The safety and efficacy of cobimetinib for the treatment of BRAF V600E or V600K melanoma

Teresa Amaral, Noura Nouri & Claus Garbe

To cite this article: Teresa Amaral, Noura Nouri & Claus Garbe (2016): The safety and efficacy of cobimetinib for the treatment of BRAF V600E or V600K melanoma, Expert Review of Anticancer Therapy, DOI: 10.1080/14737140.2016.1192469

To link to this article: http://dx.doi.org/10.1080/14737140.2016.1192469

Accepted author version posted online: 24 May 2016.
Published online: 24 May 2016.

Submit your article to this journal

Article views: 13

View related articles

View Crossmark data
Drug profile

The safety and efficacy of cobimetinib for the treatment of BRAF V600E or V600K melanoma

Authors: Teresa Amaral, MD¹,²; Noura Nouri, MD¹; Claus Garbe, MD¹

Affiliations: 1- Center for Dermatooncology, Department of Dermatology, Liebermeisterstrasse 25, University Hospital Tübingen, 72076 Tübingen, Germany; 2- Portuguese Air Force Health Direction, Paço do Lumiar, 1649-020 Lisbon, Portugal

To whom correspondence should be addressed:

Prof. Dr. Claus Garbe

Center for Dermatooncology

Department of Dermatology

University Hospital Tübingen

Liebermeisterstrasse 25, 72076 Tübingen

Tel.: +49-(0) 7071-29 87110;

Fax: +49-(0)7071-29-5187

e-mail: claus.garbe@med.uni-tuebingen.de
Abstract

Introduction: In the recent years, melanoma patients’ outcome and survival improved, mainly because of systemic treatment improvement with targeted therapy and checkpoint blockade. Targeted therapy with BRAF and MEK inhibitors was approved to treat patients with unresectable or metastatic melanoma, harboring BRAF V600 mutations. This paper addresses the safety and efficacy of cobimetinib, when used in combination with vemurafenib, in the previous mentioned setting.

Areas covered: This article presents an overview on the rationale for clinical development of cobimetinib, as well as the mechanism of action, the efficacy and safety, and the most important trials that led to the approval of the combination therapy with vemurafenib. We searched the PubMed for published papers related to safety and efficacy of cobimetinib, and resistance mechanisms to BRAF inhibition. The abstract databases of the American Society of Clinical Oncology and European Society for Medical Oncology were also searched for updates on the mentioned clinical trials.

Expert review: Patients treated with targeted therapy experience a rapid tumor response. However, virtually all patients will develop resistance to treatment. Therapeutic combinations to overcome resistance mechanisms are currently addressed. In the future, targeted therapy strategy will include three or more drugs, probably from different therapeutic classes.
Keywords

Cobimetinib, MAPK pathway, BRAF mutation, BRAF mutated metastatic melanoma,
BRAF/MEK inhibition, combination targeted therapy
1 Introduction

1.1 Background

In 2015, the number of new estimated cases of melanoma in the US, according to SEER statistics was 73,870, which represent about 4.5% of all new cancer cases. [1] In the same year, 9,940 patients were estimated to die from melanoma, which represent 1.7% of all cancer deaths.

At primary diagnosis, statistics show that between 82% and 85% of the patients will present with a primary tumor only, 10% to 13% with loco-regional metastases, and 2% to 5% with distant metastasis. [1] Melanoma has a better prognosis when diagnosed in earlier stages, as almost all malignancies. [2]

Cytotoxic chemotherapy has been largely ineffective, but can still be considered as a valid option for palliative treatment in stage IV melanoma.

In the first trials with dacarbazine, investigators reported an objective response in up to 25%. However, the most recent multicenter trials, with a more critical evaluation and with more patients included, showed response rates between 5 and 12%. [3]

1.2 BRAF and MEK inhibition

BRAF is a proto-oncogene encoding a serine/threonine protein kinase integrated in the RAS-RAF-MEK-ERK kinase pathway (see figure 1).

BRAF activating mutations are able to induce cell growth and proliferation, since they can constitutively activate the MAPK (mitogen-activated-protein-kinase) pathway. [4]

The MAPK pathway is responsible for transducing extracellular signals that are able to activate intracellular responses, using protein interaction and/or phosphorylation. The extracellular signals can have distinct nature, namely cytokines and growth factors. [5]
In human cancer cells, signaling pathways can be deregulated. Therefore, and taking advantage of that, some of these deregulations/mutations were selected as specific therapeutic targets (see figure 1).

BRAF inhibitors vemurafenib and dabrafenib are oral inhibitors. The FDA approved vemurafenib and dabrafenib in 2011 and 2013, respectively, to treat patients with unresectable or metastatic melanoma and presence of a BRAF V600 mutation. These molecules were designed to target one specific mutation in the V600 codon. [6, 7]

The first results from clinical trials using BRAF inhibitors showed a rapid clinical and imaging response. [8, 9]

One phase 1 clinical trial, testing the combination of vemurafenib plus cobimetinib, showed that the combination was safe and with promising antitumor activity. [6] Subsequent phase 3 trials showed that combination of BRAF/MEK inhibitors was superior to BRAF inhibitors alone. [10-12]

Although most patients initially respond to BRAF inhibition, almost all will develop resistance to therapy later on, suggesting that cellular resistance mechanisms overcome initial inhibitory response. These resistance mechanisms will be analyzed in the following section.

1.3 MAPK pathway and RAF inhibition resistance

The MAPK pathway is activated in the majority of cutaneous melanomas. Activation of this pathway occurs in an early phase of melanoma oncogenesis, and seems to persist in the different phases of tumor progression. [13]

In order to activate MAPK pathway, an interaction between a growth factor receptor and its ligand is necessary. When this cellular process takes place, it triggers a cascade of events that leads to cellular growth, inhibition of apoptosis and increasing survival.
The genomic classification of cutaneous melanoma, published in 2015 by The Cancer Genome Atlas, shows that between 25 and 30% of these tumors harbor a \textit{NRAS} mutation that is known to play a major role in melanoma pathogenesis. \cite{14}

When a somatic mutation in \textit{NRAS} gene is present, it can promote constitutive activation of the \textit{NRAS} protein, preventing inactivation. This type of mutation is responsible to activate serine/threonine kinases that are able to promote cell growth, transformation, survival and proliferation.

