Research Review™
STUDY REVIEW

Patient-reported outcomes in patients with resected, high-risk melanoma with BRAF^{V600E} or BRAF^{V600K} mutations treated with adjuvant dabrafenib plus trametinib (COMBI-AD): a randomised, placebo-controlled, phase 3 trial

Making Education Easy 2021

Independent commentary by Associate Professor Matteo Carlino
BMedSc, MBBS, FRACP, PhD

Associate Professor Matteo Carlino is a Medical Oncologist at Westmead and Blacktown Hospitals, a Clinical Associate Professor at The University of Sydney, and a faculty member and chair of education at the Melanoma Institute Australia. He undertook a PhD examining predictors of response and mechanisms of resistance to BRAF and MEK inhibitor treated melanoma. He continues to be involved in translational research particularly examining response and mechanisms of resistance to both targeted and immunotherapy.

He has a clinical interest in the treatment of melanoma and non-melanoma skin cancer and is an investigator on multiple Phase I, II and III clinical trials in this area.

Publication overview

Patients with stage III melanoma are at increased risk of recurrence after resection, but this risk can be significantly reduced with adjuvant therapy. The COMBI-AD trial was a randomised, double-blind, placebo-controlled, phase III study, conducted to examine the efficacy of dabrafenib, an inhibitor of the mutated BRAF kinase, specifically the BRAF^{v600} mutations, plus the MEK inhibitor trametinib, in patients with stage IIIA (lymph nodes metastases > 1 mm), IIIB or IIIC cutaneous melanoma (based on the American Joint Committee on Cancer [AJCC] 7th edition criteria) with BRAF^{V600E} or BRAF^{V600K} mutations. Of note, mutations in the gene that encodes that BRAF protein are seen in approximately 40% to 60% of melanomas, with the V600E variant comprising the vast majority of such mutations.[1] This review presents and discusses patient-reported outcomes from the COMBI-AD trial, which suggest no detrimental impact on health-related quality of life (HRQoL), and highlight the impact of relapse on HRQoL, in patients who receive adjuvant dabrafenib plus trametinib after complete surgical resection of stage III cutaneous melanoma.

Introduction

While the incidence of cutaneous melanoma continues to increase, for patients with stage I or II disease, the prognosis following primary surgical resection is excellent, with 5-year survival rates of 98% and 90%, respectively.[2, 3] In contrast, outcomes for patients with stage III disease are less positive, with 5-year survival rates ranging from 20% to 70%, depending largely on the nodal tumour burden.[3] However, outcomes for patients with stage III disease have significantly improved following the introduction of newer adjuvant therapeutics in two major classes, the immunotherapeutics and targeted therapies.[2] In addition to survival, it is important to also consider patient quality of life with the use of adjuvant therapies, particularly as most are associated with significant adverse events, and to consider the impact of disease relapse on patient quality of life.

Study background

The COMBI-AD study was a multicentre, randomised, double-blind, placebo-controlled, phase III study, performed at 169 sites in 25 countries. COMBI-AD was conducted to evaluate the efficacy of oral dabrafenib in combination with trametinib in patients who had undergone complete surgical resection of stage IIIA (lymph node metastases >1 mm), IIIB, or IIIC cutaneous melanoma (based on the AJCC 7th edition criteria) with BRAF^{V600E} or BRAF^{V600K} mutations, with a primary endpoint of relapse-free survival versus placebo. The primary endpoint of relapse-free survival was significantly improved with the treatment of adjuvant dabrafenib in combination with trametinib at 3 years versus placebo. This was published in the *NEJM* in September 2017, followed by the 60-month results showing that improved relapse-free survival was maintained, also published in the *NEJM*, in September 2020.

Expert comment

One year of treatment with combination dabrafenib/trametinib significantly reduces the risk of recurrence in patients with resected stage III, BRAF mutant melanoma. The recently published update from the COMBI-AD study shows that this benefit is maintained 5 years after treatment. The benefit is seen across all substages (IIIA-C, via AJCC 7th edition staging). The updated results found no difference in long-term toxicity or safety between dabrafenib plus trametinib and placebo, confirming the absence of ongoing toxicity with targeted therapy after treatment cessation.

Based on the results of COMBI-AD, one year of treatment with combination dabrafenib/trametinib is an adjuvant therapy option for patients with BRAF V600 mutant resected stage III melanoma, as is treatment with the anti-PD1 agents pembrolizumab and nivolumab. In the absence of head-to-head data, differences in toxicity profile and patient preference will guide the choice between adjuvant dabrafenib/trametinib and the anti-PD1 agents.

