CLINICAL TRIAL PERSPECTIVE

Melanoma Management

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Vemurafenib plus cobimetinib in the treatment of mutated metastatic melanoma: the CoBRIM trial

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Practice points

Only a small proportion of patients (~5%) treated with BRAF inhibitors achieve an overall complete response

- Disease progression occurs in a subset of the tumor burden so that, although lesions in complete remission do not progress, others do so even after a partial prolonged remission.
- Generally, after 6–7 months of *BRAF* inhibitor monotherapy, progression occurs because of acquired resistance due to different mechanisms of action.

BRAF inhibitors are associated with increased cutaneous squamous-cell carcinoma & keratoacanthoma

- These secondary cutaneous carcinomas have been reported to occur in about 14% of dabrafenib-treated patients and 26% of vemurafenib-treated patients, generally within the first 2 months of therapy.

The concomitant inhibition of both MEK & BRAF has shown more durable and greater tumor response than BRAF monotherapy & can decrease toxicity secondary to the BRAF inhibitor MAPK-pathway activation

- Concurrent treatment with a *MEK* inhibitor and *BRAF* inhibitor can reduce the rate of cutaneous SCCs from 15–20% to 1–5%.

The international, multicenter, randomized Phase III CoBRIM trial was designed to evaluate the efficacy & safety of combined cobimetinib & vemurafenib compared with vemurafenib alone in previously untreated patients with advanced *BRAF*-mutated melanoma

- Median progression-free survival was significantly increased with vemurafenib plus cobimetinib compared with vemurafenib alone (9.9 vs 6.2 months; hazard ratio for death or progression: 0.51; 95% CI: 0.39–0.68; $p < 0.001$) in 495 patients with advanced *BRAF*-mutated melanoma.
- Overall survival data in the CoBRIM trial were immature at time of final progression-free survival analysis but showed a hazard ratio for death of 0.65 (95% CI: 0.42–1.00; $p = 0.046$; boundary $p < 0.0000037$).
- Combination therapy was well tolerated with a reduced incidence of cutaneous squamous-cell carcinoma/keratoacanthoma.
- There appeared to be a lower rate of rapidly progressing patients after combination treatment, meaning there may be more possibility to complete subsequent treatment with ipilimumab.

The double combination of vemurafenib plus cobimetinib is not a point of arrival but rather a new starting point forming a basis for novel combination strategies with immunotherapies & other targeted therapies

- Investigations into these are already underway and will be continued over the coming years with the aim of further improving outcomes with anti-*BRAF* treatments for patients with metastatic melanoma.

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The concomitant inhibition of both *BRAF* and *MEK* can produce a more durable and greater tumor response than BRAF monotherapy while reducing BRAF inhibitor-related toxicity. Further evidence of the benefits of combined *MEK* and *BRAF* inhibition have been provided by the CoBRIM trial in which median progression-free survival was significantly increased with vemurafenib plus cobimetinib compared with vemurafenib alone (9.9 vs 6.2 months; hazard ratio for death or progression: 0.51; 95% CI: 0.39–0.68; $p < 0.001$) in 495 patients with advanced *BRAF*-mutated melanoma. Overall survival data in the CoBRIM trial were immature at time of final progression-free survival analysis but showed an hazard ratio for death of 0.65 (95% CI: 0.42–1.00; $p = 0.046$; boundary $p < 0.0000037$). Combination therapy was well tolerated with a reduced incidence of cutaneous squamous-cell carcinoma/keratoacanthoma. This combination may be a starting point for novel combination strategies with immunotherapies and other targeted therapies.

KEYWORDS
• BRAF inhibitor • cobimetinib • combination therapy • MEK inhibitor • vemurafenib

Options for the management of metastatic melanoma have dramatically improved since a meta-analysis of Phase II Cooperative Group trials conducted between 1975 and 2005 confirmed the poor prognosis achieved with chemotherapy, with median progression-free survival (PFS) of 1.7 months, median overall survival (OS) of 6.2 months and just one quarter of patients alive at 1 year [1]. Since 2010, the development of several different classes of novel anticancer drugs has revolutionized the treatment of patients with advanced melanoma. In particular, identification of the *BRAF* mutation and the advent of selective *BRAF* inhibitors represent a milestone in the history of melanoma treatment.