Published works showed that other mechanisms could also be implicated in \textit{NRAS} activation. Neurofibromatosis 1 (\textit{NF1}) is a tumor suppressor gene that is able to suppress \textit{NRAS}. Suppression occurs by promoting RAS-GTP hydrolysis to RAS-GDP, which inactivates RAS. When tumors are \textit{NF1} deficient or mutant, RAS and the downstream pathways are permanently activated. \cite{15} The Cancer Genome Atlas study shows that \textit{NF1} mutation is the third most common driving mutation in cutaneous melanoma, after \textit{BRAF} and \textit{NRAS}, accounting for one sixth of the mutations found. \cite{14}

After RAS activation, BRAF and CRAF serine/threonine kinases can act as downstream mediators (see figure 1 and 2). Activated RA\textit{F} interacts with the MAPK/MEK (extracellular signal-regulated kinase (ERK) Kinase), phosphorylating MEK that, afterwards, phosphorylates ERK. \cite{16, 17} ERK activation seems to be an important step in oncogenesis, namely because of the ability to promote cellular growth and differentiation.

BRAF and MEK inhibitors have been developed based on the known MAPK pathway mechanism and showed to be clinically active in patients with BRAF mutant melanomas. \cite{6, 7, 10} However, after an initial response, almost all patients developed resistance and progressive disease.

Resistance mechanisms to BRAF/MEK inhibitors are a largely studied topic, and can be divided in three different categories: innate – absence of response, adaptive – limited response and acquired - initial response with subsequent resistance and progression. \cite{18} MAPK
pathway reactivation can involve MAPK pathway directly or alternative/bypass pathways. [19]

Regarding the first mechanism, ERK reactivation can occur through activating molecules and substrates that are already components of the MAPK pathway. The following are published examples: overexpression of mutant BRAF [20], presence of splicing BRAFV600E isoforms, that are able to promote RAF dimerization in a RAS independent manner [21], upregulation of tyrosine kinases (e.g. platelet derived growth factor receptor β) [22], growth factors driven resistance by increased levels of tyrosine receptor kinase ligand levels [23], activating NRAS mutations [19, 22], NF1 mutation or loss [15], CRAF upregulation [24], MAPK kinases serine/threonine re-activation through COT (Cancer Osaka Thyroid), a proto-oncogene kinase [25], and MEK activating mutations [19, 26, 27].

Bypass mechanisms, outside MAPK pathway, namely activation of PI3K/PTEN/AKT (phosphatidylinositol 3 kinase/phosphatase and tensin homolog 1/AKT) pathway by insulin like growth factor receptor 1 (IGFR1) or AKT1 mutant (adaptive or genetic upregulation of AKT), have also been described. [18, 28]

Another resistance mechanism is associated with copy number changes in CDKN2A (cyclin-dependent kinase inhibitor 2A) and CCND1 (cyclin D1) and PTEN mutation/loss of expression. [29] These mechanisms could be responsible for intrinsic resistance to BRAF inhibitors. Tumor microenvironment was also implied in BRAF inhibitors resistance. The presence of plasma and stromal elevated levels of hepatocyte growth factor were associated with innate BRAF inhibition resistance. [30] The role of fibroblasts, and the paradoxical activation of the BRAF/ERK pathway through BRAF inhibition, was recently addressed. [31-33] These publications implicate fibroblast and extracellular matrix proteins in BRAF inhibition resistance. Fibronectin and upregulation of fibronectin secretion, tenascin-C, integrin β1 and focal adhesion kinase (FAK) are some of the molecules that play an important role in resistance to BRAF inhibition. Menon et al also described that melanoma cells are able to induce an in-
nate response to chronic stress with a subsequent intrinsic phenotypic change. [34] This change induces activation of several receptor tyrosine kinases, leading to FAK signaling activation and AKT and ERK hyperactivation.

In conclusion, MAPK pathway reactivation, through different mechanisms, is a major component of BRAF inhibition treatment resistance. A summary of the BRAF inhibition resistance pathways and mechanisms is shown in figure 2.

1.4 Cobimetinib plus vemurafenib

Cobimetinib (GDC-0973/XL518/RO5514041) is a reversible inhibitor of MEK1 and MEK2. [35, 36] The absolute bioavailability of cobimetinib was 46%. [35, 37] The median time to achieve peak plasma levels was 2.4h, when cobimetinib 60mg was administrated orally, once daily, in cancer patients. [35] In humans, 94.8% cobimetinib binds to plasma proteins in a concentration independent manner. [35, 36] Cobimetinib was extensively metabolized, with less than 10% of the unchanged drug being excreted in urine, feces and bile. Oxidation and glucuronidation appear to be the major pathways of metabolism. [35, 36] Clinical pharmacokinetics show that cobimetinib can be administrated without regard to food, and oral absorption was not changed by elevated gastric pH. [37]

Vemurafenib is an orally available inhibitor of BRAF mutated forms namely BRAFV600E. In vitro, vemurafenib can also inhibit other RAF kinases. [38] For vemurafenib, administered twice a day, in a dose of 960mg, for 15 days, the time to achieve peak serum concentration (T\text{max}) was approximately 3 h. [38, 39] In vitro, vemurafenib is highly bound to human plasma proteins, in a concentration >99%. [39] In FDA and EMA prescribing information is written that vemurafenib can be taken unregard food. However, the published study from Ribas et al [40] showed that a high fat meal could increase exposure to vemurafenib up to three times.
2 Clinical efficacy

2.1 MEK4592g study/ NCT00467779

MEK4592g was a phase 1, non-randomized, open-label, dose-escalation study. [41-43] This study intended to evaluate the safety and pharmacokinetics of cobimetinib, administered orally, daily, to subjects with solid tumors. Study population included patients with metastatic or unresectable solid tumors, for which standard curative or palliative measures did not exist, were no longer effective or for whom there were no known therapies that prolonged survival.

