Efficacy Outcomes in the Phase 3 COMBI-AD Study of Adjuvant Dabrafenib Plus Trametinib vs Placebo in Patients With Stage III *BRAF* V600E/K–Mutant Melanoma

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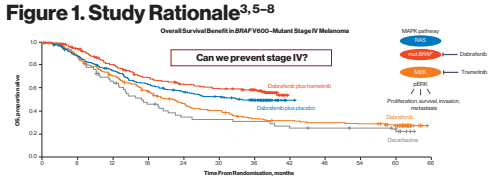
Introduction

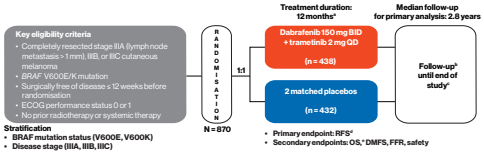
- Surgery alone is often curative for patients with localized melanoma; however, those with regional involvement (stage III disease) are at a higher risk for disease progression even with complete surgical resection.[1,2]
- In phase 3 trials involving patients with previously untreated advanced or metastatic *BRAF* V600-mutant melanoma, dabrafenib plus trametinib combination therapy improved clinical outcomes and was well tolerated.[3,4]
- The COMBI-AD study (NCT01682083) is a randomized, double-blind, placebo-controlled, phase 3 trial that evaluated the efficacy and safety of dabrafenib plus trametinib combination therapy in patients with completely resected, high-risk, stage III, *BRAF* V600E/K-mutant melanoma without prior anticancer therapy.[5]

Figure 1. Study Rationale[3,5–8]



MAPK, mitogen-activated protein kinase; mut, mutated; pERK, phosphorylated extracellular signal-regulated kinase.

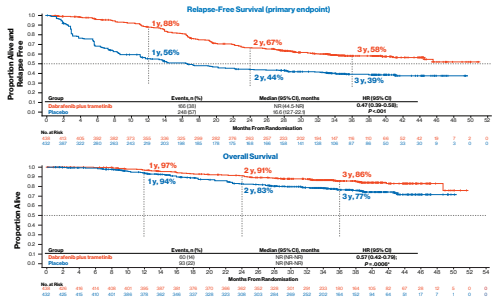
Figure 2. Study Design



BID, twice daily; DMFS, distant metastasis–free survival; ECOG, Eastern Cooperative Oncology Group; FFR, freedom from relapse; OS, overall survival; QD, once daily; RFS, relapse-free survival.
[a]Or until disease recurrence, death, unacceptable toxicity, or withdrawal of consent.
[b]Patients were followed 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]Study was designed to provide > 90% power (assuming ≈ 410 RFS events observed) to detect an HR of 0.71 with an overall 2-sided type I error rate of 5%. New primary melanoma considered as an event.
[e]OS was to be tested only if the primary endpoint (RFS) significantly favoured the combination arm.

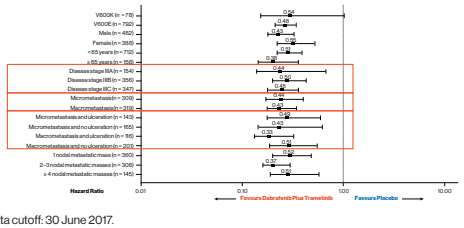
Figure 3. Primary Analysis: RFS and OS

Median follow-up: 2.8 years



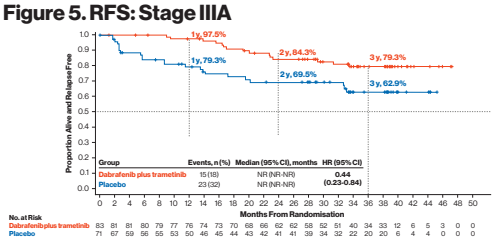
Data cutoff: 30 June 2017. NR, not reached.
[a]Prespecified significance boundary (P = .000019); next interim analysis planned when 50% of events have occurred.

