Restricted Mean Survival Time and Cure-Rate Modeling in Estimating Relapse-Free Survival Benefit With Adjuvant Dabrafenib + Trametinib Treatment in Melanoma

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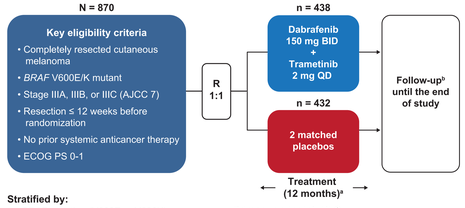
Background

- In COMBI-AD analysis, 5-year relapse-free survival (RFS) rates were 52% in patients with stage III *BRAF* V600–mutant melanoma who received ≤ 12 months of dabrafenib + trametinib compared with 36% in those who received placebo[1]
- Kaplan-Meier and Cox regression analyses have been used to assess adjuvant treatment effects based on time-to-event analyses[1-3]
- Unfortunately, these statistical methods do not account for nonproportional hazards and the fact that some patients never experience relapse[4-8]
- 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[4-7]
  - **Cure-rate modeling:** a statistical approach to model time-to-event data that estimates the proportion of patients in each arm who may never experience an event of interest (eg, relapse)[8,9]

Methods

- COMBI-AD (NCT01682083) 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 2 matched placebos 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 7 criteria)
- **RMST analysis**
  - The length of event-free survival time (ie, RFS) was estimated by assessing the area under the Kaplan-Meier curve up to 60 months of follow-up time in each treatment arm
- **Cure-rate modeling**
  - The use of a cure-rate model is considered appropriate because it is reasonable to assume there is a subset of patients in each disease substage who are "cured" by resection alone and will remain relapse free. This assumption is supported by the appearance of a plateau in RFS Kaplan-Meier curves
  - A mixed Weibull cure-rate model was used to estimate the proportion of patients who might never experience disease relapse

Figure 1. COMBI-AD Study Design



AJCC, American Joint Committee on Cancer; AJCC 7, *AJCC Cancer Staging Manual*, 7th edition; BID, twice daily; DMFS, distant metastasis–free survival; ECOG PS, Eastern Cooperative Oncology Group performance status; FFR, freedom from relapse; OS, overall survival; QD, once daily; R, randomization; RFS, relapse-free survival.

[a] Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent.

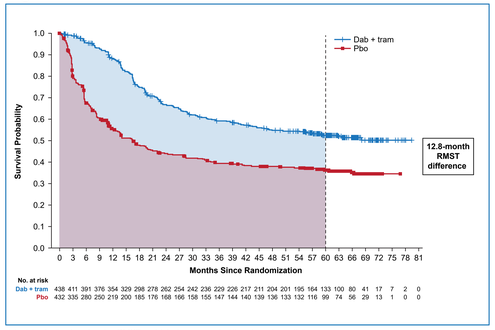
[b] Patients were followed up for disease recurrence until the first recurrence and thereafter for survival.

Results

RMST

- Median duration of follow-up was 60 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, 26.3-31.2 months]) (**Figure 2**; **Table 1**)
  - These results suggest that on average, over a 60-month period, patients treated with dabrafenib + trametinib gain an additional 12.8 months of remaining relapse free vs placebo

Figure 2. Overall RMST at 60 Months



dab, dabrafenib; pbo, placebo; RMST, restricted mean survival time; tram, trametinib.

RMST: Subgroup Analysis

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

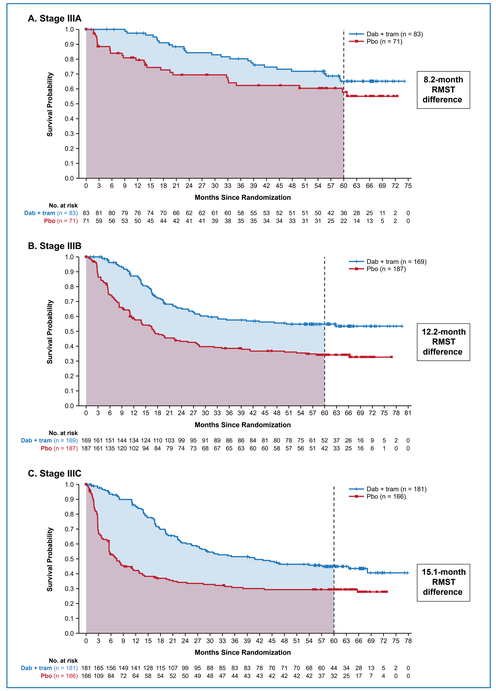
Table 1. RMST at 60 Months

	Overall		Stage IIIA[a]		Stage IIIB[a]		Stage IIIC[a]	
	Dab + Tram (n = 438)	Pbo (n = 432)	Dab + Tram (n = 83)	Pbo (n = 71)	Dab + Tram (n = 169)	Pbo (n = 187)	Dab + Tram (n = 181)	Pbo (n = 166)
Events, n	187	259	25	26	69	117	90	112
RMST (95% CI), mo	41.5 (39.4-43.6)	28.7 (26.3-31.2)	50.4 (46.7-54.2)	42.2 (36.4-47.9)	41.2 (37.7-44.7)	29.0 (25.4-32.6)	38.0 (34.6-41.3)	22.8 (18.9-26.8)
RMST difference (95% CI), mo	12.8 (9.5-16.0)		8.2 (1.4-15.1)		12.2 (7.2-17.2)		15.1 (10.0-20.3)	

dab, dabrafenib; pbo, placebo; RMST, restricted mean survival time; tram, trametinib.