The trial had five stages. The primary objectives of stage I, IA, II and IIA, were evaluation of safety and tolerability of cobimetinib administered orally, in repeated doses, and determination of the MTD (maximum tolerated dose). The primary objective of stage III was to evaluate the pharmacokinetic effect of dextromethorphan and midazolam on cobimetinib. Assessment of tumor response was an exploratory endpoint. Ninety-seven patients were included. Investigators accessed best overall response using RECIST (Response Evaluation Criteria In Solid Tumors) criteria.

Cobimetinib was administered orally, once daily (OD) in a 21/7-day regimen for stages I and II, and in a 14/14-day regimen for stages IA and IIA, of each 28-day cycle. The dose cohorts ranged between 0.05 mg/kg– 0.20 mg/kg, and 20 mg – 80 mg in the 21/7-day regimen, and 60-125 mg in the 14/14-day regimen.

Included patients had colorectal cancer (33 patients), melanoma (11 patients), colon cancer (6 patients) and other tumors (26 patients, including 1 patient with ocular melanoma and 1 patient with choroid mixed-type melanoma).

Melanoma patients were included in cohort with 100 mg 14/14-day regimen (7 patients) and in cohort with 60 mg 21/7-day regimen (4 patients).

The results showed that 6 patients experienced DLT (dose-limiting toxicity). One patient had grade 4 hepatic encephalopathy (21/7-day regimen with 40 mg), 1 patient had grade 3 acnei-
form dermatitis (21/7-day regimen with 60mg), 1 patient had grade 3 diarrhea (21/7-day regimen with 80mg), 1 patient had grade 3 blurred vision with serous macular detachment (14/14-day regimen 125mg) and 2 patients had grade 3 rash (21/7-day regimen with 60mg and 80mg).

The MTD found was 60mg for the 21/7-day regimen and 100mg for the 14/14-day regimen.

Tumor response evaluation was available for 72 patients. Six patients achieved partial response, stable disease was the best response in 28 patients and 40 patients had progressive disease. [44]

2.2 Pivotal trials

2.2.1 BRIM7/ NO25395 Study/ NCT01271803

BRIM7 study was an open-label, multicenter, phase 1b, dose escalation study. The primary objectives were evaluation of safety, tolerability and pharmacokinetics of combined MEK and BRAF inhibition using cobimetinib and vemurafenib; identification of DLT that determined the MTD of the combination and identification and recommendation of a dose and schedule for further investigation. Efficacy was a secondary endpoint.

Patients with locally advanced and unresectable or metastatic melanoma and presence of a BRAFV600E mutation, identified using cobas® 4800 BRAFV600 Mutation Test, were included.

The study population was divided in two subgroups: patients without previous treatment with BRAF inhibitor (BRAF inhibitor naïve) and patients that had progressed under vemurafenib therapy. The first subgroup included patients previously untreated and patients with previous treatment that not included BRAF inhibitors.

BRIM7 had two stages: a dose-escalation stage and a cohort expansion stage. During the dose-escalation stage, all patients received vemurafenib (720mg or 960mg) twice daily (BID), continuous dosing, in combination with cobimetinib OD. Cobimetinib (60, 80 or 100mg) was
administered in one of the following regimens (28 days cycle): 14/14 (14 days on/14 days off), 21/7 (21 days on/7 days off) or continuously, 28/0.

Ten dose-escalation cohorts were planned, in order to determine the MTD of each molecule. The MTD was used in the expansion phase.

The first report in 2014 presented data with a cutoff date of 1 October 2013. [6] The study included 129 patients. Sixty-three patients were BRAF inhibitor naïve and 66 patients were patients that progressed after vemurafenib treatment (Vemurafenib-PD).

BRAF inhibitor naïve patients were followed for a median of 12.7 months and vemurafenib-PD patients for a median of 6.3 months.

Tumor response was accessed using RECIST criteria version 1.1 (RECIST v1.1). [45] For BRAF inhibitor naïve patients, the confirmed response rate was 87.3% (95% CI: 76.7%, 94.4%). The median duration of response (DOR) was 12.5 months (95% CI: 9.7, not evaluable); median progression free survival (PFS) was 13.7 months (95% CI: 101, 17,5) and 1-year overall survival (OS) rate was estimated to be 82.8% (95% CI: 72.9%, 92.6%). Patients typically had a rapid response, with a median time to objective response of 1.4 months (95% CI: 1.2, 6.2). In vemurafenib-PD patients, the confirmed response rate was 15.2% (95% CI: 7.5%, 25.5%). The median DOR was 6.7 months (95% CI: 4.9, not evaluable), median PFS was 2.8 months (95% CI: 2.6, 3.5) and 1-year OS rate was estimated to be 32.0% (95% CI: 19.4%, 44.6%). The median time to objective response was 1.5 months (95% CI: 1.3, 4.2).

