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Updates and challenges on treatment with BRAF/MEK-inhibitors in melanoma

Zeynep Eroglu¹ and Alpaslan Ozgun¹

¹The Department of Cutaneous Oncology, Moffitt Cancer Center & Research Institute, 10920 McKinley Dr, Tampa, FL, USA

Abstract

Introduction: Breakthroughs in targeted therapy have significantly improved outcomes for many patients with advanced melanoma, including those with BRAFV600 mutant disease. Targeted therapy for BRAFV600-mutant metastatic melanoma includes combinations of BRAF inhibitors and MEK inhibitors, which improve response rates and prolong progression-free survival (PFS) and overall survival (OS) in these patients. However, while durable responses have been observed, many patients develop acquired resistance to these drugs.

Areas covered: Recent clinical trial updates and ongoing studies with targeted therapy for BRAF-V600 mutant melanoma are reviewed.

Expert opinion: Although BRAF targeted therapy remains an effective treatment for BRAF-mutant for melanoma, ongoing trials are exploring combinations with other targeted therapeutics and immunotherapeutics to determine whether tumor responses can be prolonged, and these drugs are increasingly utilized in the neoadjuvant and adjuvant settings.

Keywords

melanoma; BRAF; MEK; combination therapy

1. Introduction

Although melanoma accounts for 4% of all skin cancers, it is responsible for 80% of all skin cancer deaths.. [1] The RAS-RAF-MEK-ERK signaling pathway, also known as the mitogen-activated protein kinases (MAPK) pathway, is a key oncogenic signaling system in melanoma pathogenesis and for targeted therapies for melanoma. Activation of the MAPK pathway leads to melanoma cell proliferation, tumor growth and survival, and an understanding of the role of this pathway has led to the identification of several drug targets,

Corresponding author: Zeynep Eroglu, The Department of Cutaneous Oncology, Moffitt Cancer Center & Research Institute, 10920 McKinley Dr, Tampa, FL, USA, zeynep.eroglu@moffitt.org.

Declaration of interest

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including inhibition of BRAF and MEK. We aim to provide an overview of recent updates of studies in BRAF and MEK inhibitors in patients with melanoma.

2. Updates with BRAF/MEK inhibitors in the unresectable and metastatic setting

BRAF gene mutations increase the activity of the BRAF protein, which increases downstream signaling of the MAPK pathway, leading to tumor growth. Approximately 40–50% of patients with advanced melanomas harbor a valine to glutamine substitution (V600E) in codon 600 of the BRAF protein, and less common BRAF mutations such as lysine (V600K) or arginine substitutions (V600R) are also seen [2]. A variety of therapies targeting this pathway have been developed. Vemurafenib, dabrafenib, and encorafenib are inhibitors of the kinase domain in mutant BRAF, thereby inactivating downstream MAPK pathway signaling to prevent tumor growth in patients with BRAF-mutant melanoma. Vemurafenib was the first BRAF inhibitor FDA approved for patients with advanced melanoma, followed by dabrafenib. Both drugs prolonged progression-free (PFS) and overall survival (OS) as compared to chemotherapy in patients whose tumor contained a BRAF V600 mutation. For example, in the pivotal phase III BRIM-3 trial of 675 patients randomly assigned to either vemurafenib at 960 mg BID or dacarbazine, PFS and OS were significantly prolonged with vemurafenib compared with dacarbazine (6.9 versus 1.6 months, and 13.6 versus 9.7 months, respectively) [3, 4].

Since activated BRAF phosphorylates and activates MEK proteins, which proceed to activate downstream MAP kinases, MEK inhibitors were also tested in BRAF-mutant melanoma. The MEK inhibitor trametinib demonstrated a PFS of 4.8 months and an objective response rate (ORR) of 48% in patients with BRAF V600 mutant melanoma. [5] Other MEK inhibitors include cobimetinib and binimetinib. Due to the development of acquired resistance with single-agent BRAF inhibitors and MEK inhibitors, however, these responses were not durable for a majority of patients with advanced melanoma. This quickly led to the trials and subsequent FDA-approval of two combinations of BRAF and MEK inhibitors, vemurafenib with cobimetinib, and dabrafenib with trametinib.

