Background

In COMBI-AD analysis, 5-year relapse-free survival (RFS) rates were 52% in patients with stage III BRAF V600E-mutant melanoma who received dabrafenib + trametinib compared with 36% in those who received placebo.

Kaplan-Meier and Cox regression analyses have been used to assess adjuvant treatment effects based on time-to-event analyses.3,4

Unfortunately, these statistical methods do not account for nonproportional hazards and the fact that some patients never experience relapse.5-8

To overcome these limitations, we evaluated treatment effects in COMBI-AD using:

- Restricted mean survival time (RMST): population average for the length of event-free survival time estimated by the area under a survival curve up to a specified time point that accounts for nonproportional hazards.9

- Cure-rate modeling: a statistical approach to model time-to-event data that estimates the proportion of patients in each treatment arm who may never experience an event of interest (ie, relapse).10

Methods

COMBI-AD (NCT01626063) is a double-blind, randomized, Phase III trial that compared 12 months of adjuvant dabrafenib 150 mg twice daily + trametinib 2 mg once daily vs 3 matched placebo in patients with resected stage III BRAF V600E/K-mutant melanoma (Figure 1).

Patients were stratified by BRAF V600E or V600K status and disease stage by AJCC 7th edition criteria.11

RMST analysis:

The length of event-free survival time (ie, RFS) was estimated by the area under a survival curve up to a specified time point that accounts for nonproportional hazards.

RMST: Subgroup Analysis

- RMST was improved with dabrafenib + trametinib across all AJCC 7 stage III subgroups, with the greatest difference in RMST between arms reported in patients with stage IIIA and IIIC disease (Table 1, Figure 3A-C).

Cure-Rate Analysis: Subgroup Analysis

- The estimated cure rate was improved with dabrafenib + trametinib across all AJCC 7 stage III subgroups, with the greatest difference between arms reported in patients with stage IIIB and IIIC disease (Figure 4).

Results

RMST:

- Median duration of follow-up was 65 months in the dabrafenib + trametinib arm and 58 months in the placebo arm (data cutoff, November 8, 2019).

- RMST across the stage III patient population was improved in the dabrafenib + trametinib arm (41.5 months [95% CI, 39.4-43.6 months]) vs the placebo arm (28.7 months [95% CI, 26.3-31.3 months]) (Figure 2, Table 1).

- These results suggest that on average, a 60-month period, patients treated with dabrafenib + trametinib gain an additional 12.8 months of remaining relapse-free vs placebo.

Cure-Rate Analysis:

- The estimated cure rate in the overall stage III population was 59% (95% CI, 46%-65%) in the dabrafenib + trametinib arm compared with 35% (95% CI, 30%-40%) in the placebo arm (Figure 4).

- These analyses provide insights into long-term clinical benefits of adjuvant therapy with dabrafenib + trametinib; overall survival analysis is currently ongoing.

Conclusions

- RMST and cure-rate model analyses complement and enhance conventional statistical approaches, including Kaplan-Meier and Cox regression analyses, and facilitate clinical interpretation of treatment effects for oncologists and patients.

- Results from RMST and cure-rate modeling analyses suggest that treatment with dabrafenib + trametinib leads to durable RFS benefit compared with placebo.

- There was an absolute increase of 45% in the proportion of patients who were cured in the dabrafenib + trametinib arm vs the placebo arm.

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First Author Disclosures

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