Prediction of Melanoma Relapse-Free Survival (RFS) in Patients With Completely Resected, *BRAF* V600E/K–mutant, Stage III Cutaneous Melanoma

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Background

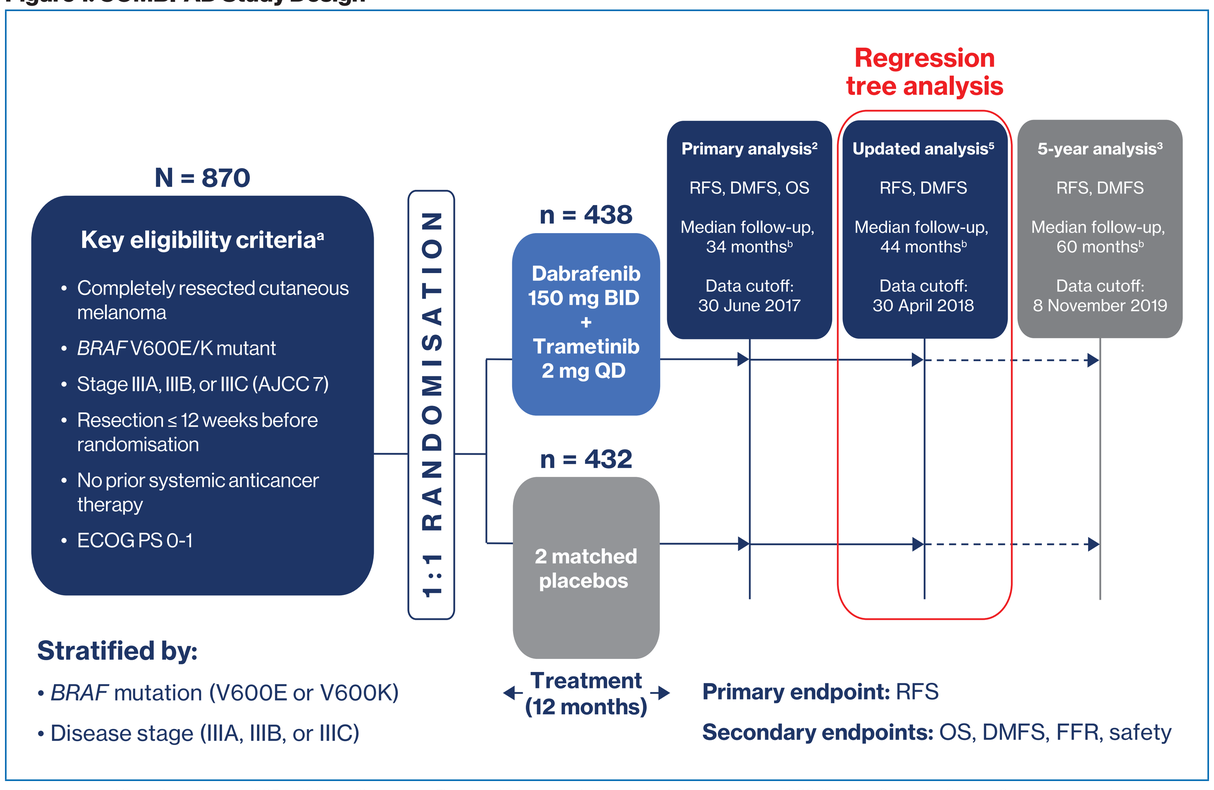
- Many patients with stage III melanoma are at high risk for disease recurrence after surgical resection, and adjuvant treatment can reduce the risk of recurrence[1]
- COMBI-AD is a randomized, Phase III study (NCT01682083) evaluating 12 months of adjuvant therapy with dabrafenib plus trametinib vs placebo after complete resection in patients with *BRAF* V600E/K mutation–positive stage III melanoma (**Figure 1**)[2]
- With a median follow-up of 60 months in the dabrafenib plus trametinib arm (data cutoff, 8 November 2019), dabrafenib plus trametinib was associated with improved long-term RFS vs placebo, with 52% vs 36% of patients alive and relapse free at 5 years, respectively (hazard ratio, 0.51 [95% CI, 0.42-0.61])[3]
- RFS benefit was consistent across all American Joint Committee on Cancer's *Cancer Staging Manual*, 7th edition (AJCC 7) stage III subcategories, and data were consistent when patients were retrospectively reclassified according to the *AJCC Cancer Staging Manual*, 8th edition (AJCC 8).[3] However, specific baseline characteristics predictive of long-term RFS benefit have yet to be identified
- Previously, we performed a regression tree analysis on pooled data from the Phase III COMBI-d and COMBI-v studies and the Phase II BRF113220 study, which helped physicians understand the baseline patient characteristics predictive of better outcomes with treatment with dabrafenib plus trametinib[4]
- We present a regression tree analysis (data cutoff, 30 April 2018) performed to evaluate the potential of baseline clinical factors as prognostic or predictive factors in the adjuvant setting