About 45% of metastatic cutaneous melanomas harbor the *BRAF* V600 mutation, which results in increased catalytic activity of the BRAF protein leading to constitutive activation and phosphorylation of *MEK* and *ERK* in the *RAS–RAF–MAPK* signaling cascade [2,3]. Vemurafenib was the first *BRAF* inhibitor to become available, being approved by the US FDA in 2011 on the basis of a Phase III trial (BRIM-3) which demonstrated improved PFS (5.3 vs 1.6 months) and OS (13.6 vs 9.7 months) compared with dacarbazine in metastatic *BRAF*-mutated melanoma [4]. Particularly remarkable in this study was a hazard ratio (HR) for death in the vemurafenib group of 0.37 at a median follow-up of 7 months (95% CI: 0.26–0.55; $p < 0.001$). The activity of vemurafenib is characterized by a fast response with a rapid improvement in symptoms and performance status, especially in patients with very poor disease status (the so-called 'Lazarus effect'), an equally rapid metabolic shutdown of the disease and a slower reduction in size of metastatic lesions. Another *BRAF* inhibitor, dabrafenib, has also shown improved PFS (5.1 vs 2.7 months), and objective response rate (ORR; 53 vs 6%) compared with dacarbazine in the Phase III BREAK-3 trial [5], which led to FDA approval in 2013. In terms of OS, it was reported a not statistically significant difference between the two arms: 20 months for dabrafenib versus 15.6 months for dacarbazine (HR for death: 0.77; 95% CI: 0.52–1.13). The final OS analysis of BREAK-3 trial is expected in 2016 [6].

However, it has been shown that only a small proportion of patients (~5%) treated with *BRAF* inhibitors achieve an overall complete response. Disease progression occurs in a subset of the tumor burden so that, although lesions in complete remission do not progress, others do so even after a partial prolonged remission [7]. Generally, after 6–7 months of *BRAF* inhibitor monotherapy, progression occurs because of acquired resistance due to different mechanisms of action [4,5]. Progression can be *MEK*-dependent, due to *RAS* mutations, *COT* overexpression, *BRAF* truncation (alternative splicing) or amplification, or *MEK1* mutations, or it may be *MEK*-independent (as via *PI3K*/*AKT*), secondary to the overexpression of RTK or their ligands [8–10].

Both vemurafenib and dabrafenib have similar toxicity profiles with rash, fatigue and joint pain the most frequent side effects, with the only differences being a higher rate of photosensitivity with vemurafenib and more frequent pyrexia with dabrafenib. Both *BRAF* inhibitors are also associated with increased cutaneous squamous-cell carcinoma (SCC) and keratoacanthoma (KA), which have been reported to occur in about 14% of dabrafenib-treated patients and 26% of vemurafenib-treated patients, generally within the first 2 months of therapy [11,12]. This specific skin toxicity seem secondary to the paradoxical activation of the MAPK pathway in keratinocytes in association with activation of signaling mediated by *RAS* mutations [13,14].

The concomitant inhibition of both *MEK* and *BRAF* can overcome the multiple genetic mechanisms of escape and has shown more durable and greater tumor response than *BRAF* monotherapy. Moreover, this double inhibition can decreases the toxicity secondary to the *BRAF* inhibitor MAPK-pathway activation. Concurrent treatment with a *MEK* inhibitor and *BRAF* inhibitor can reduce the rate of cutaneous SCCs from 15–20% to 1–5% [15].

MEK inhibitors were initially shown to be very promising based on preclinical studies which showed stronger inhibition than vemurafenib of both mutated *BRAF* and *NRAS* cell cultures [15]. The first *MEK* inhibitor to be approved by the FDA in 2014 was trametinib, which showed superior PFS (4.8 vs 1.5 months), ORR (22 vs 8%) and the rate of OS (81% in the trametinib group and 67% in the chemotherapy group despite crossover – HR: 0.54; 95% CI: 0.32–0.92; p = 0.01), compared with dacarbazine in a Phase III trial [16] of *BRAF*-mutated melanoma patients. The most frequent grade 3 side effects were hypertension, rash and fatigue. Trametinib was approved both as a single agent [16] and in combination with dabrafenib for the treatment of advanced *BRAF*-mutated melanoma [17].