The BRIM7 results were updated in the ASCO meeting 2015. [46] At this time, the median follow-up was 21 months for BRAF inhibitor naïve patients and 8 months for vemurafenib-PD patients. In BRAF inhibitor naïve patients confirmed response rate was 87% and median PFS was 13.8 months (the same as the first report). The median OS was 28.5 months with a 2-year OS of 61%. In vemurafenib-PD patients, confirmed response rate was 15%, median PFS was 2.8 months and median OS was 8.4 months (the same as the first report). The 2-year OS was 15%.
CoBRIM was a randomized, double blind, placebo controlled, multicenter, phase 3 study. [10] The primary endpoint was investigator assessed PFS. Secondary endpoints were safety, response rate, DOR, OS, independent review facility (IRF) – assessed PFS and quality of life. Patients with unresectable locally advanced or metastatic melanoma, with presence of a BRAF V600 mutation, no previous therapy for advance disease, Eastern Cooperative Oncology Group performance status 0 or 1, measurable disease (according to RECIST v1.1), history of previously treated brain metastasis (stable for at least three weeks), and adequate organ function were eligible. Adjuvant therapy, including immunotherapy was allowed.

The study had two treatment arms. Patients were randomized in a 1:1 ratio to Arm A (vemurafenib plus placebo), or Arm B (vemurafenib plus cobimetinib). Vemurafenib was administered continuously, 960mg BID, in combination with cobimetinib or cobimetinib placebo, 60mg OD, in a 21/7-day schedule.

The first report, published in 2014 in the NEJM, presented the data with a cutoff date of 10 July 2014. [10] The study included 495 patients; 247 patients received vemurafenib plus cobimetinib and 248 patients received vemurafenib plus cobimetinib placebo. The median time of follow-up for the first report was 7.3 months, ranging from 0.5 to 16.5 months.

Combination therapy improved PFS by investigator assessment, with statistical significance, HR 0.51 (95% CI: 0.39, 0.68; p<0.001), when compared to vemurafenib plus placebo. The investigator-assessed median PFS was 9.9 months for the combination arm (95% CI: 9.0, upper bound not reached) versus 6.2 months for the vemurafenib plus placebo arm (95% CI: 5.6, 7.4). The magnitude of PFS improvement when assessed by IRF was consistent with investigator assessment, HR 0.60 (95% CI: 0.45, 0.79; p<0.001). The median PFS by IRF was 11.3 months in the combination arm (95% CI: 8.5, upper bound not reached) versus 6 months in the vemurafenib plus placebo arm (95% CI: 5.6, 7.6). Overall response rate was
68% in the combination arm (95% CI: 61.4, 73.4), significantly higher than 45% in the vemurafenib plus placebo arm (95% CI: 38.5, 51.2; p<0.001 for the difference in overall response rate (ORR)). One hundred and sixty-seven patients had an objective response in the combination arm. The median DOR was not reached at the time of cut-off (95% CI: 9.3, not reached). In the vemurafenib plus placebo arm 111 patients had an objective response and the median DOR was 7.3 months (95% CI: 5.8, not reached). The rate of complete responses was higher in the combination arm, 10% versus 4%. The observed HR for OS at the first interim analysis was 0.65 (95% CI: 0.42, 1.0; p=0.046) in favor of the cobimetinib plus vemurafenib arm, but without crossing the pre-specified boundary for significance (p<0.0000037). OS data was immature at this point. Sub-group analyses of PFS based on demographic and tumor characteristics, were consistent with PFS results in the intent-to-treat population, favoring the combination therapy.

The coBRIM results were updated in the ASCO meeting of 2015, with a data cutoff date of 16 January 2015. [47] The median follow-up at this time was 14.9 months for the combination arm and 13.6 months for the vemurafenib plus placebo arm. Combination therapy improved PFS, HR 0.58 (95% CI: 0.46, 0.72), when compared to vemurafenib plus placebo. The median PFS was 12.3 months for the combination arm (95% CI: 9.5, 13.4) versus 7.2 months for the vemurafenib plus placebo arm (95% CI: 5.6, 7.5). In the combination arm, 172 patients had an objective response. The ORR was 70%, with 16% complete responses and 54% partial responses. In the vemurafenib plus placebo arm, 124 patients had an objective response. The ORR was 50%, with 11% complete responses and 40% partial responses. Table 3 presents a summary of BRIM7 and coBRIM trials results.

3 Completed clinical trials with unpublished results

Addressing two or more different signaling pathways, in order to overcome BRAF inhibition resistance, will be the future of targeted therapy. Two trials evaluating the combination of
MEK inhibitor cobimetinib with a PI3K inhibitor and an AKT inhibitor are completed. The results from these trials could have an implication on future trials design.

### 3.1.1 Cobimetinib in combination with PI3K inhibitor

MEK4572g study was an open-label, phase 1b dose-escalation study. The primary objective were to evaluate safety, tolerability and pharmacokinetics of oral dosing cobimetinib and pictilisib, a PI3K inhibitor, when administered in combination; to determinate the MTD on various dosing schedules; and to identify a recommended phase 2 dose(s) and schedule(s). Patients with metastatic or unresectable solid tumors, for which standard curative or palliative measures did not exist, were no longer effective or for whom there were no known therapies that prolonged survival, were eligible. This study has been completed. Final results are not yet published.

### 3.1.2 Cobimetinib in combination with AKT inhibitor

GE28079 study was a multicenter, phase 1b, dose-escalation study, conducted in Spain and the United States of America. This study was designed to address the safety and tolerability of escalating doses of the AKT inhibitor ipatasertib, in combination with cobimetinib. Patients with documented locally advanced or metastatic solid tumors were eligible, providing no standard therapy existed or was proven to be ineffective or intolerable.

The study had two treatment arms, testing two schedules for cobimetinib. In arm A, increased doses of ipatasertib and cobimetinib were administered orally OD on a 21/7-day schedule, of a 28-day cycle. In Arm B, increasing doses of ipatasertib were administered orally OD on a 21/7-day schedule, in combination with increasing doses of cobimetinib administered orally OD on an intermittent dosing schedule (days 1, 4, 8, 11, 15 and 18), of a 28-day cycle. This study comprised a dose escalation stage (stage 1, Arm A and B) and a cohort-
expansion stage (stage 2). The objective of stage 1 was to identify the combination MTD of ipatasertib and cobimetinib in each arm. The objective of stage 2 was to further characterize the safety and tolerability of ipatasertib and cobimetinib in combination, considering the MTD identified on stage 1. The study has been completed and closed in January 2015. Final results are not yet published.

