Association Between Baseline Disease Characteristics and Relapse-Free Survival in Patients With *BRAF* V600–Mutant Resected Stage III Melanoma Treated With Adjuvant Dabrafenib + Trametinib or Placebo

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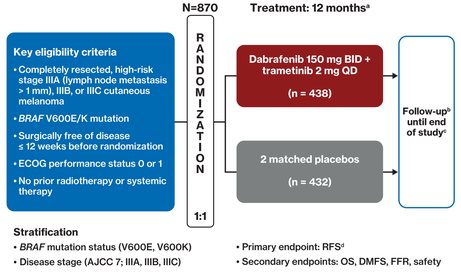
Background

- In the double-blind, randomized, phase 3 COMBI-AD trial (NCT01682083), 12 months of adjuvant dabrafenib + trametinib led to significant improvement in relapse-free survival (RFS) and distant metastasis-free survival (DMFS) vs placebo (RFS hazard ratio [HR], 0.47; $P < .001$; DMFS HR, 0.51; $P < .001$) in patients with resected *BRAF* V600–mutant stage III melanoma[1,2]
  - In the dabrafenib + trametinib arm, 3- and 4-year RFS rates were 59% and 54%, respectively[1]
  - In the dabrafenib + trametinib arm, 3- and 4-year DMFS rates were 71% and 67%, respectively[1]
- A cure-rate model estimated that treatment with dabrafenib + trametinib led to a 17% absolute increase in the proportion of patients who will remain relapse free long term[1]
- An interim analysis of overall survival (OS) showed a clinically meaningful improvement with dabrafenib + trametinib vs placebo (HR, 0.57 [95% CI, 0.42-0.79])[2]
- The safety profile of the combination was consistent with that observed in patients with metastatic melanoma[2]
- Based on these trial results, dabrafenib + trametinib has been approved by multiple regulatory agencies globally, including the US Food and Drug Administration and European Commission, for the treatment of patients with resected *BRAF* V600–mutant stage III melanoma[3-6]
- **Previous subgroup analysis of RFS demonstrated similar treatment benefit favoring dabrafenib + trametinib regardless of baseline factors, including[1]:**
  - **Disease stage (per American Joint Committee on Cancer [AJCC] 7th and 8th editions)**
  - **Micrometastases/macrometastases**
  - **Ulceration of the primary tumor**
- We present an updated analysis evaluating the association between baseline disease characteristics and RFS to identify patient subgroups likely to benefit from adjuvant treatment

Methods

- COMBI-AD was a randomized, phase 3 study of dabrafenib + trametinib in patients with completely resected stage III *BRAF* V600E/K–mutant melanoma (**Figure 1**)[1,7]

Figure 1. Study Design



BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; QD, once daily.
[a]Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent; [b]Patients were followed up for disease recurrence until the first recurrence and thereafter for survival; [c]The study will be considered complete and final OS analysis will occur when ≈ 70% of randomized patients have died or are lost to follow-up; [d]New primary melanoma considered as an event.

Analysis of the Association of Baseline Factors With RFS

- Within each subgroup, the Kaplan-Meier method was used to estimate RFS, and HRs were calculated using a Pike estimator
  - Covariates including age, sex, T stage, N stage, in-transit metastases, and histological subtype were analyzed
  - Tumor staging was assessed according to AJCC 7th edition criteria

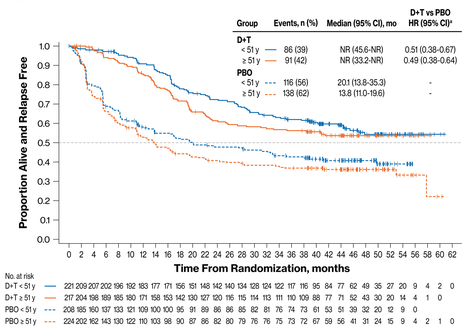
Data Set

- Analyses were based on the data cutoff date for an updated analysis of the COMBI-AD study (April 30, 2018)
  - Minimum follow-up was 40 months for 870 enrolled patients (dabrafenib + trametinib, n = 438; placebo, n = 432)

