

Additional clarification questions
Received via email correspondence: Mon 06/09/2010 16:51

1. Page 58, Table 5.7 and Page 149 Table 6.23: The PFS probabilities in Table 6.23 (page 149) are different from those given in Table 5.7 (page 58), e.g. for chlorambucil (PFS 36 months). Table 5.7 cites 1.5% whereas Table 6.23 cites 3%. Please clarify.

This is an error. The data presented in Table 6.23 in the original submission report (page 149) represented the results of the analysis of time to progression where death is censored rather than considered as an event and where patients who were not examined are excluded. For both of these reasons the data do not match Table 5.7 (page 58). This was the analysis used to inform the time to progression estimates in the model and is not the appropriate data for comparing the model predictions against the clinical trial data. The corrected table which still excludes the patients who were not examined but considers death as an event is provided below. Note that this still will not match Table 5.7 (pg. 58 of submission) as the patients who were not examined are excluded from the table below.

Revised Table 6.23 Summary of model results compared with clinical data

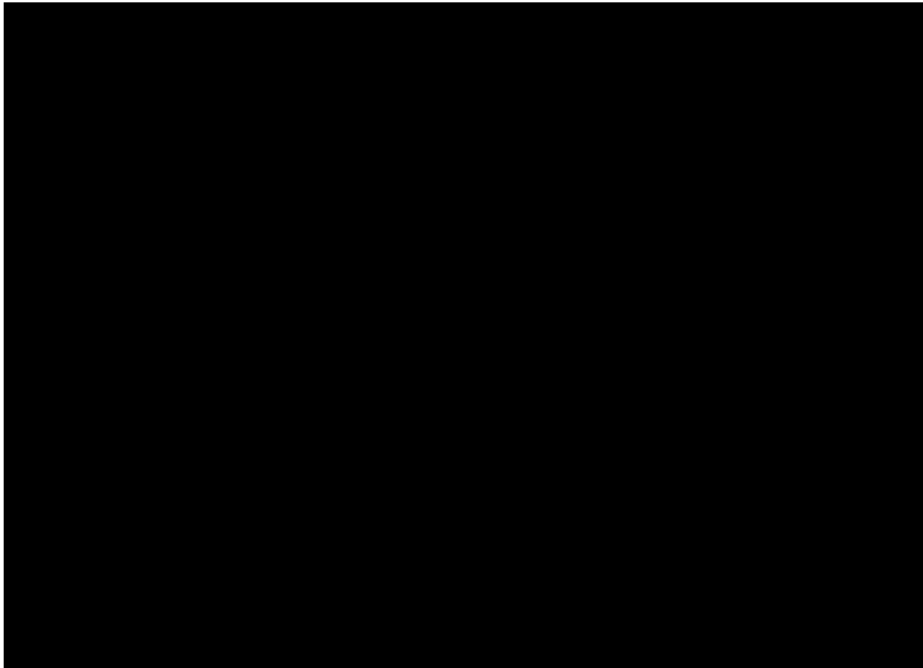
Outcome	Bendamustine		Chlorambucil	
	Clinical trial result	Model result	Clinical trial result	Model result
Response rates	Input directly from trial			
Median PFS	21.6 months	21 months	8.3 months	9 months*
<u>PFS at 12 months</u>	<u>80%</u>	<u>74%</u>	<u>33%</u>	<u>31%</u>
<u>PFS at 24 months</u>	<u>48%</u>	<u>42%</u>	<u>3%</u>	<u>6%</u>
<u>PFS at 36 months</u>	<u>31%</u>	<u>21%</u>	<u>1%</u>	<u>1%</u>
<u>Median OS</u>	<u>Not yet reached</u>	<u>99 months</u>	<u>66 months</u>	<u>69 months</u>
<u>OS at 30 months</u>	<u>88%</u>	<u>88%</u>	<u>83%</u>	<u>81%</u>
<u>OS at 60 months</u>	<u>73%</u>	<u>71%</u>	<u>54%</u>	<u>57%</u>
Adverse events	Input directly from trial			

*Median occurs at between 6 and 9 months.

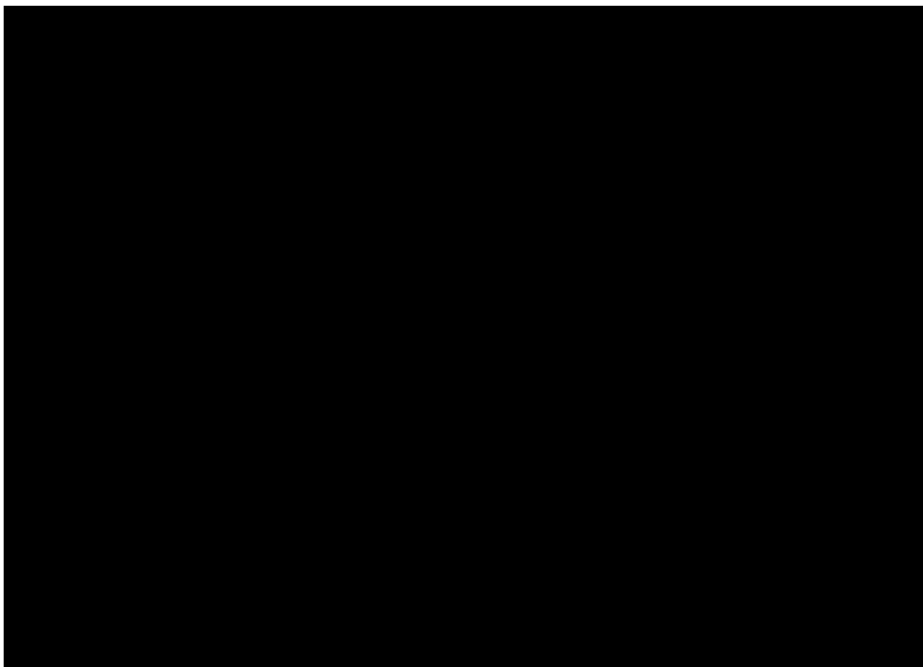
2. Pages 162-163, Section 6.10.5: Please provide the updated overall survival data referred to in this section, including Kaplan-Meier estimates and numbers at risk.

Below are the overall survival curves for the two groups. Also below are the overall survival curves for the complete response (CR) and overall response (OR) for patients receiving either bendamustine or chlorambucil. Where overall response is defined as CR and partial response (PR). These curves

demonstrate the relationship between response rate and overall survival, independent of the therapy received.



Overall survival– Patients with CR compared to all others



Overall survival– Patients with OR compared to all others



3. Appendix 16 (p238-9): In this section, there are details of the number of patients receiving 2nd-line drugs. Please could you provide the total dosage (total mg), summed over all patients, separately for each treatment arm, of: bendamustine, fludarabine, rituximab as second-line treatment

We have checked with the investigator and this data was not collected during the study. Therefore, unfortunately, we are unable to answer this question.