Pretreated *BRAF*-mutated patients were treated for the first time with the combination of dabrafenib plus trametinib in a Phase I/II trial which identified the combination doses of 150 mg of dabrafenib and 2 mg of trametinib. Median PFS in the combination group was 9.4 months compared with 5.8 months in the dabrafenib monotherapy group with an HR for progression or death of 0.39 (95% CI: 0.25–0.62; p = 0.03) [16]. Following this, the Phase III COMBI-D trial [18] compared the combination of dabrafenib plus trametinib versus dabrafenib alone in 423 *BRAF*-mutated, untreated patients. The primary end point of PFS was 9.3 months in the dabrafenib plus trametinib arm and 8.8 months in the dabrafenib alone arm. HR for progression or death in the dabrafenib plus trametinib group was 0.75; 95% CI: 0.57–0.99; p = 0.03). Overall response rate was 67% in the combination arm and 51% in the monotherapy arm (p = 0.002). HR for death was 0.63 (95% CI: 0.42–0.94; p = 0.02). Toxicity profile was similar in both groups, but SCC rate was higher in the dabrafenib arm (9 vs 2%), while pyrexia rate was higher in the combination arm (51 vs 28%).

The combination of dabrafenib plus trametinib was also compared with vemurafenib alone in another Phase III trial, the COMBI-V trial [19], which included 704 *BRAF*-mutated, untreated patients. HR for death in the combination therapy arm was 0.69 (95% CI: 0.53–0.89; p = 0.005) and median PFS was 11.4 months with combination therapy and 7.3 months with vemurafenib monotherapy (HR: 0.56; 95% CI: 0.46–0.69; p < 0.001). The ORR was 64% (95% CI: 59–69) in the dabrafenib plus trametinib group versus 51% (95% CI: 46–57) in the vemurafenib group (p < 0.001).

Interestingly, Dabrafenib plus trametinib demonstrated modest clinical efficacy in patients with *BRAF* inhibitor-resistant melanoma [20]. For this reason, such regimen should be used in *BRAF* inhibitor naive patients or who previously had a benefit from *BRAF* inhibitor monotherapy lasting more than 6 months, whereas this combination demonstrates minimal efficacy after rapid progression with *BRAF* inhibitor therapy [20].

Another potent *MEK* inhibitor is cobimetinib [21], which was assessed in combination with vemurafenib for the treatment of *BRAF* V600-mutated metastatic melanoma in the Phase Ib BRIM 7 trial [22]. In this study, doses were escalated until the maximum tolerated dose for each single agent was reached, with vemurafenib administered continuously and cobimetinib given as a 21 days on/7 days off regimen. In BRAF inhibitor-naive patients, ORR was 87% and PFS was 13.7 months, while a much shorter PFS was observed in *BRAF* inhibitor pretreated patients (2.8 months). Rash, diarrhea, photosensitivity and AST/ALT elevation were the most common toxicities and were similar to those with single agent monotherapy, while there was a reduced incidence of cutaneous SCC and KA.

Introduction to the CoBrim trial

On the basis of these findings in the BRIM7 study, the international, multicenter, randomized Phase III CoBRIM trial [23] was designed to evaluate the efficacy and safety of combined cobimetinib and vemurafenib compared with vemurafenib alone in previously untreated patients with advanced BRAF-mutated melanoma.

Background & rationale

• Design

Between January 2013 and January 2014, 495 patients aged ≥18 years old with histologically confirmed, unresectable, locally advanced

stage IIIC–IV melanoma harboring *BRAF V600* mutations with measurable disease according to RECIST criteria and an ECOG performance status of 0–1 were randomized in a 1:1 ratio to receive cobimetinib 60 mg once daily (21 days on, then 7 days off) plus vemurafenib 960 mg twice daily (n = 247) or vemurafenib plus placebo (n = 248). Treatment was continued until disease progression, unacceptable adverse events or consent was withdrawn. The primary efficacy end point of the trial was investigator-assessed PFS, and secondary efficacy end points included OS, ORR and duration of response. The prespecified number of progression events (206) was estimated to provide at least 95% power to detect an HR for death or disease progression of 0.55 with an α-level of 0.05; this number was reached in May 2014.

Results

Both treatment arms were well balanced at baseline for age, sex, ECOG performance status, disease stage (IIIC, M1a, b, c), lactate dehydrogenase (LDH) level, brain metastases and *BRAF* mutation status (V600E or K). Median follow-up of patients was 7.3 months.