The randomized phase 3 trial CoBRIM demonstrated that the combination of vemurafenib at 960 mg BID and cobimetinib 60 mg 21 of 28 days improved PFS and OS compared with vemurafenib monotherapy in 495 treatment-naïve patients with BRAF mutant melanoma. [6, 7] (See Table 1.) The results of this trial were updated in 2016; PFS and OS were improved in the combination arm (PFS was 12.3 versus 7.2 months and OS was 22.3 versus 17.4 months) with an improved ORR rate of 70% versus 50%. Serious adverse events were observed in 37% of patients on the combination arm (pyrexia and dehydration most common), compared to 28% in the vemurafenib group; rash, arthralgia, and diarrhea were the most common side-effects overall with the combination.

The phase 3 COMBI-d trial randomized 423 patients with stage IIIC or 4 BRAFV600 E/K mutant melanoma to dabrafenib at 150 mg/trametinib at 2 mg versus dabrafenib monotherapy. [8, 9] The survival data was also updated in 2017, with similar outcomes to above results. Median PFS was 11.1 months for the combination arm vs 8.8 months with

monotherapy, and median OS was 25.1 months for the combination and 18.7 months for dabrafenib alone. As expected, the tumor response rate was higher at 68% with the combination versus 55% for monotherapy. Genomic analysis results were also presented based on whole exome sequencing of pre-treatment tumors; CKDN2A mutations and deletions were associated with poorer OS and PFS, while high tumor mutation rates and normal serum lactate dehydrogenase (LDH) were associated with longer OS [9, 10]. In another phase 3 trial (COMBI-v), comparing the dabrafenib-trametinib combination to vemurafenib monotherapy, the median PFS of the 352 patients who received the combination was comparable to the other phase 3 trials at 12.6 months, and significantly better than the 7.3 months seen with vemurafenib.[11–13] Median OS for the combination arm was 25.6 months, while it was 18 months for the vemurafenib arm, again with higher ORR of 66% with the dual therapy versus 53% in the vemurafenib arm. Grade 3 or 4 adverse events were observed in 52% of the patients in the combination therapy group and in 63% of those in the vemurafenib group.

Recently, five-year outcomes from an earlier phase 2 trial of dabrafenib and trametinib in 162 patients with metastatic BRAF-mutant melanoma were published. [14]. In this study, patient had received the combination (dabrafenib at 150 mg with either 1 or 2 mg of trametinib) versus dabrafenib alone in one of the study cohorts. Patients who received dabrafenib only were able to cross-over to the combination if they had progression of disease. Five-year PFS rate was 13%, while the 5-year OS rate was 28%. The 5-year OS rate was comparable to what has been reported from a phase 1 trial of nivolumab in patients with metastatic melanoma (5-year OS of 31%)[15], also demonstrating a plateau in long term survival for patients treated with BRAF/MEK-inhibitors. [16]. This long-term analysis also found that patients who had an elevated LDH level at start of treatment had a superior 5-year OS rate of 45%; further improvement was seen with in patients with both normal LDH and fewer than three organ sites with metastasis, with 5-year OS rate of 51%. In accordance with this data, a combined analysis of both phase 3 COMBI-v and COMBI-d trials observed that baseline sum of tumor lesion diameters (SLD) also predicted PFS along with LDH and organ sites; patients with normal LDH, SLD <66 mm, and <3 organ sites (33% of all patients) had the best outcomes with 3-year PFS of 42%. [17] These results provide useful predictive indicators for patients about to start treatment with BRAF/MEK-inhibitor therapy for their metastatic melanoma.

Encorafenib plus binimetinib is another BRAF and MEK inhibitor combination therapy, with FDA approval recently granted in the advanced melanoma setting. In a phase 1b/2 trial of patients with metastatic BRAF-mutant melanoma treated encorafenib and binimetinib, median PFS was 11.3 months and ORR was 74.5%. [18] Based upon the results, the combination of encorafenib at 450 mg daily plus binimetinib at 45 mg BID was compared with encorafenib alone at 300 mg daily, and vemurafenib alone in the phase 3 COLUMBUS trial of 577 patients with a BRAFV600 mutant melanoma.[19]. At a median follow-up of 66 months, the primary endpoint of the trial, PFS, was significantly increased compared with either BRAF inhibitor alone (median 14.9 versus 7.3 months, HR 0.54, 95% CI 0.41–0.71). Furthermore, a median overall survival of 33.6 months with the combination vs 16.9 with vemurafenib was observed. [20]. The most common grade 3–4 adverse events seen with encorafenib and binimetinib were increased gamma-glutamyl transferase (GGT, 9%),

increased creatine kinase (7%), and hypertension (16%). In part 2 of the COLUMBUS trial, encorafenib at 300 mg daily with binimetinib was compared to encorafenib alone, with median PFS of 12.9 months with the combination.[21] While the encorafenib and binimetinib combination has not been directly compared with either the other two BRAF/MEK-inhibitor combinations directly, it does appear to have a longer median PFS and a different toxicity profile, with less frequent episodes of pyrexia or photosensitivity.

