Supplementary Materials: Low-Intensity and Chemo-Free Treatments in Ph+ ALL: Progression-Free Survival Based on Indirect Comparisons

Melania Rivano, Daniele Mengato, Marco Chiumente and Andrea Messori

Text S1.

Indirect head-to-head efficacy comparisons within individual regimens included in each of the three combination treatment strategies (TKICHE, TKISTE, and TKIBLI).

Introduction

This supplemental material describes the methods and the results of the post-hoc analyses carried out for each of the three combination treatment regimens (TKICHE, TKISTE, and TKIBLI). In these 3 analyses, PFS was the endpoint.

Methods

In designing our main analysis, the regimens reported in at least two different trials were pooled into a single patient group provided that they belonged to the same pharmacological class (TKICHE, TKISTE, and TKIBLI). This choice to pool similar (or even identical) combination treatments from different trials into a single patient group was aimed at avoiding an excessive fragmentation of statistical results but exposed our analysis to an increased risk of underestimating between-trial variability. To manage this issue, each case of data pooling of similar or identical treatments across at least two trials of the same pharmacological class was investigated by a further post-hoc survival analysis, in which the survival data from different trials were kept separate and heterogeneity was assessed formally. In these post-hoc analyses, the patient inclusion criteria of individual trials were also reviewed; this information was then reported in narrative form in Table 1. Heterogeneity was assessed according to the likelihood ratio and concordance tests.

Results

3.1. Survival analysis for the TKICHE regimen (3 trials)

The first group of similar/identical treatments included the combination of TKIs plus chemotherapy according to 3 trials, namely dasatinib + chemotherapy in the trials by Rousselot et al18 and Chiaretti et al20, and nilotinib+ chemotherapy in the Graaph-2014 Study by Rousselot et al.19 The post-hoc analysis for this regimen is described in Figure 1S. Medians of PFS for these three patient groups were the following:

- -Trial [a]: 29.7 months (95%CI, 12.3 to 33.7 months);
- -Trial [b]: not computable (95%CI, 22.5 months to not computable).
- -Trial [c]: not computable (95%CI, 34.0 months to not computable).

Indirect head-to-head comparisons gave the following values of HR:

- Trial [a] vs [b]: HR = 0.47 (95%CI, 0.29 to 0.78);
- Trial [a] vs [c]: HR = 0.57 (95%CI, 0.34 to 0.95);
- Trial [b] vs [c]: HR = 0.83 (95%CI, 0.40 to 1.69).

As shown above, among the 3 head-to-head indirect comparisons, 2 were significant, whereas the third was not. The likelihood ratio test showed a quite strong heterogeneity (likelihood ratio test= 103.7 on 2 df, $p<0.001$) which likely depends on the presence of two significantly different comparisons. Concordance was 0.692 (se = 0.019).

3.2. Survival analysis for the TKISTE regimen (3 trials)

The second group of pharmacologically similar treatments included the combination of TKIs plus steroids, for which three trials were available, namely those by Vignetti et al21, Foà et al22 and Martinelli et al.23 The post-hoc analysis for this regimen is described in Figure 2S. Medians of PFS for these three patient groups were the following:

- -Trial [d]: 21.67 months (95%CI, 11.97 to not computable)
- -Trial [e]: 14.69 months (95%CI, 10.65 to 24.0)
- -Trial [f]: 8.66 months (95%CI, 4.38 to not computable).

The values of HR for the indirect head-to-head comparisons were the following:

- -Trial [e] vs Trial [d]: HR= 1.22 (95%CI, 0.71 to 2.11);
- -Trial [f] vs Trial [d]: HR= 1.53 (95%CI, 0.82 to 2.88);
- -Trial [f] vs Trial [e]: HR=1.26 (95%CI, 0.55 to 2.89).

Finally, the likelihood ratio test (1.76 on 2 df, p=0.4) showed an acceptable homogeneity among these three patient groups. Concordance was 0.533 (se = 0.037).

3.3. Survival analysis for the TKIBLI regimen (2 trials)

Finally, the third group of similar/identical treatments regarded blinatumomab combined with a second or third generation TKI. In this group, we included two trials, namely blinatumomab combined with the second-generation dasatinib as reported by Chiaretti et al24 and blinatumomab combined with the third generation ponatinib reported as preliminary results by Short.25 Quite interestingly, in this case, the two curves were nearly identical (Figure 3S). Since no events were reported in the dasatinib+blinatumomab trial by Chiaretti et al24, both the HR and the likelihood ratio test could not be computed. Likewise, medians -of course- could not be computed from these two curves. However, concordance was high (concordance= 0.799, se = 0.025).

