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

<u>On Sheet 'PF_Ipilimumab'</u>

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

<u>On Sheet 'PF_Comparator</u>

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$63*($S67-1)
Cell U67= $U$66+$T$63*($S67-1)

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
  =R45*(IF(util_bydrug="Yes", u_prog_ipi, p_u_progressive,)) + ...

to
  =R45*(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:

  = IF(J239=0,E239, IF(J239=1,H239, IF(J239=2,I239,K239))) *** IF(Mod_D=0, 1, Results_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):

	Mean (kg)	SD	LogNormal μ	LogNormal σ
Males	86.62	16.95	4.423954	0.193847
Females	70.66	16.01	4.207816	0.223748

Where by method of moments

$$\sigma = [\, Ln(\, 1 + SD^2 / mean^2 \,) \,]^{\,0.5}$$
$$\mu = Ln(\, mean \,) - \sigma^{\,2}$$

50mg vials	Weight limit (kg)	Males Cum.freq (Log Normal)	Frequency in band	Females Cum.freq (Log Normal)	Frequency in band
1	16.66667	0.000000000	0.000000000	0.000000000	0.000000000
2	33.33333	0.000001108	0.000001108	0.000861787	0.000861787
3	50.0	0.004134259	0.004133150	0.093085320	0.092223533
4	66.66667	0.123669764	0.119535505	0.485540701	0.392455381
5	83.33333	0.497724912	0.374055149	0.831735426	0.346194725
6	100.0	0.825064913	0.327340001	0.962125087	0.130389661
7	116.66667	0.958190198	0.133125286	0.993146367	0.031021280
8	133.33333	0.992216442	0.034026243	0.998899352	0.005752985
9	150.0	0.998763059	0.006546617	0.999833418	0.000934066
10	166.66667	0.999821538	0.001058479	0.999975352	0.000141934
11	183.33333	0.999975644	0.000154106	0.999996353	0.000021001
12	200.0	0.999996768	0.000021124	0.999999453	0.000003100
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(-rate value), and the 7-day value is exp(-7*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(-rate value), and the 7-day value is exp(-7*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

= IF (Mod_E=0, [original formula], [reference to the corresponding ERG value])