Figure 4. Primary Analysis: RFS by Subgroup



Data cutoff: 30 June 2017.

Figure 5. RFS: Stage IIIA



NR, not reached.

Figure 6. RFS: Stage IIIB

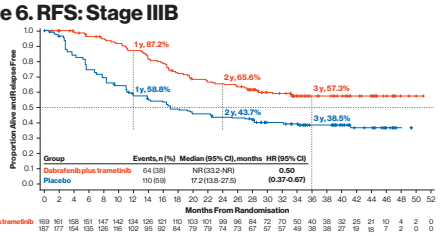


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Figure 7. RFS: Stage IIIC

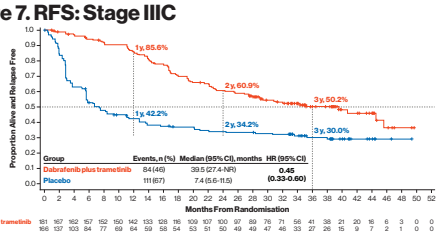

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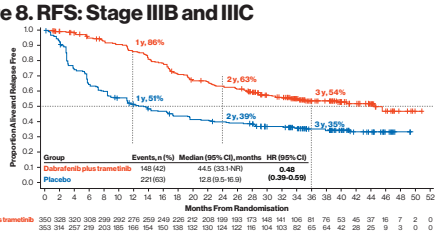
Figure 8. RFS: Stage IIIB and IIIC



NR, not reached.

Figure 9. RFS: Micrometastases

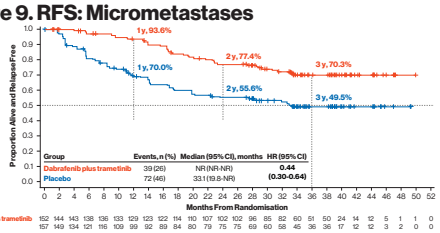


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Figure 10. RFS: Macrometastases

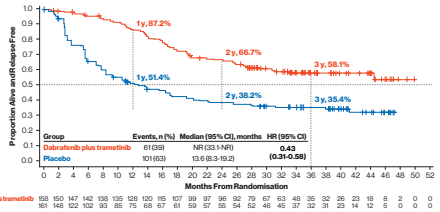

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Figure 11. RFS: Without Primary Tumour Ulceration

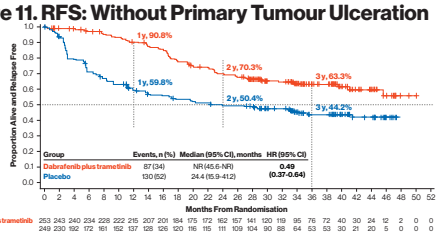

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Figure12. RFS: With Primary Tumour Ulceration

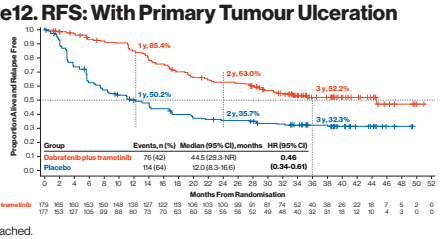

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Table 1. Type of Recurrence at First Recurrence

Type of recurrence, n (%)	Dabrafenib Plus Trametinib (n = 166)	Placebo (n = 248)
Distant recurrence	103 (62)	133 (54)
Local/regional recurrence	61 (37)	114 (46)
Secondary primary melanoma	7 (4)	8 (3)
Death	3 (2)	1 (< 1)

Table 2. Primary Analysis: Safety Summary

AE Category, n (%)	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Any AE	422 (97)	380 (88)
AEs related to study treatment	398 (91)	272 (63)
Grade 3/4 AEs related to study treatment	136 (31)	21 (5)
Any SAE	155 (36)	44 (10)
SAEs related to study treatment	117 (27)	17 (4)
AEs leading to dose interruption	289 (66)	65 (15)
AEs leading to dose reduction	167 (38)	11 (3)
AEs leading to treatment discontinuation[a]	114 (26)	12 (3)
Fatal AEs related to study drug	0	0

AE, adverse event; SAE, serious adverse event.
[a]Most common AEs leading to treatment discontinuation in the dabrafenib plus trametinib arm were pyrexia (9%) and chills (4%).

