Evidence Review Group - SHTAC

Bortezomib for induction therapy in multiple myeloma before HDT-ASCT

Erratum to ERG report

Amended paragraphs

Page 6-7

Secondary outcomes included progression free survival (PFS), time to progression (TTP) and overall survival (OS). Unadjusted PFS hazard ratios (HRs) showed a statistically significant longer PFS for VTD compared with TD (Pethema HR 0.65, 95% CI 0.45, 0.92, p=0.015; Gimema HR 0.63, 95% CI 0.45, 0.88, p=0.0061) with median follow-up of 35.9 months (Pethema) and 36 months (Gimema). The unadjusted TTP HR showed a statistically significantly lower hazard of progression in patients treated with VTD compared with TD (Pethema HR 0.64 95% CI 0.44, 0.93, p=0.017; not reported for Gimema). There were no statistically significant differences between VTD and TD for OS. Data for the proportion of patients who underwent stem cell transplant (SCT) were not powered nor were statistical tests reported so it is unclear whether there is a significant difference between groups in the Pethema trial.[a] Adverse events were similar for both treatments except for any grade 3/4 adverse event in the Gimema trial where they were statistically significantly higher for VTD compared with TD (relative risk (RR) 1.69, 95%CI 1.36, 2.08) and any treatment-related adverse event in the Pethema trial where they were statistically significantly higher for VTD compared with TD (RR 1.42, 95% CI 1.17, 1.73). In addition, there was a greater incidence of peripheral neuropathy in patients receiving bortezomib (VTD) than TD (Pethema 6.2% vs 0, no p values; Gimema 10% vs 2%, p=0.0004).

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- There are a number of issues around the outcome measures: post-induction response rate is a surrogate outcome and it is not clear how strong[b] a predictor of long term outcomes it is. Furthermore, long-term outcomes (PFS, OS) may be confounded by post-induction consolidation and maintenance therapies which do not reflect current UK clinical practice. There is also uncertainty in the PFS and OS results due to the high censoring of data and the reporting of data unadjusted for maintenance therapy.
- There are key concerns over the mixed treatment comparison (MTC) analysis due to the assumptions made to develop a network of evidence in the absence of trial data, and heterogeneity across the trials.

[a] Amended further to manufacturer's Factual Error Check report.

[b] "good" replaced with "strong" further to manufacturer's Factual Error Check report

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ORR results for the Pethema and Gimema trials were not reported in the trial publications.[1;2] ORR is defined in the MS (p.67) as 'the proportion of patients who achieve PR or better; ORR = CR+nCR+VGPR+PR.' However, data presented in the MS (Table 24, p.83) for the Pethema trial do not correspond to the sum of these individual response rates. Clarification requested from the manufacturer stated that ORR is generally defined as CR+nCR+VGPR+PR, provided that all these response categories are reported and that patients belong to only one of them. ORR was comprised of CR+nCR+PR in the Pethema trial (VGPR was assessed in a post-hoc analysis in the trial paper[1] and thus not reported in the CSR[8]); whilst ORR comprised CR+nCR+VGPR+PR in the Gimema trial.[c,d]

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Overall, the manufacturer's approach to the trial statistics is appropriate and reasonably well reported. However, [e] the MS did not comment on the high censoring rate in the PFS and OS analyses, and the PFS and OS data should be interpreted with caution.

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Results for the different categories of response are shown in **Error! Reference source not found.**. It should be noted that patients in the Gimema trial received two consecutive ASCTs compared to one ASCT in the Pethema trial which may have had an impact on the post-transplant response rates and thus makes comparisons between the studies difficult.[f]

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- There are uncertainties around the appropriateness of the primary outcome measure in these trials. Response rate is a surrogate outcome and it is not clear how strong[g] a predictor of long term outcomes it is; post-transplant response may be better than post-induction response. There is also a need for the whole treatment pathway to be considered in assessing treatment effectiveness.[h]
- Long term outcomes (PFS, TPP, OS) may be confounded by consolidation/ maintenance therapy which does not reflect current UK practice, particularly for the Gimema trial (but also for Hovon and MRC MMIX); it is also unclear how two consecutive ASCTs that patients in the Gimema, Hovon and IFM trials underwent would affect the results.