The trial met its primary end point, with vemurafenib plus cobimetinib significantly increasing median PFS to 9.9 months, compared with 6.2 months for vemurafenib alone (HR for death or progression: 0.51; 95% CI: 0.39–0.68; $p < 0.001$). This benefit was observed in all prespecified subgroups of patients (by disease stage, age, sex, geographic region, ECOG performance status, LDH level, prior adjuvant therapy and BRAF mutation status). ORR was 68% in the combination arm and 45% in the monotherapy arm ($p < 0.001$). Complete response rate was also higher in the combination arm (10 vs 4%). Median duration of response was not reached in the combination arm, but was 7.3 months with vemurafenib. Median OS was not reached at the time of the analysis, but the assessment of OS, performed at the time of the final analysis of PFS, showed a 9 months survival rate of 81% for vemurafenib plus cometinib compared with 73% with vemurafenib alone (HR for death: 0.65, 95% CI: 0.42–1.00; $p = 0.046$; boundary $p < 0.0000037$).

Most of the toxicity observed with the combination of vemurafenib and cobimetinib was mild to moderate (grade 1–2). Combination therapy was associated with a higher incidence of grade 3 or 4 adverse events compared with vemurafenib alone (65 vs 59%), although there were no differences in terms of adverse events leading to study drug discontinuation (13 vs 12%). In the vemurafenib plus cobimetinib group most grade 3 toxicities were laboratory abnormalities (AST, ALT or creatine-kinase elevation) without any symptoms. Several *MEK* inhibitor-specific grade 2–3 toxic events were observed, including central serous retinopathy [24,25] or transient drug-induced retinopathy. Most of these events (86%) were grade 1 (clinically asymptomatic) or grade 2 (moderate decrease in visual acuity) [25] and reversible without any treatment. In the vemurafenib arm, toxicity was comparable to that seen in the Phase II and III trials.

Conclusion

In the CoBRIM study, the combination of cobimetinib plus vemurafenib showed a significant improvement in PFS and ORR. These data were consistent with the results obtained with combined dabrafenib plus trametinib versus vemurafenib alone [19] in the COMBI-V trial. PFS and ORR in the vemurafenib arm were consistent with previous randomized trials of vemurafenib [4,12].

The benefits of combining a *MEK* inhibitor and *BRAF* inhibitor are clear when the data are compared with *BRAF* inhibitor monotherapy. In Phase II–III clinical trials of both the *BRAF* inhibitors, median PFS was generally 5.5–6 months. However, another observation from the COMBI-D and COMBI-V trials was the positive outcomes with monotherapy alone, with PFS of 8.8 months for dabrafenib and 7.6 months for vemurafenib. It should be noted, however, that from S compared with dacarbazine, that about 70% of patients in these two studies had normal LDH levels and, as observed in several clinical trials, patients with normal LDH levels have a better outcome with *BRAF* inhibitor therapy [12]. In the CoBrim study, about 50% of patients in each arm had elevated LDH levels and there was no limit to the maximum LDH level at study entry **(Table 1)** [23].

Both the CoBrim and the COMBI-V trial showed a similar ORR (68 and 64%) with complete responses achieved by 10 and 13% of patients, partial responses by 57 and 51% and stable disease in 20% and 26% of patients in the two respective studies [19,23].

OS data in the CoBRIM trial were still immature at the time of analysis, but the assessment performed at the time of the final analysis of PFS showed a HR for death of 0.65 (95% CI:

Table 1. Comparison between experimental arms of BRAFi plus MEKi Phase III trial.

Trial	Patients (n)	High LDH patients (%)	ORR (%)	mPFS months (HR; 95% CI)	OS HR (95% CI)	Previous immunotherapy (%)
CoBrim	Vemurafenib + cobimetinib: 247 Vemurafenib: 248	46	68 (95% CI: 61–73)	9.9† (HR: 0.51; 95% CI: 0.39–0.68) 11.3‡ (HR: 0.60; 95% CI: 0.45–0.79)	0.65 (95% CI: 0.42–1.00)	0
COMBI-V	Dabrafenib + trametinib: 352 Vemurafenib: 352	34	64 (95% CI: 59–69)	11.4 (HR: 0.56; 95% CI: 0.46–0.69)	0.69 (95% CI: 0.53–0.89)	17
COMBI-D	Dabrafenib + trametinib: 211 Dabrafenib: 212	37	67 (95% CI: 60–73)	9.3 (HR: 0.75; 95% CI: 0.57–0.99)	0.63 (95% CI: 0.42–0.94)	27

†According to investigator assessment.
‡According to assessment by independent review facility.
HR: Hazard ratio; mPFS: Median progression-free survival; OS: Overall survival.