While clinical trials to date with BRAF and MEK-inhibitors have mostly excluded patients with untreated brain metastases, dabrafenib and trametinib was explored specifically in a phase 2 trial of patients with BRAF-mutant melanoma brain metastases.[22] Eligibility criteria included a target lesion in the brain between 0.5 to 4 cm in diameter, and up to two prior systemic treatments for melanoma were allowed. Of the 76 asymptomatic BRAFV600E-mutant patients in the first cohort without prior local therapy such as radiation, 44 patients (58%; 95% CI 46–69) achieved an intracranial response. However, median PFS was only 5.6 months, with 72% of patients progressing with intracranial or intra and extracranial metastases, and a median OS of 10.8 months. In the other smaller study cohorts looking at patients with prior localized treatment, or symptomatic brain metastases, intracranial ORR was similar; however, intracranial ORR was only 44% in the cohort of 17 patients with BRAFV600D/K/R mutations, with median PFS of 4.2 months. These results bring up several questions with regards to the shorter intracranial duration of response of BRAF and MEK-inhibitors as compared to extracranial responses, such as whether there may be insufficient MAPK pathway inhibition in the brain, or an inferior immune response, or acquired resistance mechanisms that may be unique in the CNS.

While patients who progress on treatment with BRAF/MEK-inhibitors will generally receive anti-PD-1 and/or CTLA-4 immunotherapy, especially if they have not received prior immunotherapy, the question of whether patients could successfully be re-challenged with BRAF/MEK-inhibitors has also been explored. One retrospective analysis investigated 116 patients, 72% of whom had stopped treatment due to disease progression after an initial treatment response.[23] (Remainder had stopped for drug toxicity or achieving a complete response.) While a majority initially received a BRAF-inhibitor alone, 41 (35.3%) received a combination of BRAF/MEK inhibitors. An ORR of 37% was observed in patients re-treated with BRAF/MEK inhibitor therapy after prior progression; PFS was 5 months with OS of 9.8 months. A prospective phase 2 trial had comparable results; an ORR of 32% was found in 25 patients previously treated with BRAF-targeted therapy (64% with dabrafenib plus trametinib), who were re-treated with dabrafenib/trametinib, after having been off of BRAF-targeted therapy for at least 12 weeks. [24] While being able to re-challenge patients who had prior progression of their melanoma on BRAF-targeted therapy is an intriguing proposition, questions remain such as the optimal time off treatment before re-challenging with BRAF/MEK inhibitors, and the impact of intervening treatments.

3. Updates with BRAF/MEK inhibitors in the neoadjuvant / adjuvant setting

Results of adjuvant and neoadjuvant use of BRAF and MEK-inhibitors have also recently become available. In the phase 3 BRIM8 trial, 498 adults with resected stage IIC–IIIA–IIIB (cohort 1) or stage IIIC (cohort 2) were randomized to a year of adjuvant vemurafenib versus placebo.[25] In the cohort 2 stage IIIC patients, median relapse-free survival (RFS) was 23.1 months with vemurafenib vs 15.4 months in placebo (HR 0.8, 95% CI 0.54–1.18). In cohort 1, median RFS was not reached with vemurafenib (versus 36.9 months with placebo), but this was not significant due to prespecified study parameters. Vemurafenib was discontinued for adverse events in 20% of patients; most common grade 3/4 adverse events with vemurafenib included keratoacanthoma, arthralgias, squamous cell carcinomas, and rash. Interestingly the authors noted that the recurrence risk and survival of patients with stage IIC melanoma was quite similar to the results from patients with stage IIIB melanoma, suggesting a role for adjuvant studies in stage IIC patients. With regards to the optimal length of treatment, a single-arm phase 2 study explored 4 months of adjuvant dabrafenib in patients with resected stage 3C melanoma, but the 2-year RFS rate in 21 patients was only 28.6%. [26]

