Three-year pooled analysis of factors associated with clinical outcomes across dabrafenib and trametinib combination therapy phase 3 randomised trials

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Abstract  

Aim: Understanding predictors of long-term benefit with currently available melanoma therapies is the key for optimising individualised treatments. A prior pooled analysis of dabrafenib plus trametinib (D + T)—randomised trials (median follow-up, 20.0 months) identified baseline lactate dehydrogenase (LDH) and number of organ sites with metastasis as predictive factors for progression-free (PFS) and overall (OS) survival. However, longer-term follow-up analyses are needed to confirm which patients treated with D + T can achieve maximum benefit.

Methods: Three-year landmark data were retrospectively pooled for D + T patients in phase 3 trials (COMBI-d [NCT01584648]; COMBI-v [NCT01597908]). Univariate and multivariate analyses assessed prognostic values of predefined baseline factors; regression tree analysis determined hierarchy and interactions between variables.

Results: Long-term pooled outcomes were consistent with individual trial results (N = 563; 3-year PFS, 23%; 3-year OS, 44%). Baseline LDH level and number of organ sites remained strongly associated with and/or predictive of PFS and OS. In addition, baseline sum of lesion diameters (SLD) was identified as a predictor for progression. In the most favourable prognostic group (normal LDH, SLD < 66 mm, < 3 organ sites; n = 183/563 [33%]), 3-year PFS was 42%. Baseline number of organ sites was also predictive of outcomes in patients with PFS ≥ 6 months.

Conclusion: Using the largest phase 3 data set available for BRAF/MEK inhibitor combination therapy in melanoma, these results demonstrate that durable responses lasting ≥ 3 years are possible in subsets of patients with BRAF-mutant melanoma receiving D + T. Although the best predictive model evolved with longer follow-up, factors predicting clinical outcomes with the combination remained consistent with previous analyses.

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1. Introduction

In the era of multiple targeted therapies (i.e. BRAF and MEK inhibitors) and checkpoint inhibitor immunotherapies (i.e. anti-CTLA-4, anti-PD-1) available for the treatment of BRAF V600-mutant melanoma, determining which patients derive the greatest benefit from each drug class is crucial for optimising individualised treatment strategies. Although currently available metastatic melanoma therapies have improved response and/or survival over previous standards of care [1–6], emerging updated landmark data (i.e. ≥ 2 years) for randomised trials of targeted and immune therapies show that many patients still relapse and die from the disease [5–10]. Despite this remaining unmet need to improve outcomes in all patients with metastatic melanoma, a relevant proportion of those who have received approved treatments have achieved long-term clinical benefit, indicating that some subsets of patients have a greater potential to benefit from therapy than others [5,7–11]. As exploration of novel treatment regimens continues in an effort to develop the next major therapeutic advancement for metastatic melanoma (e.g. BRAF inhibitor [BRAFi] plus MEK inhibitor [MEKi] plus anti-PD-1/PD-L1 triplet combinations [12–14]), characterisation of patients who derive long-term benefit from each treatment will be of particular importance moving forward.

A previous 2-year landmark-pooled analysis of BRAF inhibitor—naive patients treated with dabrafenib plus trametinib (D + T) across phase 2 (BRF113220,
part C) and phase 3 (COMBI-d, COMBI-v) registration trials (median follow-up, 20.0 months [15]) demonstrated that pooled progression-free survival (PFS; median, 11.1 months; 2-year, 30%) and overall survival (OS; median, 25.6 months; 2-year, 53%) were consistent with those of individual reports for combination BRAFi and MEKi phase 3 trials [6–8]. In addition, baseline serum lactate dehydrogenase (LDH) level and number of organ sites with metastasis were identified as the most predictive factors for durable response and survival, with patients with normal LDH level and <3 organ sites with metastasis achieving the greatest benefit with D + T (2-year PFS, 46%; 2-year OS, 75%). Outcomes also varied by Response Evaluation Criteria In Solid Tumors (RECIST) response, whereby patients who achieved a complete response (CR) had the most favourable outcomes (2-year PFS, 68%; 2-year OS, 88%). In addition, survival after progression varied by site(s) of progression (i.e. baseline lesions, new non-central nervous system [CNS] lesions, new CNS lesions, both new and baseline lesions). To confirm which patients treated with D + T can achieve maximum benefit and to assess whether additional factors beyond those at the time of treatment initiation are relevant in predicting clinical outcomes, further analyses with extended follow-up are needed.