0.42–1.00; p = 0.046; boundary p < 0.0000037), which is similar to the HR for death of 0.69 with dabrafenib plus trametinib in the COMBI-V trial. Speculating on these data, we can predict a significant impact on OS of vemurafenib plus cobimetinib compared with vemurafenib alone, despite the treatment provided to both groups of patients after progression.

The revolution in the treatment of metastatic melanoma has involved both targeted therapies and immune checkpoint inhibitors, with improved outcomes for *BRAF*-mutated patients being provided by the completion of both treatment types. Around 40–45% of patients who progress after *BRAF* inhibitor monotherapy have rapid disease progression with a very poor prognosis, and survival of just 30–40 days. Given that all four treatment cycles of the *CTLA-4* inhibitor ipilimumab are required for a significant impact on survival, these patients do not have the opportunity to benefit from ipilimumab treatment [26,27]. The CoBrim trial seems to show a lower rate of rapidly progressing patients after combination treatment, meaning there may be more possibility to complete subsequent treatment with ipilimumab. However, mature data are needed for a more definitive conclusion on this potential benefit. Anti *PD-1*s, the 'game changers' of melanoma treatment, offer faster, as compared with ipilimumab, and durable responses in patients regardless of mutational status. Specific prospective studies will establish the right schedule for combination or sequence with *BRAF*/*MEK* inhibitors, with or without ipilimumab, in the treatment of *BRAF*-mutated metastatic melanoma patients [28,29].

With regard to toxicity profile, the combination of vemurafenib plus cobimetinib was associated with a higher incidence of grade 3 or 4 adverse events compared with vemurafenib alone although there was no increase in adverse-event related discontinuation of therapy. Some specific side effects of *MEK* inhibitors, including diarrhea, serous retinopathy, elevated creatine phosphokinase and increased AST/ALT levels were commonly observed with the combination arm, but resolved quickly, without impact on quality of life of the patient. In fact, most toxicity was grade 1 or 2 and occurred in the first 4 months of treatment. Ocular toxicity, a *MEK*-inhibitor specific side effect, rarely lead to the interruption or discontinuation of cobimetinib, and resolved in most patients without treatment. Moreover the double inhibition of *BRAF* and *MEK*, as previously described in the literature, reduced the incidence of cutaneous SCC/KA compared with vemurafenib alone (4 vs 18%).

It is probable that the on/off administration schedule of cobimetinib [21] may beneficial in combination therapy with vemurafenib. The on/off blockade of *BRAF* signaling appears to delay the increase in acquired resistance in preclinical models [29]. Moreover, ocular toxicity was more manageable with this schedule because in the seven 'off' days, patients generally recovered from this specific side effect without any other therapy and could continue treatment with vemurafenib and cobimetinib without dose reduction or interruption.

The identification of the *BRAF* mutation and the development of anti-*BRAF* therapies can be considered a milestone in the treatment of metastatic melanoma. Since 2011, when vemurafenib was approved, recognition of resistance mechanisms underlying the progression of disease during anti-*BRAF* treatment and the need

to overcome the typical 6–7 months period of response has led to various combination strategies being assessed in clinical trials. In the CoBRIM trial, the combination of vemurafenib and cobimetinib resulted in an improvement in PFS and ORR compared with vemurafenib alone. The study results to date provide early evidence of an OS advantage, increased possibility to complete subsequent treatment lines (e.g., with ipilimumab) after disease progression, and a reduced cutaneous toxicity profile among patients with advanced *BRAF*-mutated melanoma.

Overall, the concomitant inhibition of both *MEK* and *BRAF* has resulted in a more durable and greater tumor response than *BRAF* monotherapy, overcoming the multiple genetic mechanisms of escape. Furthermore, this double inhibition prevents acquired resistance and decreases the toxicity secondary to *BRAF* inhibitor-induced *MAPK*-pathway activation. However, the double combination of vemurafenib plus cobimetinib is not a point of arrival but rather a new starting point forming a basis for novel combination strategies with immunotherapies and other targeted therapies. Investigations into these are already underway and will be continued over the coming years with the aim of further improving outcomes with anti-*BRAF* treatments for patients with metastatic melanoma.

Financial & competing interests disclosure

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