Results

- The median age of patients in COMBI-AD was 51 years. Kaplan-Meier analysis of RFS based on age (< median or ≥ median) demonstrated improved RFS in patients treated with dabrafenib + trametinib vs placebo regardless of age (**Figure 2**)
  - Age < 51 years: Median RFS was not reached in the dabrafenib + trametinib arm vs 20.1 months in the placebo arm (HR, 0.51 [95% CI, 0.38-0.67])
  - Age ≥ 51 years: Median RFS was not reached in the dabrafenib + trametinib arm vs 13.8 months in the placebo arm (HR, 0.49 [95% CI, 0.38-0.64])

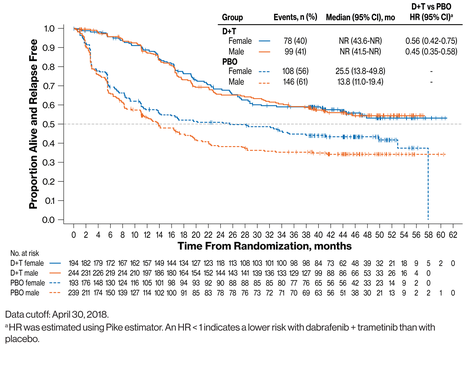
Figure 2. Investigator-Assessed Kaplan-Meier RFS Curves by Age



Data cutoff: April 30, 2018.
D, dabrafenib; NR, not reached; PBO, placebo; T, trametinib.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

- Kaplan-Meier analysis demonstrated that dabrafenib + trametinib improved RFS vs placebo regardless of patients' sex (**Figure 3**)
  - Female patients: Median RFS was not reached in the dabrafenib + trametinib arm vs 25.5 months in the placebo arm (HR, 0.56 [95% CI, 0.42-0.75])
  - Male patients: Median RFS was not reached in the dabrafenib + trametinib arm vs 13.8 months in the placebo arm (HR, 0.45 [95% CI, 0.35-0.58])

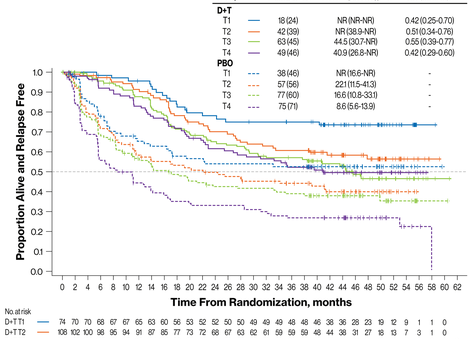
Figure 3. Investigator-Assessed Kaplan-Meier RFS Curves by Sex



Data cutoff: April 30, 2018.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

- RFS benefit consistently favored dabrafenib + trametinib vs placebo across all T stages classified per AJCC 7th edition criteria (**Figure 4**)
  - T1: Median RFS was not reached in the dabrafenib + trametinib or placebo arms (HR, 0.42 [95% CI, 0.25-0.70])
  - T2: Median RFS was not reached in the dabrafenib + trametinib arm vs 22.1 months in the placebo arm (HR, 0.51 [95% CI, 0.34-0.76])
  - T3: Median RFS was 44.5 months in the dabrafenib + trametinib arm vs 16.6 months in the placebo arm (HR, 0.55 [95% CI, 0.39-0.77])
  - T4: Median RFS was 40.9 months in the dabrafenib + trametinib arm vs 8.6 months in the placebo arm (HR, 0.42 [95% CI, 0.29-0.60])