Here, univariate, multivariate and regression tree analyses of pooled 3-year landmark data across the randomised, phase 3 D + T trials COMBI-d and COMBI-v were used to further characterise clinical factors associated with outcomes in patients treated with the combination after extended follow-up. Potential time-dependent predictors of clinical outcomes in patients treated with D + T who had PFS lasting ≥6 months were also explored, which may be helpful for physicians and patients deciding whether to continue or switch therapy.

2. Methods

2.1. Study design and participants

Treatment-naive patients with BRAF V600E/K-mutant metastatic melanoma randomised to receive dabrafenib 150 mg twice daily plus trametinib 2 mg once daily in COMBI-d [1,7,16] (NCT01584648; D + T arm, n = 211; data cutoff, February 15, 2016) and COMBI-v [2,8] (NCT01597908; D + T arm, n = 352; data cutoff, July 15, 2016) were included in the pooled analysis population (intent-to-treat population).

2.2. Statistical methods

Factors for analyses, identified a priori, included baseline clinical characteristics and known prognostic factors for advanced stage IIIC resectable or stage IV metastatic melanoma (Table A1) [17]. The prognostic value for each individual factor (univariate analysis), each factor in conjunction with other factors (multivariate analysis) and hierarchy and interactions between variables (regression tree analysis) were assessed. Cox proportional hazards models [18] were used to model independent predictors of progression or death for univariate analysis or to jointly model all risk factors simultaneously as predictors of progression or death for multivariate analysis. A Poisson regression tree method for categorical outcome and an exponential regression tree method for survival outcome (i.e. progression status and death) [19,20] were performed to identify homogeneous prognostic subgroups.

3. Results

3.1. Patients

A total of 563 patients randomised to dabrafenib plus trametinib in COMBI-d (n = 211) and COMBI-v (n = 352) were included in the pooled analysis population (Table A2; Fig. A1). Baseline characteristics were similar across trials (Table A3). With an extended median follow-up of 22.1 months (range, 0–47.3) across studies, efficacy outcomes with D + T continued to be similar for COMBI-d and COMBI-v: overall response rate was 68% and 67% (Table A4), 3-year PFS was 22% [7] and 24% (Figure A2), and 3-year OS was 44% and 45% (Fig. 1A), respectively.

3.2. Pooled clinical outcomes

Progression events occurred in 402 patients (71%) in the pooled population (Table A2), with a median PFS of 11.1 months (95% CI, 9.5–12.9) and 3-year PFS of 23% (95% CI, 20–27%; Fig. 1B). A total of 304 (54%) patients had died (Table A2), with a median OS of 26.2 months (95% CI, 22.9–32.0) and 3-year OS of 44% (95% CI, 40–49%; Fig. 1C). RECIST response was observed in 380 (67%) patients, with 106 (19%) achieving a CR, 274 (49%) achieving a partial response, and 134 (24%) having stable disease (Table A4).

3.3. Baseline factors associated with progression and survival

Baseline factors with categories found to be significantly associated (p < 0.05) with PFS or OS by both univariate and multivariate analyses were age, ECOG PS, sex, number of organ sites with metastasis and LDH level (Table 1). Factors not associated with PFS or OS were BRAF genotype and prior adjuvant immunotherapy by univariate analysis, and M stage, baseline sum of lesion diameters (SLD) and prior adjuvant immunotherapy by multivariate analysis.
Using regression tree analysis, five baseline prognostic groups were found to best predict PFS: normal LDH level, SLD < 66 mm, and <3 organ sites with metastasis; normal LDH level, SLD < 66 mm, and ≥3 organ sites with metastasis; normal LDH level and SLD ≥ 66 mm; LDH level < 1 to ≥ 2 × ULN; and LDH level ≥ 2 × ULN (Fig. 2A). The influence of these identified baseline factors on PFS can be visualised in Kaplan–Meier curves by these baseline risk groups (Fig. 2B). In the 183 (33%) patients in the most favourable prognostic group (normal LDH level, SLD < 66 mm, <3 organ sites with metastasis), median PFS was 24.0 months, and 3-year PFS was 42%. In contrast, in the 65 patients (12%) in the most unfavourable subgroup (≥2 × ULN), median PFS was 5.5 months, and no patients remained progression free at 3 years. With extended follow-up, baseline LDH level predicted OS (Fig. 2C). In patients with normal (n = 366/563 [65%]) and elevated (n = 197/563 [35%]) LDH level, median OS was not reached and 12.8 months, respectively, and 3-year OS was 55% and 22% (Fig. 2C and D), respectively. Other baseline factors included in the regression tree analysis (Table A1) were not identified as being predictive of PFS or OS.

