFS for the GP100 arm of the trial

3) PFS for all patients receiving ipilimumab+-GP100 in the trial

4) OS for the GP100 arm of the trial

5) OS for all patients receiving ipilimumab+-GP100 in the trial

For columns 2 & 3, trial Kaplan-Meier point estimates of survival are used up to and including day 365. Thereafter, each value is obtained as the product of the previous value and a fixed factor, corresponding to an exponential projection. The 1-day multiplier is then \( \exp(-\text{rate value}) \), and the 7-day value is \( \exp(-7\times\text{rate value}) \).

For columns 4 & 5, trial Kaplan-Meier point estimates of survival are used up to and including day 770. Thereafter, each value is obtained as the product of the previous value and a fixed factor, corresponding to an exponential projection. The 1-day multiplier is then \( \exp(-\text{rate value}) \), and the 7-day value is \( \exp(-7\times\text{rate value}) \).

In column 2 the exponential rate value is 0.0031897.
In column 3 the exponential rate value is 0.0009544.
In column 4 the exponential rate value is 0.0020073.
In column 5 the exponential rate value is 0.0004329.

These ERG estimates were implemented in columns O & P of worksheets 'PF_ipilimumab' and 'PF_comparator' by means of a simple IF statement of the form

\[
= \text{IF} ( \text{Mod}_E=0, \text{[original formula]}, \text{[reference to the corresponding ERG value]} )
\]