4 Ongoing clinical trials

The following ongoing clinical trials – one phase 1 and three phase 2 clinical trials – focus on the combination of cobimetinib with immunotherapy and cobimetinib with vemurafenib in different settings (neo-adjuvant, intermittent dosing and active melanoma brain metastases).

4.1 Cobimetinib in combination with immunotherapy

GP28363 study is a phase 1b, open-label, multicenter study. This study intends to evaluate the safety, tolerability and pharmacokinetics of intravenous dosing of MPDL3280A – atezolizumab (an anti-PDL1 antibody) and cobimetinib when administered in combination. Patients with metastatic or locally advanced, unresectable solid tumors, for which no standard therapy exists are eligible. This study comprises a dose escalation stage (stage 1) and a dose expansion stage (stage 2). Stage 1 was designed to establish the combination MTD for MPDL3280A – atezolizumab and cobimetinib, which will be used in the dose expansion stage. Completion is expected in 2017.

Combination of targeted therapy and immunotherapy was tested with a non-favorable toxicity profile. However, a recent case series report with ten patients showed that, in this population, the combination of vemurafenib and ipilimumab was safe with a promising clinical outcome. Another combination of MEK and/or BRAF inhibitor with anti-PDL-1
antibody is also under evaluation. [54] The GP28363 study combining cobimetinib and atezolizumab will add new data on the possibility of safely combine targeted therapy and immunotherapy in melanoma patients.

4.1.1 Neo-adjuvant therapy with cobimetinib plus vemurafenib

The NEO-VC is a phase 2, single armed clinical trial that intends to evaluate the safety, efficacy and biological effects of cobimetinib in combination with vemurafenib, in patients with the presence of a BRAFV600 mutation, limited metastasis of melanoma stage IIIC/IV and MAPK inhibitor treatment naïve, using a neo-adjuvant approach. [55] The primary outcome is percentage of patients that become operable after 18 weeks with the combination therapy. This trial is currently open and recruiting patients.

4.1.2 Cobimetinib plus vemurafenib intermittent versus continuous dosing

Preclinical data showed that intermittent therapy with BRAF inhibitors could delay the onset of acquired resistance. [56] The intermittent dosing of BRAF inhibitors in combination with MEK inhibitors could be of clinical value since acquired resistance mechanisms to combination therapy are very similar to the acquired resistance mechanisms to BRAF inhibitors therapy alone. [57]

The NCT02583516 study is a randomized, phase 2 trial, evaluating the efficacy and safety of cobimetinib plus vemurafenib continuous versus intermittent, in patients with unresectable locally advanced or metastatic, treatment naïve, BRAFV600 mutated melanoma. [58] The primary outcome is PFS. Other outcomes are OS, ORR, PFS at one and two years, adverse events (AE) and serious AE occurrence. This trial is ongoing and recruiting patients.
4.1.3 Cobimetinib plus vemurafenib in patients with brain metastasis

The subpopulation of patients with melanoma and brain metastasis has been studied with particular interest, and there is already evidence that BRAF inhibitors are active and can safely be used in patients with brain metastasis. [59, 60]

The coBRIM-B trial is a single arm, open label, multicenter, phase 2 study. [61, 62] This study intends to determine the safety and efficacy of the combination of cobimetinib and vemurafenib in patients with BRAF mutated melanoma and active melanoma brain metastases. The primary objective is to determine the investigator assessed objective intracranial response rate, using modified RECIST criteria. Secondary objectives include safety and tolerability, extra and intracranial ORR, PFS, OS and DOR. Patients with melanoma and presence of a BRAF V600 mutation, with more than one measurable intracranial target lesion and no previous therapy with MEK and/or BRAF inhibitors, are eligible. The coBRIM-B study, presented as an abstract in the ASCO meeting in 2015, is currently open and recruiting patients.

5 Safety

The adverse events reported for the combination therapy in BRIM7 and coBRIM trials are acceptable and manageable. [6, 10] Table 4 presents an overview of the safety profile for BRIM7 and coBRIM.

In BRIM7 trial BRAF inhibitor naïve patients had more side effects than those enrolled after progression with BRAF inhibitor therapy. According to the authors, this could be explained by the longer exposure time to therapy. The most common AE (all grades >40% included patients) in the combination therapy, considering the Medical Dictionary for Regulatory Activities (MEDRA), were: non-acneiform rash, diarrhea, fatigue, photosensitivity or sunburn, liver enzymes abnormality, nausea, arthralgia, increase in creatine phosphokinase, pyrexia
and vomiting. With a longer follow-up, authors reported that the frequency and seriousness of side effects remained stable. [46]

In the coBRIM trial, the authors defined the most common AE as the AE that occurred in at least 20% of the included patients in either treatment group. The majority of common adverse effects, in both groups, were grade 1 and 2. The frequency of AE classified as grade > 3, was also similar. [10] Grade 4 AE were reported in 13% of the patients in the cobimetinib plus vemurafenib arm versus 9% in the vemurafenib plus placebo arm. Patients treated with MEK inhibitors were reported to have ophthalmological complications. [10] Most cases in the coBRIM trial were asymptomatic or mild symptomatic, and resolved with conservative approach (without any specific therapy) or dose reduction. Patients treated with MEK inhibitors should be advised to report new or worsening visual disturbances and, in this case, ophthalmologic examination is recommended. [35]

Some side effects were less common in patients treated with cobimetinib plus vemurafenib, than with vemurafenib alone. Cutaneous squamous cell carcinoma and keratoacanthoma are class side effects of BRAF inhibitors. These cutaneous tumors are related to the paradoxical MAPK activation in keratinocytes [63, 64], mitigated by MEK inhibitors. Patients that received vemurafenib or combination therapy should maintain regular clinical evaluation for early detection of cutaneous malignancies. The exact period of time is unknown, since they can be detected up to 52 weeks after therapy. [65]