3.4. Factors associated with subsequent outcomes in patients remaining progression free at 6 months

At 6 months, 373 (66%) patients in the pooled population remained progression free. Of these 373 patients, LDH level was normal for 263 (71%) at baseline and 240 (64%) at 6 months. With a median follow-up of 36.2 months (range, 6.2–47.3), subsequent progression was observed in 246 (66%) patients, and deaths occurred in 165 (44%) patients (Table A2).

Of the 373 patients who remained progression free at 6 months, 191 (51%) maintained normal LDH levels from baseline to 6 months (Table A5). Among those with normal LDH levels at baseline but elevated LDH levels at 6 months (n = 72/373 [19%]), OS was reduced with continued follow-up compared with those who maintained normal LDH levels with time (3-year OS, 55% and 67%, respectively), a trend that was not observed for PFS in these patient groups (3-year PFS, 40% and 37%, respectively; Fig. 3A and B). Patients with elevated LDH levels at baseline had poorer outcomes than patients with normal baseline LDH levels, regardless of LDH status at 6 months (Fig. 3A and B).

Regression tree analysis of baseline and postbaseline factors for outcomes in patients who had PFS lasting ≥6 months showed that the best predictor of both subsequent PFS and OS was baseline number of organ sites with metastasis (Figs. A3A and A3B). Compared with those who had ≥3 organ sites with metastasis at baseline, patients with <3 organ sites with metastasis had improved PFS (3-year, 19% and 31%, respectively) and OS (3-year, 41% and 71%, respectively). Notably, postbaseline factors included in the analysis (i.e. ECOG PS, LDH level, SLD at 6 months) did not improve prediction of progression or survival in these patients.

3.5. Analysis of response

PFS and OS varied by best response; patients achieving a CR demonstrated the longest PFS and OS, followed by patients with partial responses, stable disease, or progressive disease, and patients who were non-evaluable (Fig. 4A and B). RECIST response also varied by prognostic groups identified by regression tree analyses for PFS and OS (Tables A6 and A7), where response was highest in the best prognostic group for PFS (normal LDH level, SLD < 66 mm, <3 organ sites with metastasis: overall response rate, 83%); however, a
Table 1
Univariate and multivariate analysis of baseline factors associated with progression-free survival and overall survival in patients treated with dabrafenib plus trametinib (N = 563).

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Effect tested</th>
<th>Univariate analysis</th>
<th></th>
<th></th>
<th>Multivariate analysis</th>
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<td></td>
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<td>PFS</td>
<td>OS</td>
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<td></td>
<td></td>
<td>HR 95% CI p</td>
<td>HR 95% CI p</td>
<td>HR 95% CI p</td>
<td>HR 95% CI p</td>
<td></td>
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<tr>
<td>Age, years</td>
<td>10-year increments</td>
<td>0.928 0.861–0.999</td>
<td>0.0459</td>
<td>0.911 0.836–0.993</td>
<td>0.0345</td>
<td>0.911 0.844–0.982</td>
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<td>Sex</td>
<td>Female/male</td>
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<td>0.0265</td>
<td>0.697 0.553–0.879</td>
<td>0.0022</td>
<td>0.735 0.600–0.900</td>
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<tr>
<td>M stage</td>
<td>M0/M1c</td>
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<td>0.407 0.192–0.864</td>
<td>0.0193</td>
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<td>M1a/M1c</td>
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<td>M1b/M1c</td>
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<td>0.0003</td>
<td>0.532 0.388–0.729</td>
<td>&lt;0.0001</td>
<td>0.997 0.731–1.358</td>
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<td>BRAF genotype</td>
<td>V600E/V600K or V600E and V600K</td>
<td>0.780 0.585–1.039</td>
<td>0.0894</td>
<td>0.809 0.584–1.121</td>
<td>0.2029</td>
<td>0.676 0.502–0.910</td>
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<td>ECOG PS</td>
<td>0/1</td>
<td>0.585 0.473–0.724</td>
<td>&lt;0.0001</td>
<td>0.405 0.320–0.511</td>
<td>&lt;0.0001</td>
<td>0.715 0.571–0.895</td>
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<td>Lactate dehydrogenase</td>
<td>Normal/≥2 × ULN</td>
<td>0.243 0.181–0.327</td>
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<td>0.172 0.124–0.239</td>
<td>&lt;0.0001</td>
<td>0.318 0.227–0.447</td>
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<td>≥1 to &lt;2 × ULN</td>
<td>0.492 0.356–0.680</td>
<td>&lt;0.0001</td>
<td>0.400 0.282–0.568</td>
<td>&lt;0.0001</td>
<td>0.554 0.396–0.774</td>
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<td>Baseline disease characteristics</td>
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<tr>
<td>Number of organ sites with metastasis</td>
<td>&lt;3/≥3</td>
<td>0.540 0.443–0.658</td>
<td>&lt;0.0001</td>
<td>0.416 0.329–0.525</td>
<td>&lt;0.0001</td>
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<td>Sum of lesion diameters</td>
<td>≤/median (58 mm)</td>
<td>0.534 0.438–0.651</td>
<td>&lt;0.0001</td>
<td>0.478 0.380–0.603</td>
<td>&lt;0.0001</td>
<td>0.898 0.699–1.155</td>
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<td>Prior adjuvant ipilimumab</td>
<td>No/yes</td>
<td>0.616 0.198–1.918</td>
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<td>Prior adjuvant non-ipilimumab immunotherapy</td>
<td>No/yes</td>
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<td>0.1560</td>
<td>0.804 0.565–1.143</td>
<td>0.2245</td>
<td>0.854 0.620–1.176</td>
</tr>
</tbody>
</table>