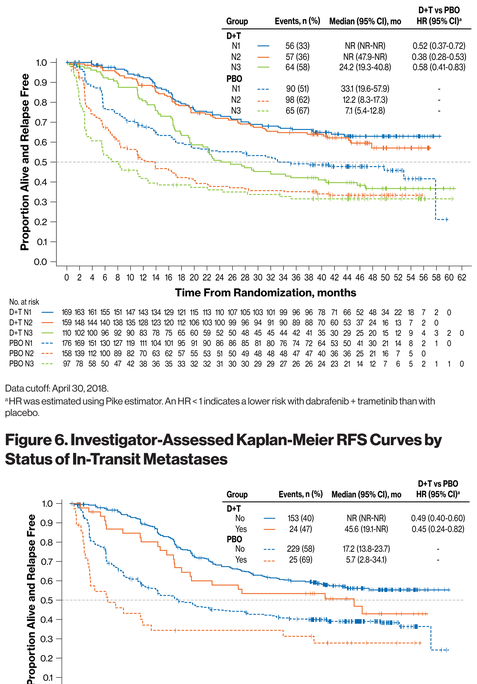
Figure 4. Investigator-Assessed Kaplan-Meier RFS Curves by T stage



Data cutoff: April 30, 2018.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

- RFS was longer with dabrafenib + trametinib than with placebo across all N stages classified per AJCC 7th edition criteria (**Figure 5**)
  - N1: Median RFS was not reached in the dabrafenib + trametinib arm vs 33.1 months in the placebo arm (HR, 0.52 [95% CI, 0.37-0.72])
  - N2: Median RFS was not reached in the dabrafenib + trametinib arm vs 12.2 months in the placebo arm (HR, 0.38 [95% CI, 0.28-0.53])
  - N3: Median RFS was 24.2 months in the dabrafenib + trametinib arm vs 7.1 months in the placebo arm (HR, 0.58 [95% CI, 0.41-0.83])
- RFS benefit favored dabrafenib + trametinib vs placebo regardless of the absence or presence of in-transit metastases (**Figure 6**)
  - In patients without in-transit metastases, median RFS was not reached in the dabrafenib + trametinib arm vs 17.2 months in the placebo arm (HR, 0.49 [95% CI, 0.40-0.60])
  - In patients with in-transit metastases, median RFS was 45.6 months in the dabrafenib + trametinib arm vs 5.7 months in the placebo arm (HR, 0.45 [95% CI, 0.24-0.82])

Figure 5. Investigator-Assessed Kaplan-Meier RFS Curves by N stage

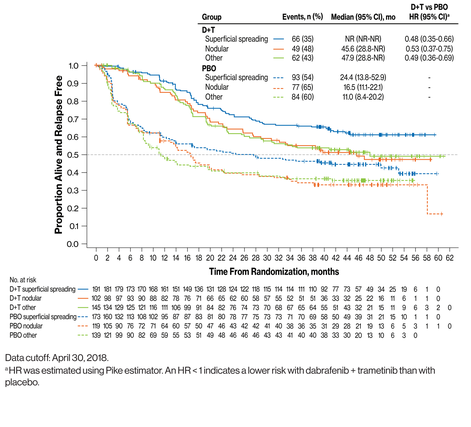


Data cutoff: April 30, 2018.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

Figure 6. Investigator-Assessed Kaplan-Meier RFS Curves by Status of In-Transit Metastases

Data cutoff: April 30, 2018.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

Figure 7. Investigator-Assessed Kaplan-Meier RFS Curves by Histological Subtype (superficial spreading, nodular, other)



Data cutoff: April 30, 2018.
[a]HR was estimated using Pike estimator. An HR < 1 indicates a lower risk with dabrafenib + trametinib than with placebo.

- Dabrafenib + trametinib improved RFS vs placebo regardless of histological subtype (**Figure 7**)
  - In patients with nodular melanoma, median RFS was 45.6 months in the dabrafenib + trametinib arm vs 16.5 months in the placebo arm (HR, 0.53 [95% CI, 0.37-0.75])
  - In patients with superficial spreading melanoma, median RFS was not reached in the dabrafenib + trametinib arm vs 24.4 months in the placebo arm (HR, 0.48 [95% CI, 0.35-0.66])

Conclusions

- RFS benefit favored dabrafenib + trametinib in patients with completely resected stage III *BRAF* V600E/K–mutant melanoma vs placebo regardless of the following baseline factors, confirming previous findings[1]:
  - Age
  - Sex
  - T stage
  - N stage
  - Status of in-transit metastases
  - Histological subtype
- This updated analysis supports the use of dabrafenib + trametinib regardless of clinical and pathological factors at treatment initiation

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