[a] Per American Joint Committee on Cancer's *AJCC Cancer Staging Manual*, 7th edition.

Figure 3. RMST at 60 Months in the (A) Stage IIIA, (B) Stage IIIB, and (C) Stage IIIC Subgroups (AJCC 7)

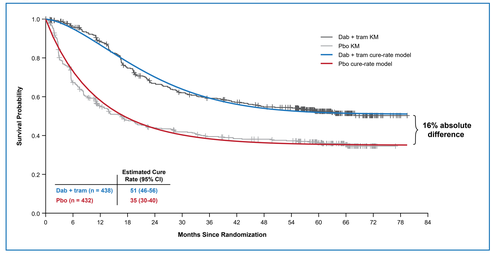


AJCC, American Joint Committee on Cancer; AJCC 7, *AJCC Cancer Staging Manual*, 7th edition; dab, dabrafenib; pbo, placebo; RMST, restricted mean survival time; tram, trametinib.

Cure-Rate Analysis

- The estimated cure rate in the overall stage III population was 51% (95% CI, 46%-56%) in the dabrafenib + trametinib arm compared with 35% (95% CI, 30%-40%) in the placebo arm (**Figure 4**)

Figure 4. Cure-Rate Model Analysis

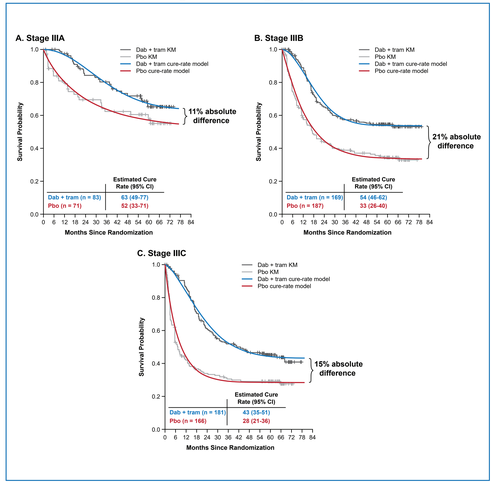


dab, dabrafenib; KM, Kaplan-Meier; pbo, placebo; tram, trametinib.

Cure-Rate Analysis: Subgroup Analysis

- The estimated cure rate was improved with dabrafenib + trametinib across all AJCC 7 stage III substages, with the greatest difference between arms reported in patients with stage IIIB and IIIC disease (**Figure 5A-C**)

Figure 5. Cure-Rate Model Analysis for the (A) Stage IIIA, (B) Stage IIIB, and (C) Stage IIIC Subgroups (AJCC 7)



AJCC, American Joint Committee on Cancer; AJCC 7, *AJCC Cancer Staging Manual*, 7th edition; dab, dabrafenib; KM, Kaplan-Meier; pbo, placebo; tram, trametinib.

Conclusions

- RMST and cure-rate model analyses complement and enhance conventional statistical approaches, including Kaplan-Meier and Cox regression analyses, and may 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
  - RMST analysis suggests that over a 60-month period, patients treated with dabrafenib + trametinib gain 12.8 months of RFS on average compared with placebo
  - There was an absolute increase of 16% in the proportion of patients who were cured in the dabrafenib + trametinib arm vs the placebo arm
- These analyses provide insights into long-term clinical benefits of adjuvant therapy with dabrafenib + trametinib; overall survival analysis is currently ongoing

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Acknowledgements

We thank the patients and their families for participating in this study.

We also thank all investigators and site staff for their contributions.

We thank Lali Sandalic (Novartis Pharmaceuticals Corporation) for providing statistical analysis support.

We also thank Maurizio Voi, MD (Novartis Pharmaceuticals Corporation), for guidance and critical review.

We thank Zareen Khan, PhD, from ArticulateScience LLC, for medical editorial assistance with this presentation, which was funded by Novartis Pharmaceuticals Corporation (East Hanover, NJ), in accordance with Good Publication Practice (GPP3) (https://www.ismpp.org/gpp3) guidelines and International Committee of Medical Journal Editors recommendations.

This study was sponsored by GlaxoSmithKline; dabrafenib and trametinib are assets of Novartis as of March 2, 2015.

COMBI-AD is registered at ClinicalTrials.gov (NCT01682083) and conducted in accordance with Study Protocol BRF115532.

First Author Disclosures

JM Kirkwood reports grants and personal fees from Amgen, Bristol Myers Squibb, Checkmate Pharmaceuticals, and Novartis, and grants from Castle Biosciences, Immunocore LLC, and Iovance, outside of the presented work.

Presented online as part of the Winter Clinical Dermatology Virtual Conference 2021; January 16-24, 2021.

Previously presented online as part of the ESMO Virtual Congress 2020; September 19-21, 2020.

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