Abbreviations: ECOG PS, Eastern Cooperative Oncology Group performance status; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; ULN, upper limit of normal.

* Where increases of age in 10-year increments corresponded with decreased risk of progression or death.

b Any organ with ≥1 metastasis. Organ site categories were central nervous system, bone (bone or bone marrow), lung, lymph nodes, liver, skin and subcutaneous and all other organs.

c Sum of lesion diameters was dichotomised at the median (58 mm) for ease of interpretation in Cox proportional hazards analyses.

d Of 539 patients with disease stage information available at diagnosis, all 3 patients with prior adjuvant ipilimumab had stage III disease at diagnosis; of all other patients, 284 (53%) had stage < III.

e Of 539 patients with disease stage information at diagnosis, 33 patients (56%) in the prior adjuvant non-ipilimumab immunotherapy subgroup had stage ≥ III disease at diagnosis; of all other patients, 225 (47%) had disease stage ≥ III.
high level of response was still observed across other prognostic groups, including in patients in the least favourable prognostic group (LDH level ≥2 × ULN), who had a 50% response rate. In addition, of patients with a CR (n = 106), 95 (90%) had normal LDH levels, 91 (86%) had SLD < 66 mm, and 90 (85%) had <3 organ sites with metastasis at baseline (Table A8).

4. Discussion

This updated pooled 3-year landmark analysis of the largest cohort available for BRAFi plus MEKi combination therapy in BRAF V600E/K-mutant melanoma demonstrated continued consistency of efficacy across phase 3 D + T studies. As shown in previous individual trial reports of long-term efficacy analyses of D + T [7,8,21], a relevant subset of patients treated with the combination achieved durable outcomes, with 23% remaining progression free and 44% remaining alive at 3 years. In addition, further characterisation of patients with durable outcomes in this analysis confirmed that although some benefit with D + T was observed across all prognostic groups identified, long-term outcomes were reflected by individual prognostic factors for melanoma. Furthermore, these data provide a foundation with which to compare upcoming planned 5-year landmark analyses for these studies.

Although a prior pooled analysis of patients randomised to receive D + T in the context of 2-year landmark efficacy outcomes identified factors predictive of clinical outcomes with the combination [15], this current updated analysis using a 3-year landmark data set allowed preliminary exploration of whether and how predictive markers evolve over time (e.g. with longer survival). As previously identified [15], baseline LDH level and number of organ sites with metastasis remained strongly associated with PFS and OS in D + T-treated patients at 3 years. In addition, with extended follow-up, baseline SLD was also identified as a predictor for PFS. Baseline number of organ sites containing metastasis also remained an important predictive factor for outcomes in patients treated with the combination who were progression free at 6 months. Although factors with significant associations with PFS and OS identified by Cox proportional hazards models in this updated 3-year landmark data set were similar to those previously reported for randomised dabrafenib plus trametinib 2-year outcomes [15], ECOG PS did not remain predictive for
OS by regression tree analysis in this study. Additional follow-up confirmed that \textit{BRAF} genotype and prior adjuvant therapy were not predictive for PFS or OS in this patient population; however, it should be noted that these factors included small sample sizes and were thus more unlikely to yield conclusions for this analysis.