The combination therapy with BRAF/MEK inhibitors had more side effects than the mono-therapy with BRAF inhibitors, as it would be expected. The most common are gastrointestinal disorders: diarrhea, nausea, abdominal pain, stomatitis and constipation. These side effects were mainly grade 1 and 2, and the number of patients discontinuing therapy because of AE was similar in both arms. [10]

Since these are palliative therapies, quality of life is an important aspect to consider. Two publications addressed this issue and both reported improved quality of life in patients
treated with combination therapy. Therefore, the toxicity associated with the combination therapy reported in clinical trials seems to be more “subjective” than clinically meaningful. [66, 67]

6 Expert commentary

Metastatic melanoma treatment has changed dramatically in the last years. The BRIM7 and coBRIM trials showed that the combination of cobimetinib plus vemurafenib improved patients’ outcomes, in comparison to vemurafenib alone, with an acceptable and manageable toxicity profile. [6, 10, 68] These two trials defined the combination therapy as standard for patients with the BRAF mutation, and led to approval of the combined schedule by the FDA and EMA. MEK inhibitor cobimetinib, oppositely to trametinib, is not approved in monotherapy, only in combination with vemurafenib. [35, 36, 69, 70]

There are competing combined drug schedules to the cobimetinib plus vemurafenib combination. The combination of trametinib plus dabrafenib was approved based on two phase 3 trials: the COMBI-D trial evaluated trametinib plus dabrafenib versus dabrafenib plus placebo, and the COMBI-V trial evaluated trametinib plus dabrafenib versus vemurafenib in an unblinded study. [11, 12] So far, no superiority of efficacy was seen between the previously described BRAF/MEK inhibitors combinations. Both have a comparable outcome. The side effects profile is, however, different and most of the switching between these combined regimens is related to the different toxicities. With the cobimetinib plus vemurafenib combination, patients had more photosensitivity and arthralgia whereas in the trametinib plus dabrafenib combination, pyrexia was more important. [10-12]

Another BRAF/MEK combination, encorafenib plus binimetinib, is still under evaluation. [71, 72] This combined schedule will need to be evaluated and compared to the two already known combination therapies, in terms of efficacy and side effects profile.
Different approaches to cobimetinib plus vemurafenib inhibition are neo-adjuvant and intermittent therapy. [55, 58] Data from these ongoing clinical trials could change the approved indications in the future.

7 Five years view

The combination of BRAF/MEK inhibitors already became the standard therapy in unresectable metastatic melanoma, carrying the BRAF V600 mutation. In this setting, monotherapy with BRAF or MEK inhibitors will no longer be used as first-line therapy.

Considering the myriad of resistance mechanisms to MAPK pathway inhibition, more complex combination therapies or “drug cocktails”, targeting more than one signaling pathway and/or mutation will be developed. Some of these combinations are under evaluation or have already been evaluated in pre-clinical and clinical trials.

Recently, nelfinavir, a HIV1-protease inhibitor, was described as a re-sensitizer of BRAF and NRAS mutant melanoma cells that developed resistance. [73] The authors describe an early drug tolerance to MAPK inhibition, related to the upregulation of the MITF oncogene, than can be overcame with combination therapy with nelfinavir.

Melanoma cells with V600E/K mutation can also be re-sensitize to BRAF inhibition, using PRIMA-1\(_{\text{Met}}\) (APR-246) to reactivate suppressed p53. The p53 direct activator PRIMA-1\(_{\text{Met}}\) (APR-246) was used in combination with vemurafenib. These two compounds had a synergic activity inducing apoptosis, suppressing cell proliferation (in vitro) and tumor growth (in vivo). [74]

Cross-resistance to MEK1/2 and PI3K/mTOR inhibitors was described in cells resistant to BRAF inhibitors. Penna et al showed that co-targeting MEK1/2 and PI3K/mTOR could counteract primary resistance to BRAF inhibition with better results when compared to BRAF and PI3K/mTOR co-targeting, favoring the first combination in future trials. [75]
The combined inhibition of BRAF/MEK/MET with encorafenib plus binimetinib plus capmatinib in patient-derived xenograft models also showed complete and sustained tumor regression. [76]

Atiq et al described an interesting approach focused on avoiding the development of BRAF inhibitors resistance by forcing oncogene-induced growth arrest in BRAF mutated cancers. The oncogene-induced growth arrest was the result of MAPK hyperactivation, through inhibition of phosphatase 2A protein by a synthetic long-chain fatty acid (MEDICA). [77]

As mentioned in section 3, efficacy and safety results from the combination of cobimetinib with PI3K and AKT inhibitors are not yet published. [48, 49] Other combinations with BRAF and MEK inhibitors are under evaluation in order to overcome acquired resistance. [78, 79]

The previously mentioned trials indicate that new combinations with three or more targeted therapy agents will certainly have a place in the future treatment of metastatic melanoma with BRAF V600 mutation. Careful selection of patients and therapies, based on mutation analysis, could minimize treatment failures.

8 Key issues

- BRAF inhibitors were the first targeted therapy approved to treat patients with unresectable or metastatic BRAF mutant melanoma (40-50% of the cutaneous melanoma harbor BRAF targetable mutations).
- Clinical and imaging (rapid) responses can be achieved with BRAF inhibitors. However, virtually all patients develop resistance and progress under therapy. MAPK pathway reactivation plays an important role in resistance mechanism to RAF inhibition.
- Different mechanisms, either involving MAPK pathway components or bypass/alternative pathways have been implicated in BRAF inhibition resistance. Three different types of resistance were described: innate – absence of initial response,
adaptive – limited response and acquired - initial response with subsequent resistance and progression.

• Phase 1 and 3 clinical trials showed that BRAF/MEK inhibitors combination therapy is safe and effective.