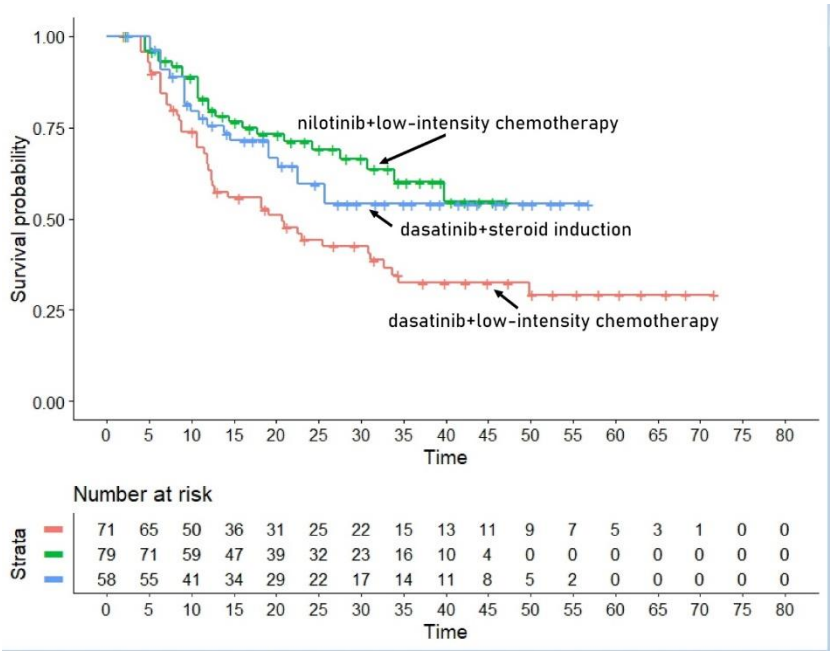

Figure S1. Post-hoc analysis for the TKICHE regimen. The treatments shown in this Kaplan-Meier graph include dasatinib in combination with low-intensity chemotherapy (Rousselot et al [18]) in red, dasatinib plus steroids induction followed by dasatinib alone (Chiaretti et al [20]) in blue, nilotinib combined with chemotherapy (Rousselot et al [19]) in green.

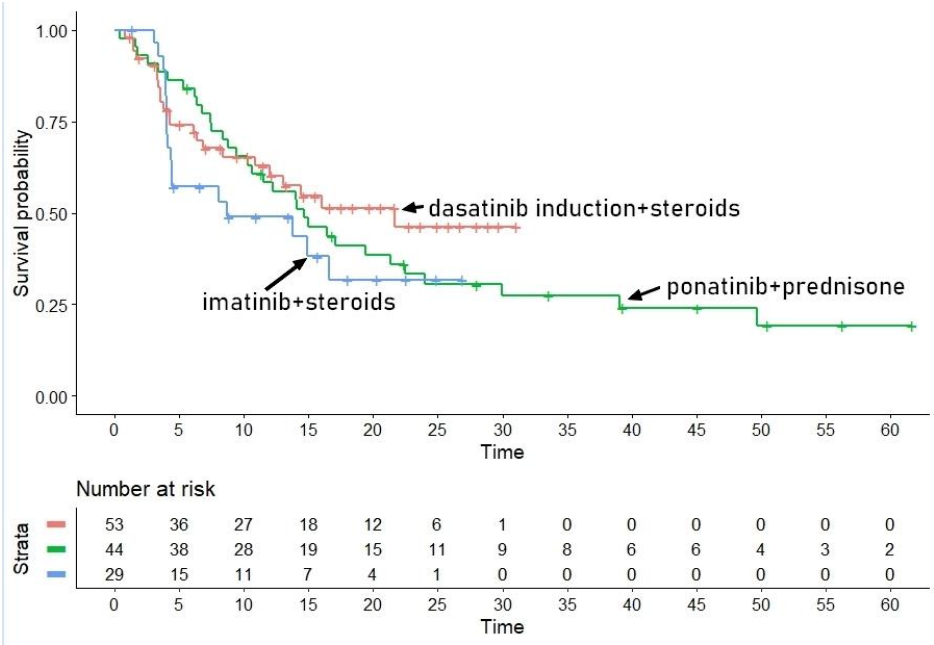

Figure S2. Post-hoc analysis for the TKISTE regimen. In blue imatinib combined with steroids (Vignetti et al [21]), in red dasatinib induction therapy combined with steroids (Foà et al [22]), and in green ponatinib plus prednisone (Martinelli et al [23]).

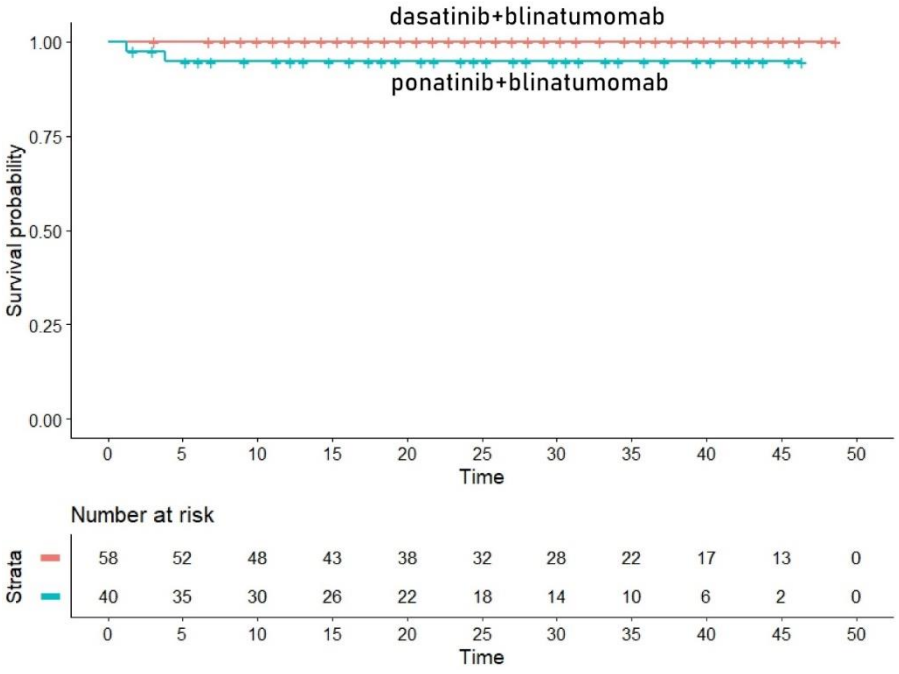

Figure S3. Post-hoc analysis for the TKIBLI regimen. In red dasatinib plus blinatumomab (Chiaretti et al [24]) and in blue, ponatinib plus blinatumomab (Jabbour et al [25]).