Beneficial Effect of Adjuvant Dabrafenib Plus Trametinib on Recurrence-Free Survival in Patients With Resected *BRAF*^{V600}-Mutant Stage III Melanoma Seems to be Short-Lived

TO THE EDITOR:

In their recent article in *Journal of Clinical Oncology*, Hauschild et al¹ reported relapse-free survival (RFS) results after extended follow-up in a randomized trial with adjuvant dabrafenib (D) plus trametinib (T) in patients with resected *BRAF*^{V600}-mutant stage III melanoma. They reported an overall hazard ratio estimate of 0.47 in favor of D plus T. Kaplan-Meier plots suggest that there is a sustained treatment effect because the 4-year RFS rates were 54% in the D plus T arm and 38% in the placebo arm.

Using the methods and R code described in the article by Guyot et al,² I reconstructed a reasonable facsimile of the individual patient RFS data from the study on the basis of the published Kaplan-Meier plots. From these reconstructed data, I generated Kaplan-Meier curves similar to the ones shown in Figure 2A in the article by Hauschild et al.¹ According to my data, the 1- and 4-year RFS rates are 88% and 54% for D plus T; for the control arm, the 1- and 4-year RFS rates are 56% and 38%.

Conventionally, the hazard ratio is used to measure the treatment effect (ie, effect of treatment on RFS). The hazard ratio is assumed constant over time. Violations of this proportional hazards assumption are not well diagnosed by inspection of the Kaplan-Meier curves. Additional analyses are needed. One approach to

assess violations of the proportional hazards assumption is to smooth rescaled Schoenfeld residuals to yield estimates of the time-varying hazard ratio.³ As shown in Fig 1, the estimated hazard ratio is 0.18 (95% CI, 0.12 to 0.25) at 3 months, 0.26 (95% CI, 0.18 to 0.37) at 6 months, 0.58 (95% CI, 0.40 to 0.84) at 12 months, 1.14 (95% CI, 0.80 to 1.64) at 18 months, and 1.65 (95% CI, 0.96 to 2.85) at 36 months.

Alternatively, we can partition survival time into multiple intervals and estimate the hazard ratio separately in each interval. If we partition time into 0 to 6 months, 6 to 12 months, and longer than 12 months, the average hazard ratio is 0.10 (95% CI, 0.05 to 0.18) for 0 to 6 months, 0.42 (95% CI, 0.26 to 0.69) for 6 to 12 months, and 1.19 (95% CI, 0.85 to 1.67) for longer than 12 months. Among patients surviving 12 months, the 4-year conditional recurrence-free survival is 61% for D plus T and 68% for control subjects.

Additional insight into the data can be obtained by inspecting the hazard functions for each treatment arm.⁴ The hazard rate at a given time is the conditional failure rate among those patients remaining under follow up at that time. Mathematically, the hazard rate is the negative first derivative of the log survival function. In contrast to the Kaplan-Meier plots of the cumulative RFS probabilities, the corresponding hazard function estimates shown in Fig 2 indicate that while the D plus T hazard rate starts low and gradually rises for the first 20 months and then slowly declines, the placebo hazard function starts high and then declines rapidly, crossing the D plus T hazard function at approximately 15 months. After 15 months, the two hazard functions are similar. The early separation of the hazard functions followed by convergence clearly illustrates that the advantage of D plus T treatment over placebo is limited to the first 12 to 15 months of follow-up.

FIG 1. Hazard ratio function estimate.

FIG 2. Hazard function estimates by treatment arm.

Thus it is wrong to conclude that there is an ongoing treatment effect for D plus T on the basis of data from this trial. The treatment effect is real but transient in nature. This illustrates the importance of not relying solely on the Kaplan-Meier estimates to assess the effects of treatment on times to events. Analyses of the hazard and hazard ratio function are important to gain additional insight into clinical data.

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST AND DATA AVAILABILITY STATEMENT

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AUTHOR'S DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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