Methods

Regression Tree Analysis

- A regression tree analysis was performed on clinical data sets from COMBI-AD to identify and classify subgroups of patients with similar outcomes in terms of RFS (data cutoff, 30 April 2018)
- Baseline characteristics evaluated included age, sex, geographical region, *BRAF* mutation status, disease stage (AJCC 8), ulceration status, histological subgroup, presence of in-transit disease, number of positive lymph nodes, baseline lactate dehydrogenase level, smoking history, and cancer history. Treatment received (dabrafenib plus trametinib or placebo) was also considered (**Table 1**)
- During development, 80% of data were used to train and develop models, identify key baseline factors, and assess their importance; the remaining 20% were used to validate the discriminative ability of the model, as measured by C index (**Figure 2**)

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; RFS, relapse-free survival.
[a] COMBI-AD is registered at ClinicalTrials.gov (NCT01682083). [b] Median follow-up shown is for the dabrafenib plus trametinib arm.

Figure 2. Statistical Methods

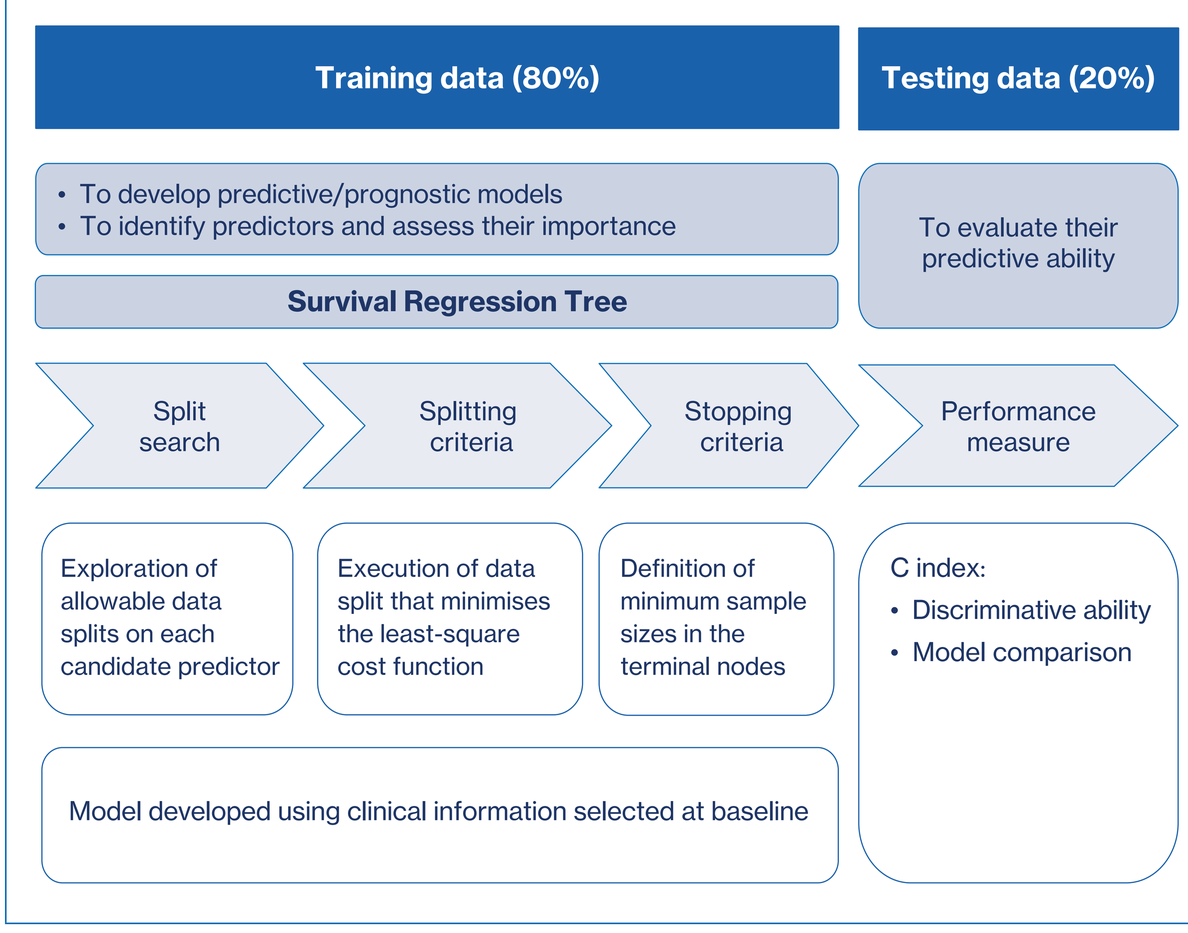


Table 1. Baseline Characteristics Evaluated

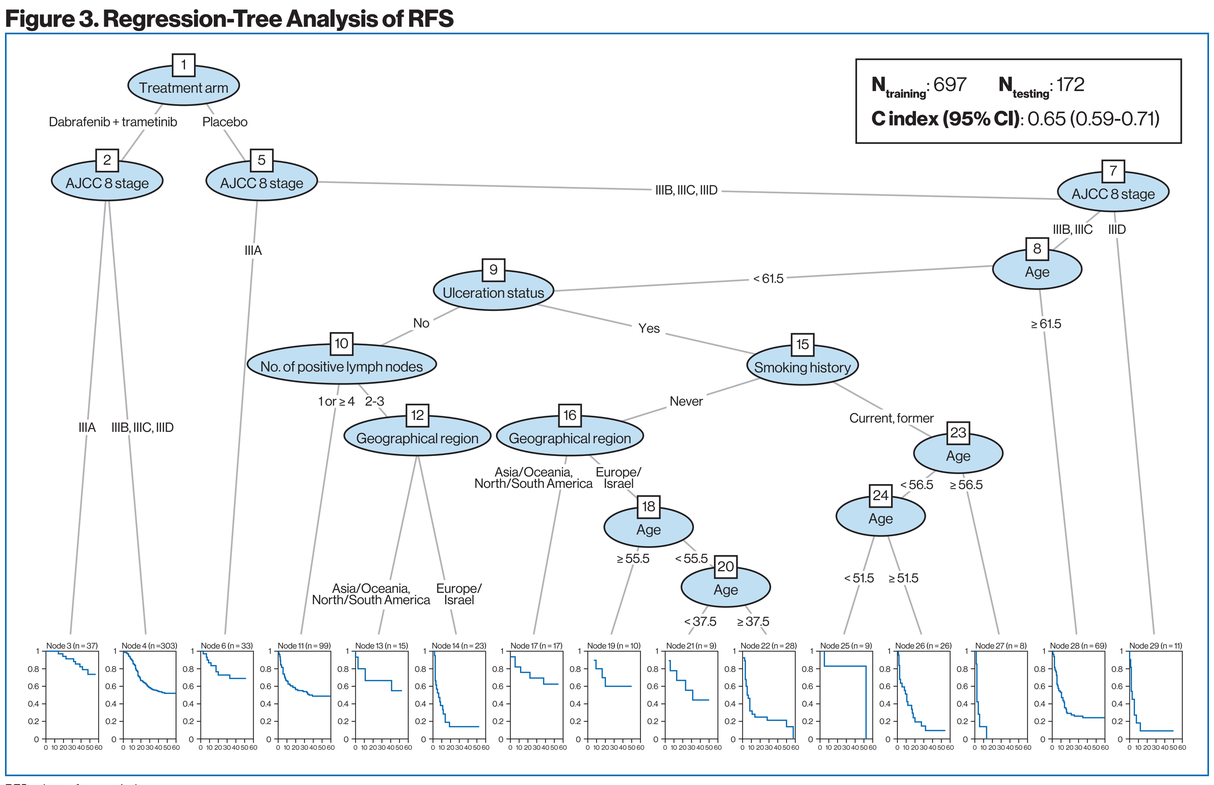
Characteristic	Categories
Age	Numerical variable
Sex	Male or female
Geographical region	Asia/Oceania, North/South America, or Europe/Israel
BRAF mutation at randomisation	V600E or V600K
AJCC 8 melanoma stage	IIIA, IIIB, IIIC, or IIID
Treatment arm	Dabrafenib plus trametinib or placebo
Ulceration status	Yes or no
Histological group	Superficial spreading melanoma, nodular melanoma, or other
In-transit disease	Yes or no
No. of positive lymph nodes	1, 2-3, or ≥ 4
Baseline LDH level	> ULN or ≤ ULN
Smoking history	Current/former or never
History of other cancers	Yes, no, or unknown