Study design and methods

Patients and treatment

The COMBI-AD study enrolled patients aged ≥ 18 years who had undergone complete surgical resection of stage IIIA (lymph node metastases > 1 mm), IIIB or IIIC cutaneous melanoma with BRAF^{V600E} or BRAF^{V600K} mutations. Enrolled patients were required to have had complete lymphadenectomy with no evidence of residual nodal disease, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1. Patients were randomised 1:1 to receive either oral dabrafenib (150mg twice daily) plus oral trametinib (2mg once daily) or two matched placebos for 12 months or until disease recurrence, unacceptable toxicity, consent withdrawal or death.

Endpoints and analyses

The primary endpoint of COMBI-AD was relapse-free survival, with secondary endpoints including overall survival, distant metastasis-free survival, freedom from relapse, and safety. The current paper reports the prespecified exploratory endpoint of HRQoL, assessed using the European Quality of Life 5-Dimensions 3-Levels (EQ-5D-3L) questionnaire, at baseline and every 3 months during treatment, with further regular assessment during follow-up.

Study results

Patient characteristics

A total of 438 patients were randomised to receive dabrafenib plus trametinib and 432 to receive matching placebos, with median follow up in the two patient groups of 34 and 33 months, respectively. More than 95% of patients completed the EQ-5D-3L questionnaire at baseline. The number of patients available for patient-reported outcome assessment decreased over time (**Table 1**), although the proportion of available patients completing the assessment was at least 90% in both groups out to 36 months.

Table 1. **Patients completing the EQ-5D-3L questionnaire over time**

	Dabrafenib plus trametinib (n=438)	Placebo (n=432)
Baseline	430 (98%)	422 (98%)
Month 3	383 (87%)	366 (85%)
Month 12	338 (77%)	237 (55%)
Month 24	254 (58%)	172 (40%)
Month 36	186 (42%)	132 (31%)
Month 48	43 (10%)	31 (7%)

EQ-5D-3L= European Quality of Life 5-Dimensions 3-Levels

EQ-5D-3L

EQ-5D-3L visual analogue scale (VAS) and utility scores were similar in both groups at baseline (**Table 2**) and remained similar to baseline scores during the treatment phase, with no clinically meaningful changes from baseline in either group.

Figure 2. **Effect of pyrexia on EQ-5D-3L VAS scores**

	Dabrafenib plus trametinib (n=438)		Placebo (n=432)	
	EQ-5D-3L VAS	EQ-5D-3L utility	EQ-5D-3L VAS	EQ-5D-3L utility
Baseline mean (SD)	79.0 (21.9)	0.8577 (0.1763)	80.4 (19.1)	0.8676 (0.1707)

EQ-5D-3L= European Quality of Life 5-Dimensions 3-Levels; **SD** = standard deviation; **VAS** = visual analogue scale

Moreover, during the treatment phase, there were no clinically meaningful differences between the two treatment groups in either VAS or utility scores (**Figure 1**). The proportions of patients reporting some or extreme problems across each of the five dimensions of the EQ-5D-3L (mobility, self-care, usual activities, pain or discomfort and anxiety or depression) were similar at baseline, although, at 12 months, a higher proportion of patients in the dabrafenib plus trametinib group than in the placebo group reported problems with mobility (15% vs 8%) and usual activities (19% vs 13%), and more placebo group patients reported problems in the anxiety and depression dimension (27% vs 22%). During the follow-up period, between 15 months and 48 months, there were again no clinically significant changes from baseline or differences between groups for either adjusted mean VAS or adjusted mean utility scores.