Together, results from this analysis indicate that continued follow-up of these patients is warranted and provide a basis for future studies needed to further characterise the influence of known melanoma prognostic factors with extended melanoma treatment. Specifically, it could be hypothesised that (1) predictive markers are absolute, where more mature data only marginally alter statistical thresholds and result in merely a slightly different hierarchy of the same or similar variables (e.g. appearance of tumour volume with concurrent disappearance of tumour sites in the predictive model with extended follow-up); or (2) different sets of predictive markers are relevant depending on the time point used to define the risk of early death (e.g. 1 year, between 2 and 3

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**Fig. 3.** Kaplan–Meier-estimated (A) progression-free survival and (B) overall survival by change in lactate dehydrogenase level (LDH) from baseline to 6 months after the randomisation in patients who remained progression free at 6 months. NE, not evaluable; OS, overall survival; PFS, progression-free survival. *Missing at baseline or at 6 months.
Fig. 4. Descriptive Kaplan–Meier-estimated (A) progression-free survival and (B) overall survival by RECIST response. CR, complete response; NE, not estimable; OS, overall survival; PD, progressive disease; PFS, progression-free survival; PR, partial response; RECIST, Response Evaluation Criteria In Solid Tumors; SD, stable disease. *Maximum PFS time is much less than the landmark time point (SD, 24.0 months; PD, 6.3 months; NE, 8.9 months).
years or ≥3 years), where shorter follow-up models identify predictive factors mostly associated with early death (e.g., poor ECOG PS) and longer follow-up models increase the relative impact of predictive markers of intermediate or late death.

Patients with melanoma who achieved a CR while on treatment had the most favourable outcomes, with a 3-year OS rate of 86%, which is consistent with previous reports demonstrating longer survival in patients achieving CR to mitogen-activated protein kinase-targeted therapies [15,22,23]. Complete responders also appeared to have good prognostic features at baseline (CR rate, 42% in the group with normal LDH levels, SLD <66 mm, <3 organ sites with metastasis; 0% in the group with LDH levels >2 × ULN).

This retrospective analysis was limited by the available classically recognised baseline markers and assessment performed in each individual study included. Thus, although LDH level was again identified as a highly predictive factor of patient outcomes with D + T among the factors assessed in this updated pooled analysis, many potential other factors (e.g., disease kinetics, molecular biomarkers, immune response) could not be considered. Analyses where postbaseline variables are considered predictive factors should, however, be interpreted with caution.

Comparison of these results with pooled data sets for other melanoma therapies will help determine whether prognostic factors identified in this study apply to patients receiving other treatments. A recent pooled analysis of patients receiving combination vemurafenib and cobimetinib also showed that risk of progression or death on treatment is higher in patients with elevated baseline LDH level and identified disease stage as an important risk factor [24]. Furthermore, a recent retrospective analysis of the coBRIM phase 3 study evaluating vemurafenib plus cobimetinib versus vemurafenib plus placebo (median follow-up, 18.5 months) showed that PFS and OS were also improved with this combination in patients with factors identified in this study, including lower baseline LDH level, <3 involved organs, and lower SLD [25]. In addition, a recursive partitioning decision tree method used in a pooled analysis of patients treated with vemurafenib plus cobimetinib identified baseline LDH level as the most predictive factor for post-progression survival with this targeted therapy combination [11]. Preliminary reports of retrospective pooled analyses of patients treated with checkpoint inhibitor immunotherapies suggest that PFS and OS are also poorer in patients with elevated baseline LDH levels who are treated with pembrolizumab, nivolumab, or nivolumab plus ipilimumab [26–30]. However, to date, OS data with checkpoint inhibitor immunotherapies by baseline LDH level specifically in patients with BRAF V600-mutant melanoma has been limited.

The findings presented here may provide a framework for translational studies that aim to understand the mechanisms behind resistance compared with prolonged response and survival using melanoma tissue from patients. Additional analyses with longer-term follow-up and/or further defined windows of therapy duration may be needed to confirm which patients treated with D + T can achieve maximum benefit. Integration of molecular and/or immune markers to determine potential associations with efficacy, such as biomarker analyses ongoing for phase 3 D + T studies, may also further delineate patients with favourable long-term outcomes with D + T.

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Conflict of interest statement

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Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejca.2017.05.033.

References

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