

Scenario	Response criterion	Response level	VRS cycles	Total APEX sample			1-prior therapy sample		
				nRi (a)	pRi (b)	rOS vi (c)	nRi (d)	pRi (e)	rOS vi (f)
5	M-protein	CR+PR	3						
6			4						
7		CR+PR+MR	3						
8			4						

pRi - represents the percent of responders after the ith cycle of all responders by end of APEX. rOS\_vi — percent reduction in Velcade survival associated with implementing a stopping rule at the ith cycle.

1. The absolute number of responders by the ith cycle, nRi<sub>i</sub>, is lower in subgroup of patients with 1-prior therapy than in the overall APEX trial population; compare columns (a) and (d)
2. The percentage of responders after the ith cycle of all responders in the sample, pRi<sub>i</sub>, is not statistically different between the overall APEX trial sample population and the 1-prior therapy sample population; compare columns (b) and (e).
2. The effect on the percent reduction in Velcade survival there is changed by ≤1% in all scenarios; compare columns (c) and (f)

0.0% 0.0%  
0.0% 0.0%

Scenario	Response criterion	Response level	Stopping cycles	VRS cycles	Total APEX sample			1-prior therapy sample		
					Inc. cost (a)	Inc QALY (b)	CE (c)	Inc. cost (d)	Inc QALY (e)	CE (f)
5	M-protein	CR+PR			Not options					
6										
7		CR+PR+MR	3	0	£21,733	8.2	£31,994	£21,576	7.9	£32,669
8			4	0	£22,570	8.4	£32,316	£22,410	8.2	£32,991
9			3	3	£19,177	8.2	£28,231	£19,020	7.9	£28,799
10			4	4	£19,145	8.4	£27,417	£18,986	8.2	£27,950

1. Inc. costs are lower < £200 in 1-prior therapy sample than total APEX sample; compare columns (a) and (d).
2. Inc. QALY is < 0.3 months lower in 1-prior therapy sample than total APEX sample; compare columns (b) and (e).
3. CE differs by < £700 between 1-prior therapy sample and total APEX sample; compare columns (c) and (f).

#### Full incremental CE analyses

1. Applying the VRS rule lowers costs without affecting OS and both are below £30,000.
2. Costs are lower with 4-cycle stopping rule than 3-cycle rule while inc. OS is higher.
3. Hence, scenario 10 dominates scenarios 7-9 in higher inc. OS and lower costs.

#### Effect of adding MR to response on TTP

1. We modeled the effect of the stopping rule only on survival because the initial submission in 2006 considered life-years gained on CR+PR. For consistency sake, we did not change the computations to consider effect on TTP.
2. The effect on rOS\_vi by adding MR is < 0.5% in the full sample and <2.5% in the 1-prior therapy sample.
3. The effect of a reduction of 0.5 - 2.5% on QALY is slight considering that the difference in utilities between TTP and post-progression is only 0.166, perhaps amounting to a change in QALYs for Velcade of -0.1 to -0.2 months.