AJCC, American Joint Committee on Cancer; AJCC 8, *AJCC Cancer Staging Manual*, 8th edition; LDH, lactate dehydrogenase; ULN, upper limit of normal.

Results

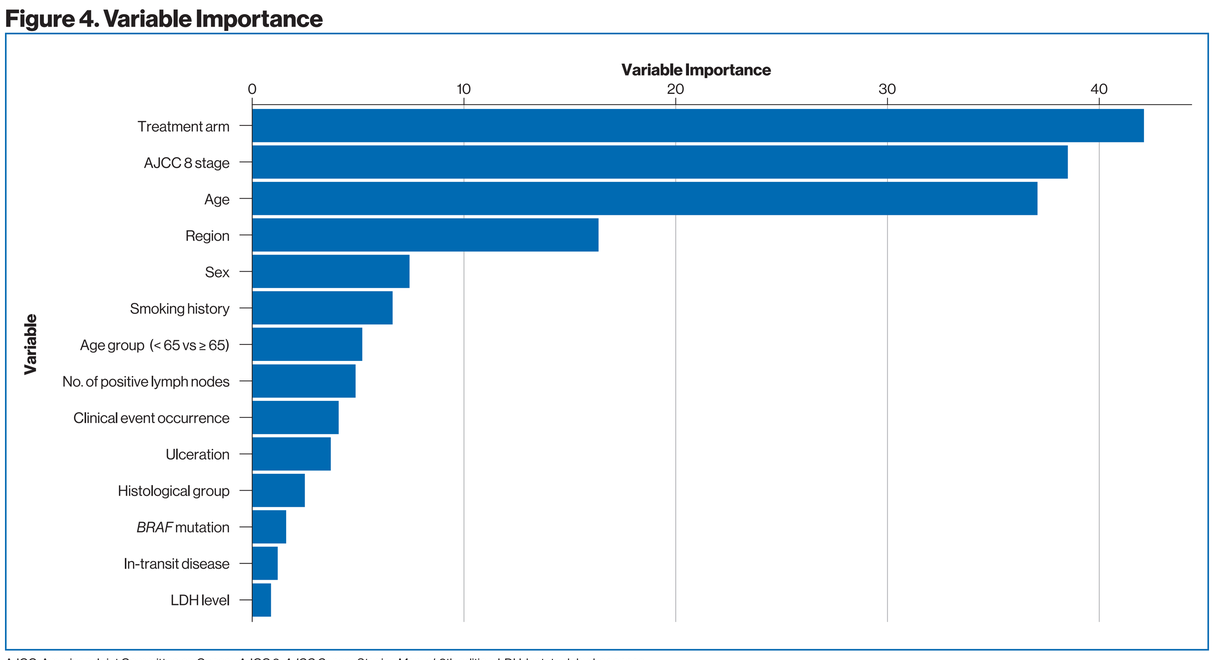
- The model ($N_{training}$ = 697; $N_{testing}$ = 172) was developed using baseline clinical characteristics. Treatment, disease stage, age, ulceration status, number of positive lymph nodes, smoking history, and geographical region emerged as factors upon which patients were separated according to the model. The final partition of the original sample resulted in 15 groups, each indicated by a Kaplan-Meier estimate (C index, 0.65 [95% CI, 0.59-0.71]) (**Figure 3**)
- The first split is based on treatment (dabrafenib plus trametinib vs placebo), separating a group of 340 patients who received dabrafenib plus trametinib from a group of 357 patients who received placebo. This result confirms previous findings of a strong treatment effect of adjuvant dabrafenib plus trametinib vs placebo
- Amongst patients who received dabrafenib plus trametinib, a second split occurred at node 2 and is based on AJCC 8 disease stage; 37 patients with stage IIIA disease were separated from 303 patients with stage IIIB/IIIC/IIID disease
  - Patients with stage IIIA disease had better RFS outcomes relative to patients with stage IIIB/IIIC/IIID disease, confirming the prognostic value of disease stage[1] and demonstrating consistency with subgroup analyses performed in COMBI-AD[3]
- Amongst patients who received placebo, 33 patients with stage IIIA disease were separated from 324 patients with stage IIIB/IIIC/IIID disease (node 5); 313 patients with stage IIIB/IIIC were separated from 11 patients with stage IIID disease (node 7)
  - Patients with stage IIIA disease had better RFS outcomes relative to patients with stage IIID disease, again consistent with the prognostic value of disease stage[1]