• Phase 3 trials proved that BRAF/MEK inhibitors combination therapy is superior in terms of efficacy to BRAF inhibitors monotherapy.

• Cobimetinib is a MEK inhibitor approved to treat patients with unresectable or metastatic melanoma, with BRAF V600 mutation. Cobimetinib is approved only in combination with vemurafenib.

• In the pivotal coBRIM trial, cobimetinib plus vemurafenib improved OS, PFS and response rate, in comparison to vemurafenib plus placebo.

• The combination therapy of cobimetinib plus vemurafenib has an acceptable and manageable toxicity profile.

• Other combination therapies are currently under evaluation, including in the neo-adjuvant setting. Results could impact future treatment options for melanoma patients.

• In the next five years, probably “drug cocktails” involving three or more targeted agents and/or signaling pathways will have a place in metastatic melanoma treatment.

Financial and competing interests disclosure

Garbe has received grants and personal fees from Roche, personal fees from Amgen, grants and personal fees from BMS, personal fees from MSD, grants and personal fees from Novartis and personal fees from LEO. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.
References


46. Pavlick, A., et al., *Extended follow-up results of phase Ib study (BRIM7) of vemurafenib (VEM) with cobimetinib (COBI) in BRAF--mutant melanoma*. J Clin Oncol 33, 2015 (suppl; abstr 9020).

47. Larkin , J., et al., *Update of progression-free survival (PFS) and correlative biomarker analysis from coBRIM: Phase III study of cobimetinib (cobi) plus vemurafenib (vem) in advanced BRAF-mutated melanoma*. J Clin Oncol 33, 2015 (suppl; abstr 9006).


MAPK pathway comprises RAS/RAF/MEK/ERK, activated in a sequential form. Punctual mutations, namely BRAFV600 mutations, were used as targets for the development of BRAF and MEK inhibitors. The figure displays BRAF and MEK inhibitors, approved/in evaluation, for mono and combination therapy, at this time.

**Legend:**

- BRAF Inhibitors: Vemurafenib, Dabrafenib, Encorafenib
- MEK Inhibitors: Cobimetinib, Trametinib, Binimetinib, Pimasertib
Figure 2: MAPK pathway and potential mechanisms of resistance to BRAF inhibition in melanoma cells

Legend: MAPK pathway activating mutations can be effectively targeted with BRAF and MEK inhibitors (red stars). This results in oncogenic pathway inhibition and disease response. However, commonly after an initial response, reactivation occurs, leading to disease progression. Potential mechanisms of resistance include:

1. MAPK pathway dependent activation mechanisms (facing the figure, on the left) – these mechanisms commonly involve MAPK pathway components (NRAS, mutant BRAF forms, tyrosine receptors kinase ligands, NF1, MEK activating mutations and COT overexpression)

2. MAPK pathway independent reactivation (facing the figure, on the right) – this mechanism, normally involves bypass pathway activation, namely PI3K/PTEN/AKT pathway

3. Tumor microenvironment factors, namely stromal or plasma elevated levels of HGF, phenotypic change due to chronic stress exposure, fibroblast and ECM proteins interaction, possibly related to initial/early resistance (yellow star)

4. TRK: tyrosine receptors kinase; HGF: hepatocyte growth factor; ECM: extracellular matrix
### Table 1: Summary of cobimetinib phase 1 trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population</th>
<th>Treatment</th>
<th>Objective</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>MEK4592g study/ NCT00467779</td>
<td>Metastatic or unresectable solid tumors with no standard therapy approved</td>
<td>Cobimetinib monotherapy</td>
<td>Safety, tolerability, Pharmacokinetic evaluation</td>
<td>Completed</td>
</tr>
<tr>
<td>MEK4752g study/ NCT00996892</td>
<td>Metastatic or unresectable solid tumors with no standard therapy approved</td>
<td>Cobimetinib plus pictilisib (PI3K inhibitor)</td>
<td>Safety, tolerability, Pharmacokinetic evaluation</td>
<td>Completed</td>
</tr>
<tr>
<td>GE28079 study/ NCT01562275</td>
<td>Metastatic or unresectable solid tumors with no standard therapy approved</td>
<td>Cobimetinib plus ipatasertib (AKT inhibitor)</td>
<td>Safety, tolerability, Pharmacokinetic evaluation</td>
<td>Completed</td>
</tr>
<tr>
<td>GP28363 study/ NCT01988896</td>
<td>Metastatic or unresectable solid tumors with no standard therapy approved</td>
<td>Cobimetinib plus MPDL3280A – atezolizumab ( anti-PDL1 antibody)</td>
<td>Safety, tolerability, Pharmacokinetic evaluation</td>
<td>Ongoing Recruiting</td>
</tr>
</tbody>
</table>

### Table 2: Summary of cobimetinib phase 2 trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Study population</th>
<th>Treatment</th>
<th>Objective/outcomes</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>NEO-VC/NCT02303951</td>
<td>Patients with BRAF V600 mutation, limited metastasis of melanoma stage III/IV and MAPK inhibitor treatment naïve</td>
<td>Cobimetinib plus vemurafenib</td>
<td>Safety, efficacy and biological effects of the combination therapy. Percentage of patients that become operable after the combination therapy during 18 weeks</td>
<td>Ongoing</td>
</tr>
<tr>
<td>NCT02583516/ GEM-01-15/ 2014-005277-36</td>
<td>Patients with unresectable locally advanced or metastatic, treatment naïve, BRAF V600 mutated melanoma</td>
<td>Cobimetinib plus vemurafenib, continuous versus intermittent</td>
<td>PFS, OS, ORR, PFS at one and two years, AE and serious AE occurrence.</td>
<td>Ongoing</td>
</tr>
<tr>
<td>coBRIM-B/ NCT02230306</td>
<td>Patients with BRAF V600 mutated melanoma, &gt;1 measurable intracranial, active, target lesion and MEKi and BRAFi treatment naïve</td>
<td>Cobimetinib plus vemurafenib</td>
<td>Investigator assessed objective intracranial response rate, safety, tolerability, extra and intracranial ORR, PFS, OS and DOR</td>
<td>Ongoing</td>
</tr>
</tbody>
</table>