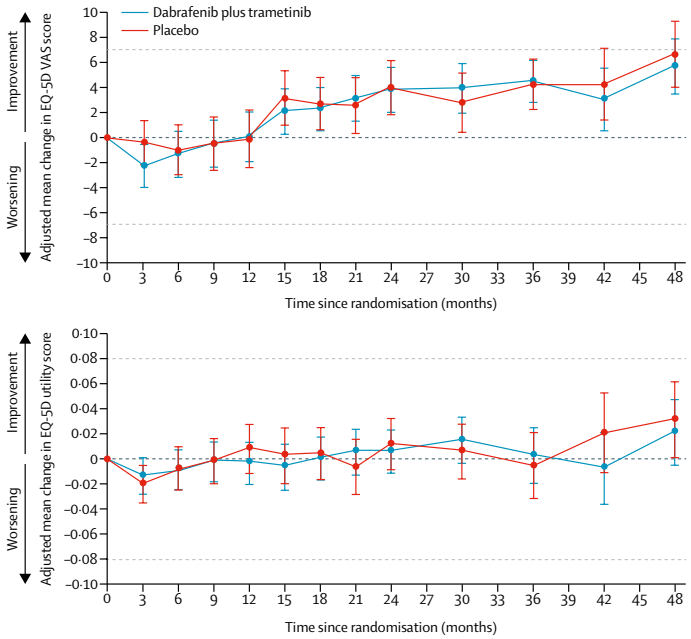

Figure 1: Change from baseline in EQ-5D-3L VAS and utility scores

Adjusted mean change (95% CI) from baseline in European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L) during treatment and long-term follow-up.

Patient-reported outcomes in patients with adverse events

A post-hoc analysis was performed to determine if EQ-5D-3L findings were influenced by experiencing some of the most common adverse events at any point during treatment. Overall, in patients who received dabrafenib plus trametinib, there were no clinically meaningful differences in EQ-5D-3L utility scores during treatment between patients who did and those who did not experience pyrexia, the most frequent adverse event (**Figure 2**), nausea, headache, chills, diarrhoea, vomiting, arthralgia or rash. VAS scores also failed to show any clinically meaningful differences during treatment between patients who did and those who did not experience any of these adverse events. Moreover, VAS scores improved over time in patients who experienced these common adverse events. The only patient group in which any significant differences in the EQ-5D-3L scores were seen were those with gastrointestinal adverse events, with significantly lower scores in those who experienced nausea, vomiting and diarrhoea than in those who did not, but these differences were only seen after the end of treatment, starting at 15 months, and continuing to 30 months' follow-up for nausea, and only at the 30-month follow-up for diarrhoea and vomiting.

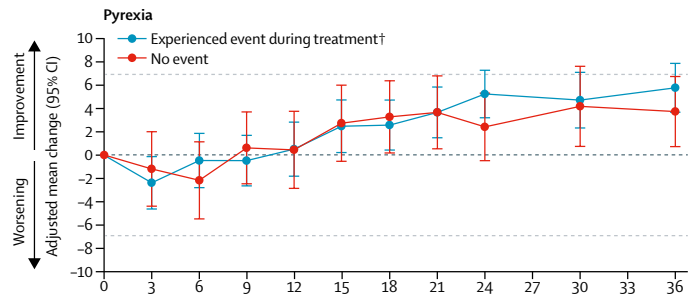

Figure 2. Effect of pyrexia on EQ-5D-3L VAS scores

Adjusted mean change (95% CI) from baseline in European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L) in patients in the dabrafenib plus trametinib arm based on pyrexia experienced during treatment.

Disease recurrence

Disease recurrence was associated with significantly decreased patient quality of life, with significant decreases in both mean VAS scores and mean utility scores in both treatment groups among patients who experienced disease recurrence (**Figure 3**). Additionally, disease recurrence was associated with worsening scores, again in both treatment groups, on the anxiety or depression dimension of the EQ-5D-3L.

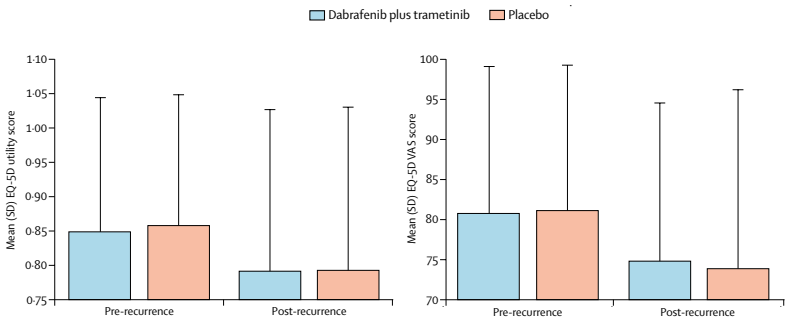

Figure 3: Effect of recurrence on mean (SD) European Quality of Life 5-Dimensions 3-Levels visual analogue scale (EQ-5D-3L) VAS (**A**) and utility (**B**) scores

Expert comment

In the adjuvant setting, patient-reported quality of life is an important clinical trial endpoint. In the advanced disease setting, a reduction in disease-related symptoms may offset the impact of treatment toxicity on quality of life. In the setting of advanced melanoma, dabrafenib/trametinib is associated with an improvement in quality-of-life measures.

