25th January 2014

Dear Frances,

## Question

'in the real world population will 32% of the population survive >26 months and what would the attrition rate be for these survivors. If you could point us to the data that would be most relevant for a typical UK population, that would be most helpful'.

## Answer

The simple answers to the question that you ask is YES to part 1 but the attrition rate for survivors beyond 26 months is difficult to estimate as there are no good quality registry data with reliable outcome information. Part 2 of your question - there are no specific UK data that are reliable but I can extrapolate from other sources.

I am not sure how the above question informs the current discussion, but having only been involved in the STA early in the process, I will expand into territory that may be directly relevant to the STA and the PAS. The data that I will discuss below are extracted from the following sources: MDS-004 study analysis of patients with isolated del(5q) which is the EMEA licensed indication,(Mufti et al., 2013) a comparative study of MDS 003/004 data (LEN treated) with a multicenter international registry collaboration (untreated),(Kuendgen et al., 2012) a matched pair analysis (propensity scoring) of LEN treated patients in a French compassionate use programme vs. untreated patients in French clinical trials before the advent of lenalidomide (untreated)(Ades et al., 2012), a smaller French cohort from the compassionate use programme(Le Bras et al., 2011) and finally the community-based EUMDS Registry programme (unpublished) which has registered >1500 patients from 131 centres with low-risk MDS from diagnosis and has a median follow up of 2 years.(Smith et al., 2013)

1. **Are the trial and comparative study populations representative of the real-world?**
   All study populations are younger than the EUMDS population. The oldest study population is the Ades study but the median age is still nearly 4 years younger than EUMDS.
2. **Is this difference clinically significant in the context of overall survival?**
   Maybe not. Within the EUMDS we have not yet analysed outcome for the patients with isolated del(5q) but have a substudy with that intention. However the median (2yr) OS for patients within the subgroups that will contain those with del(5q), namely 'MDS with 5q syndrome', RCMD and RAEB-1 is 83%, 77% and 73% respectively. We have no data on the influence of LEN on these outcomes. This is comparable to the 2yr OS in untreated patients in the Kuendgen series (74%).
3. **What is the OS in LEN treated patients?**
   In a posthoc subgroup analysis of the MDS 004 study patients with isolated del(5q) only treated with LEN 10mg (EMEA licenced indication and dose),

median OS is 4 yrs (median age 69y). Age was a significant determinant of OS in multivariate analysis but only of borderline significance in univariate analysis. In the Ades, series median OS for the LEN treated group was 150 months from diagnosis with a 4 yr survival of 67% from the onset of LEN treatment.

4. **What is the OS in responders to LEN?**
   Difficult to answer confidently but for what it is worth a landmark analysis on relatively small numbers in the 004 study group with isolated del(5q) indicates an OS for responders of 5.7 yrs.
5. **What is the duration of response to LEN?**
   Probably around 2- 2.5 years median response duration. MDS 004 data for isolated del(5q) response duration is not yet reached but 1.6yrs is the lower end of the 95% CI. For all patients with del(5q) the Le Bras study quotes 2 yr response duration of 77%.

I hope that this information will be of help,

Yours sincerely,

Prof David Bowen

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