Author’s response to reviews

Title: Response to Imatinib Therapy is Inferior for e13a2 BCR-ABL1 Transcript Type in Comparison to e14a2 Transcript Type in Chronic Myeloid Leukaemia

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We appreciate the reviewer comments provided and agree that the changes suggested enhance the quality of the manuscript. Detailed below are the individual responses to the suggestions made:

1. The method used for quantitative PCR is inadequately described since only a plasmid is referenced. The method should be described plus the method of conversion to the international scale. This is critical since the data is largely based on molecular data and the assessment of milestone molecular responses according to the ELN. Please also provide a reference for the gel electrophoresis method or include the primer sequences. – The methods section has been adjusted to include the appropriate references for this techniques. Line 139-147

2. Figure 1. Please explain what 12 month exc changer means. There is no legend to explain the color coding. – This has been explained in the figure legend and a legend to include colour coding has been incorporated into figure.
3. Figure 2 would be better shown as cumulative incidence graphs with appropriate competing risks. These have been included in the figure for both MMR and MR4.5. A section has been added to the text line 198 including p values for these curves.

4. Figure 2C. How was the probability graph generated? This is not mentioned in the statistics section. Please include the P value and indicate whether the x axis represents months since achieving MMR. –This was calculated using a Kaplan Meier methodology. P value is indicated in text and figure legend.

5. Line 200-204. The text is quite confusing. "There was no significant difference evident between the two groups on comparison of the percentage of patients losing MMR having previously achieved it at any stage. (e13a2: 25.0%, e14a2: 22.5%) however there was a trend towards earlier achievement in the e14a2 group. (e13a2: 9.33months, e14a2: 15.4months) ". Is this a median time to achievement? This would be evident from a cumulative incidence graph. –This appears to have been a typo error. The text has been corrected and the cumulative incidence graphs included as above.

6. Figure 2C. There are a substantial number of patients who did not maintain MMR. It is not clear if these patients developed resistance or whether this was a transient rise above MMR. Please clarify. The majority (70%) were transient loss of MMR. This has been included in the text. See line 209.

7. Figure 4. Please outline what events were included for EFS. –This has been included in the figure legend.

8. Discussion line 300. What does 'real world population' mean? –An unselected patient population without any excluding entry criteria for age, comorbidities etc. This has been noted in the text.
Minor point

1. Statement and reference line 89: "This can represent clonal evolution with acquisition of a mutation in the genomic sequence encoding the BCR-ABL1 transcript in some instances.(10)"
The reference is incorrect since it does not refer to the typical location of the BCR-ABL1 mutations, which is the kinase domain, not the SH2-SH3 domains. Please provide an appropriate reference for kinase domain mutations. – The reference has been adjusted. The new reference is O'Hare T, Eide CA, Deininger MW. Bcr-Abl kinase domain mutations, drug resistance, and the road to a cure for chronic myeloid leukemia. Blood. 2007;110(7):2242-9