- Most common AEs in the dabrafenib plus trametinib arm were pyrexia (63%) and fatigue (47%)

Table 3. Characterisation of Pyrexia Events

	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Patients with pyrexia events, n (%)	292 (67)	66 (15)
Median time to onset of first pyrexia occurrence (range), days	23 (1-28)	53 (1-373)
Median duration of pyrexia (range), days	3 (1-92)	3 (1-340)
Pyrexia event characteristics, n (%)[a]		
Serious adverse event	71 (24)	4 (6)
Grade 3	24 (8)	2 (3)
Grade 4	1 (< 1)	0
Number of pyrexia occurrences, n (%)[a]		
1	83 (28)	45 (68)
2	57 (20)	11 (17)
≥ 3	152 (52)	10 (15)

[a]Percentage based on number of patients with pyrexia.

Table 4. Pyrexia Management and Outcome

	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
Action taken with dabrafenib/trametinib, n (%)[a]		
Drug withdrawn	40 (14)/27 (9)	—
Dose reduced	86 (29)/18 (6)	—
Drug interrupted	202 (69)/121 (41)	—
Recovered/resolved, n (%)[a]	289 (99)	64 (97)

[a]Percentage based on number of patients with pyrexia.

Table 5. Secondary Malignancies[a]

	Dabrafenib Plus Trametinib (n = 435)	Placebo (n = 432)
New primary melanoma	11 (3)	10 (2)
New cuSCC or keratoacanthoma	8 (2)	7 (2)
New basal cell carcinoma	19 (4)	14 (3)
New nonskin malignancies	10 (2) • Endometrial, n = 2 • Lung, breast, renal cell, adenocarcinoma NOS, chronic myeloid leukaemia, B-cell lymphoma, lymphoma, prostate, n = 1 each	4 (1) • Colon, pancreatic, renal cell, bladder transitional cell, n = 1 each

cuSCC, cutaneous squamous cell carcinoma; NOS, not otherwise specified.
[a]Includes events occurring after randomisation. Data presented as: n (%).

Conclusions

- Dabrafenib plus trametinib reduced the risk of disease recurrence vs placebo in patients with resected stage III, *BRAF* V600E/K–mutant melanoma; this result was statistically significant and clinically meaningful
  - RFS HR, 0.47 (95% CI, 0.39-0.58; *P* < .001)
  - OS HR, 0.57 (95% CI, 0.42-0.79, *P* = .0006 [prespecified significance boundary, *P* = .000019])
- RFS benefit was observed in all patient subgroups
  - Stage IIIA HR, 0.44; stage IIIB HR, 0.50; stage IIIC HR, 0.45
  - Micrometastases HR, 0.44; macrometastases HR, 0.43
  - Nonulcerated HR, 0.49; ulcerated HR, 0.46
- Although pyrexia was the most common AE, it was well characterised and manageable
- Dabrafenib plus trametinib represents a significant advance for the adjuvant treatment of stage III *BRAF* V600–mutant melanoma

Acknowledgements

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References

1. Gershenwald JE, et al. *CA Cancer J Clin.* 2017;67(6):472-492.
2. Siegel RL, et al. *CA Cancer J Clin.* 2017;67(1):7-30.
3. Long GV, et al. *Ann Oncol.* 2017;28(7):1631-1639.
4. Robert C, et al. *N Engl J Med.* 2015;372(1):30-39.
5. Long GV, et al. *N Engl J Med.* 2017;377(19):1813-1823.
6. Long GV, et al. *J Clin Oncol.* 2011;29:1239-1246.
7. Jakob JA, et al. *Cancer.* 2012;118:4014-4023.
8. Chapman PB, et al. *J Clin Oncol.* 2017;35:[abstract 9526].

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