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[c] Amended further to manufacturer's Factual Error Check report

[d] "The ORR results across the two trials therefore cannot be directly compared" deleted further to manufacturer's Factual Error Check report.

[e] "different definitions of ORR between the Pethema and Gimema trials means that results cannot be directly compared and should be interpreted with caution. In addition," deleted further to manufacturer's Factual Error Check report.

[f] "In addition, ORR was defined differently and comprised of different response categories in the Pethema and Gimema trials, and therefore results cannot be directly compared (see Section **Error! Reference source not found.** for further details)." deleted further to manufacturer's Factual Error Check report.

[g] "good" replaced with "strong" further to manufacturer's Factual Error Check report.

[h] "ORR is defined differently in the Pethema trial compared to the Gimema trial (and other three trials) making comparisons difficult." deleted further to manufacturer's Factual Error Check report.

Page 40, Table 14

Trial	Treatment	Comparator
PETHEMA	**VTD** **N=130**	**TD** **N=127**
CR (CR+nCR)[i]	64 (49.2%)	22 (17.3%)
PR	46 (35.4%)	56 (44.1%)
NR (MR+SD+PD)	20 (15.4%)	49 (38.6%)

CR, complete response; NR, non-responders; MR, minimal response; PD, progressed disease; PR, partial response; SD, stable disease.

Page 44, Table 18

	Median overall survival[j]			Monthly survival probability	Monthly probability of death
	Number of months	95%CI min	95% CI max		
CR	88.6	61.4	Not reported	99.2%	0.8%
PR	39.8	33.8	61.4	98.3%	1.7%
NR	25.6	7.0	31.3	97.3%	2.7%

Data from MRC VII trial[20]

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The ERG considers that the OS data from the Pethema trial provide an appropriate contemporary validation dataset for the VTD vs. TD model, despite uncertainty about the overall robustness of the results (Section 3.1.6). Median follow-up time in Pethema was 35.9 months (MS p.91) and over 60 patients were still at risk in each arm at 30 months (MS Figure 16C, p.92).[k] These data are not used to derive the OS estimates in the model and so they are a reasonably independent means of verification. Furthermore in-trial maintenance does not confound PFS or OS in Pethema as patients were re-randomised to maintenance treatment post-transplantation (MS p.119).

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The manufacturer has addressed model methodological uncertainties by running alternative versions of the model with different assumptions. Discount rates are varied for costs and outcomes and alternative time horizons are examined.[l] An economic analysis based upon subgroups was not carried out (MS p.205).

[i] "+VGPR" deleted further to manufacturer's Factual Error Check report.

j "5 year survival time" replaced with "median overall survival" further to manufacturer's Factual Error Check report.

k "despite uncertainty about the overall robustness of the results (Section 3.1.6). Median follow-up time in Pethema was 35.9 months (MS p.91) and over 60 patients were still at risk in each arm at 30 months (MS Figure 16C, p.92)." added further to manufacturer's Factual Error Check report.

l "There is, however, no evidence that structural uncertainties have been addressed via sensitivity analysis." deleted further to manufacturer's Factual Error Check report.

Page 55, Table 21

Treatment option	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
TD	£49,414	3.06	-	-	-
VD	£62,874	3.79	£13,460	0.73	£18,318
PAD	£59,632	3.84	£10,218	0.78	£13,026

[redacted][m]

Page 56, Table 22

Treatment option	Costs	QALYs	Incremental Costs	Incremental QALYs	ICER (£/QALY)
CTD	£48,237	3.90	-	-	-
VD	£62,874	3.79	£14,637	-0.11	Dominated
PAD	£59,632	3.84	£11,396	-0.06	Dominated

[redacted][n]

[m] Footnote "[redacted]" added further to manufacturer's Factual Error Check report.

[n] Footnote "[redacted]." added further to manufacturer's Factual Error Check report.