**Legend:** PFS: progression free survival; OS: overall survival; ORR: overall response rate; DOR: duration of response.
Table 3: Summary of the pivotal clinical trials evaluating cobimetinib in advanced melanoma

<table>
<thead>
<tr>
<th>Author/trial</th>
<th>Phase</th>
<th>N</th>
<th>Treatment</th>
<th>RR %</th>
<th>Median PFS (Months)</th>
<th>Median OS (Months)</th>
<th>Primary endpoints</th>
<th>Other endpoints</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ribas et al/BRIM7 The Lancet 2014</td>
<td>Ib</td>
<td>129</td>
<td>vemurafenib (720 mg or 960 mg bid) and cobimetinib 60 mg, 80 mg, or 100 mg daily (14 days on/14 days off, 21 days on/7 days off, or continuously)</td>
<td>BRAF naïve 87</td>
<td>13.7</td>
<td>Safety, MTD, Dose-limiting toxic effects</td>
<td>Efficacy</td>
<td></td>
</tr>
<tr>
<td>Pavlick et al Update ASCO 2015</td>
<td></td>
<td></td>
<td></td>
<td>BRAF naïve 87</td>
<td>13.8</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Larkin et al CoBRIM-The NEJM 2014</td>
<td>III</td>
<td>495</td>
<td>cobimetinib 60 mg (21 days on/7 days off) plus vemurafenib (960 mg bid continuously) or vemurafenib (960 mg bid continuously) plus placebo</td>
<td>COB+VEM 68</td>
<td>9.9</td>
<td>Safety, RR, ORR, DOR, OS, PFS, QoL</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VEM+Placebo 45</td>
<td>6.2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>CoB+VEM 70</td>
<td>12.3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>VEM+Placebo 50</td>
<td>7.2</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Legend: VEM: vemurafenib; BRAF: BRAF inhibitor; COB+VEM: cobimetinib plus vemurafenib; MTD: maximum tolerated dose, bid: twice a day; ORR: overall response rate; PFS: progression free survival; OS: overall survival, RR: response rate; DOR: duration of response; IRF-PFS: independent review facility-assessed PFS; QoL: quality of life
Table 4: Summary of common AE occurring in ≥10% (All Grades) or ≥5% (Grades 3 or 4) in patients treated with cobimetinib in combination with vemurafenib.

<table>
<thead>
<tr>
<th>Adverse events</th>
<th>coBRIM Phase 3 Study GO28141</th>
<th>BRIM7 Phase 1b Study NO25395</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>VEM+Placebo (n=246)*</td>
<td>COB+VEM (n=247)*</td>
</tr>
<tr>
<td></td>
<td>All Grades (%)</td>
<td>Grades 3-4 (%)</td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>31</td>
<td>1</td>
</tr>
<tr>
<td>Nausea</td>
<td>25</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting</td>
<td>13</td>
<td>1</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>14</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>8</td>
<td>-</td>
</tr>
<tr>
<td>Constipation</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash</td>
<td>53</td>
<td>13</td>
</tr>
<tr>
<td>Photosensitivity reaction e</td>
<td>35</td>
<td>-</td>
</tr>
<tr>
<td>Pruritus</td>
<td>19</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Alopecia</td>
<td>30</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dry skin</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>Acne, dermatitis acneiform</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Hyperkeratosis</td>
<td>38</td>
<td>2</td>
</tr>
<tr>
<td>Erythema</td>
<td>13</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Neoplasms benign, malignant and pre-neoplastic conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Basal cell carcinoma</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Actinic keratosis, squamous cell carcinoma of skin</td>
<td>18</td>
<td>13</td>
</tr>
<tr>
<td>General disorders and administration site conditions</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fatigue</td>
<td>33</td>
<td>3</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>23</td>
<td>-</td>
</tr>
<tr>
<td>Edema</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Symptom</td>
<td>Prevalence</td>
<td>Grade 1</td>
</tr>
<tr>
<td>-------------------------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Asthenia</td>
<td>16</td>
<td>1</td>
</tr>
<tr>
<td>Chills</td>
<td>5</td>
<td>-</td>
</tr>
<tr>
<td>Metabolism and nutrition</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>20</td>
<td>&lt;1</td>
</tr>
<tr>
<td>Dehydration</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>16</td>
<td>2</td>
</tr>
<tr>
<td>Dysgeusia</td>
<td>11</td>
<td>1</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>Eye disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chorioretinopathy</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Vision blurred, impaired</td>
<td>4</td>
<td>-</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>&lt;1</td>
<td>-</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arthralgia</td>
<td>40</td>
<td>5</td>
</tr>
<tr>
<td>Myalgia</td>
<td>12</td>
<td>2</td>
</tr>
<tr>
<td>Pain in extremity</td>
<td>14</td>
<td>2</td>
</tr>
</tbody>
</table>

**Legend:**  
- Excludes laboratory PTs.  
- Includes the following terms: abdominal pain, abdominal pain upper, abdominal pain lower, and abdominal discomfort.  
- Includes the following terms: stomatitis, aphthous stomatitis, mouth ulceration, and mucosal inflammation.  
- Includes the following terms: rash, rash generalized, rash macular, rash maculopapular and rash morbilliform.  
- Includes the following terms: solar dermatitis, sunburn, photosensitivity reaction.  
- Includes the following terms: lymphedema, edema, and peripheral edema.  
- Includes the following terms: vision blurred, visual acuity reduced, visual impairment.  
- Safety population.  
- BRAF inhibitor naive patients.