  - Patients with stage IIIB/IIIC disease were further separated by several other factors, including age, ulceration status, number of positive lymph nodes, smoking status, and geographical region. However, due to relatively small patient numbers, it is difficult to draw meaningful conclusions based on these variables
- Clinical variables were ranked according to importance, and, consistent with the regression tree, treatment, disease stage, and age emerged as the most important clinical variables that were evaluated (**Figure 4**)
  - The model demonstrated an ability to handle multicollinearity as shown by the appearance of highly correlated variables within the graph that do not appear in the regression tree

Figure 3. Regression-Tree Analysis of RFS



RFS, relapse-free survival.

Figure 4. Variable Importance



AJCC, American Joint Committee on Cancer; AJCC 8, *AJCC Cancer Staging Manual*, 8th edition; LDH, lactate dehydrogenase.

Conclusions

- Patients with stage IIIA disease had better RFS outcomes than did patients with stage IIIB/IIIC/IIID disease regardless of treatment arm
  - Dabrafenib plus trametinib treatment, lower disease stage (stage IIIA), and age were the important predictors of RFS (C index, 0.65 [95% CI, 0.59-0.71])
- Amongst patients who received placebo, those with stage IIID disease generally had poorer outcomes than those with stage IIIB/IIIC disease
- The discriminative ability was > 60%, suggesting good differentiation between patient subgroups. The model handles multicollinearity, but there may be some challenges with data overfitting
- These results confirm the findings of a prior analysis of baseline disease characteristics with RFS benefit performed on data from the COMBI-AD study[6] and support the current modelling approach, which may be used in subsequent analyses to assess predictive factors
- Further model refinement could be conducted with the inclusion of additional clinical variables and patient characteristics, potentially including biomarkers

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

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