In the adjuvant setting, no such disease-related symptoms exist, and it is therefore reassuring that adjuvant dabrafenib/trametinib is not associated with a clinically meaningful difference in quality of life as reported via both the visual analogue scale and utility score. There was a non-statistically significant drop in EQ-5D-3L VAS in the dabrafenib/trametinib arm, but not the placebo arm, presumably related to treatment toxicity, but subsequently VAS scores returned to baseline and were consistent with those seen in the placebo arm. From the published results, it cannot be determined if this return to baseline is due to improved quality of life resulting from management or resolution of toxicity, or if patients with the most significant toxicities ceased therapy early.

It is interesting that even in patients with pyrexia, the most common dabrafenib/trametinib toxicity, there was not a fall in measured quality of life. This lack of difference may be explained by the fact that pyrexia is usually transient and managed by dose interruption, and as such not captured by the intermittent assessments, or the fact that patients may have interpreted such toxicity 'positively' as a suggestion they were on the active treatment arm of the study, not placebo.

The results presented here confirm irrespective of treatment the most significant impact on patient quality of life is disease recurrence. Adjuvant therapy, be that dabrafenib/trametinib or immunotherapy, reduces the risk of recurrence and as such quality of life is maintained despite transient toxicity while on treatment.

Study interpretation

In patients with surgically resected cutaneous melanoma, disease recurrence is associated with a significant decline in HRQoL. In COMBI-AD only 5% of patients experienced disease relapse while on the full scheduled dose of dabrafenib plus trametinib versus placebo.[4] Moreover, the maintained rate of relapse-free survival with dabrafenib plus trametinib versus placebo, out to 5 years, is particularly important in terms of HRQoL. These findings from the COMBI-AD study suggest that treatment with dabrafenib plus trametinib does not negatively impact patient perception of quality of life, during treatment or during long-term follow-up, even in patients who experience adverse events, including pyrexia. While treatment was associated with a decrease in VAS scores initially, this was not a significant or clinically meaningful decrease, and did not differ between patients receiving dabrafenib plus trametinib and those receiving placebo. Patient-reported outcomes during treatment with dabrafenib plus trametinib have been reported previously, in unresectable or metastatic melanoma, and improvements from baseline were seen in HRQoL.[6, 7] The lack of improvement in HRQoL in the current study may be a reflection of the higher baseline HRQoL in these patients who had undergone complete surgical resection, as such, patients' perceived health status may be similar to the general population at baseline.

Take home messages

- Dabrafenib plus trametinib improves relapse-free survival versus placebo without adversely impacting patient quality of life.
- The most common adverse effects of dabrafenib plus trametinib do not appear to have a significant impact on patient-reported quality of life.
- Disease recurrence significantly impacts HRQoL, highlighting the importance of the low rate of relapse with dabrafenib plus trametinib during treatment, and following treatment cessation, versus placebo.

Expert's concluding remarks

It is reassuring that despite toxicity while on treatment, one year of treatment with adjuvant dabrafenib/trametinib does not impact patient-reported quality of life and is associated with a significant reduction in relapse-free survival.

References

1. Long GV, Alexander MM, Nagrial AM, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239-46
2. Gershenwald JE, Scolyer RA, Hess KR, et al. Melanoma staging: Evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA: A Cancer Journal for Clinicians. 2017;67(6):472-92.
3. Clinical practice guidelines in oncology melanoma. V1 2021 [Internet]. 2021. Available from: https://www.nccn.org/professionals/physician_gls/pdf/cutaneous_melanoma.pdf.
4. Long GV, Hauschild A, Santinami M, et al. Adjuvant Dabrafenib plus Trametinib in Stage III BRAF-Mutated Melanoma. N Engl J Med. 2017;377(19):1813-23.
5. Dummer R, Hauschild A, Santinami M, et al. Five-Year Analysis of Adjuvant Dabrafenib plus Trametinib in Stage III Melanoma. N Engl J Med. 2020;383(12):1139-48.
6. Grob JJ, Amonkar MM, Karaszewska B, et al. Comparison of dabrafenib and trametinib combination therapy with vemurafenib monotherapy on health-related quality of life in patients with unresectable or metastatic cutaneous BRAF Val600-mutation-positive melanoma (COMBI-v): results of a phase 3, open-label, randomised trial. Lancet Oncol. 2015;16(13):1389-98.
7. Schadendorf D, Amonkar MM, Stroyakovskiy D, et al. Health-related quality of life impact in a randomised phase III study of the combination of dabrafenib and trametinib versus dabrafenib monotherapy in patients with BRAF V600 metastatic melanoma. Eur J Cancer. 2015;51(7):833-40.