In the adjuvant phase 3 COMBI-AD trial, 870 patients with completely resected BRAFV600E or K mutant melanoma were assigned to a year of dabrafenib plus trametinib or placebo.[27] Patients must have had resection of stage IIIA (limited to lymph-node metastasis of >1 mm), IIIB, or IIIC cutaneous melanoma, and undergone completion lymphadenectomy within 12 weeks of treatment start, with no prior radiation or systemic treatment allowed. At a median follow-up of 2.8 years, RFS, was significantly longer with dabrafenib plus trametinib compared with placebo, with a three-year RFS rate of 58% versus 39%. (HR 0.47, 95% CI 0.39–0.58). There was improvement regardless of patients' stage of disease or ulceration status. Furthermore, OS was also prolonged, with three-year rate of 86% versus 77% with placebo. Most common reason for early discontinuation was adverse events in the combination-therapy group (26% of patients), while disease recurrence was the reason in the placebo group (41%). Serious adverse events occurred in 36% of patients who received adjuvant dabrafenib and trametinib, most commonly pyrexia, fatigue, nausea, similar to the rate seen in use of this combination in patients with metastatic melanoma. After recurrence, 28% of the combination arm patients received systemic therapy, most common therapies were anti-PD-1 therapy (16% of patients), and targeted therapy (14% of patients). The authors did note that the rate of discontinuation of dabrafenib/trametinib due to adverse events was higher than the 14–16% rate observed in patients with metastatic disease, possibly attributing this to the nature of adjuvant therapy. The results of this trial subsequently led to FDA approval of dabrafenib and trametinib in the adjuvant stage 3 setting in melanoma. In light of the also recent approval of adjuvant nivolumab for the same patient population (reduced RFS as compared to ipilimumab, HR 0.65, 95% CI 0.51–0.83) [28], both BRAF/MEK-inhibitor and anti-PD-1 therapy have become feasible adjuvant options for these patients. Trials to explore which adjuvant treatment may be superior, and even exploring combinations of BRAF-targeted with immunotherapies are underway.

BRAF and MEK inhibitors have also been investigated in the neoadjuvant setting. The efficacy of neoadjuvant followed by adjuvant dabrafenib and trametinib versus standard of care treatment was investigated in a small phase 2 trial; patients with resectable stage III or oligometastatic stage IV BRAF-mutant melanoma were assigned to either upfront surgery and consideration for adjuvant therapy (standard of care group), or neoadjuvant (8 weeks) plus adjuvant (44 weeks) dabrafenib and trametinib.[29] Of note, of the seven patients in the standard of care arm, six opted for observation post-surgery, one for adjuvant biochemotherapy (as adjuvant anti-PD-1 or targeted therapy were not available during time of the trial.) After a median follow-up of 18.6 months, significantly more patients receiving neoadjuvant plus adjuvant dabrafenib and trametinib were alive without disease progression than those receiving standard of care (ten of 14 patients vs none of seven in the standard of care group without relapse); median event-free survival was 19.7 months vs 2.9 months). Several questions remain including the optimal duration of neoadjuvant BRAF/MEK inhibitor treatment prior to surgery (as different length of neoadjuvant treatment have been used in other studies)[30], how well pathologic responses correlate with RFS and OS, and how to determine which patients are appropriate for neoadjuvant vs adjuvant only BRAF/MEK-inhibitor treatment.

4. Updates with BRAF/MEK inhibitors in combinations with other treatments

BRAF and MEK inhibitors are also undergoing trials with different dosing regimens [31] or in combinations with other agents. Genetic alterations that upregulate the PI3K–PTEN–AKT are mechanisms of acquired resistance to BRAF-targeted therapies [32]. There is an ongoing triple-combination SWOG trial of the Akt-inhibitor GSK2141795 with dabrafenib and trametinib (NCT01902173). MDM2 is an oncogene that is a negative regulator of the tumor suppressor p53; AMG 232 is an inhibitor of MDM2 and combined with dabrafenib and trametinib in a phase 1/2 trial; preliminary data showed tumor responses in 4 of 6 patients with BRAF-mutant melanoma, although toxicity remains a concern.[33] Heat shock protein 90 (HSP90) inhibitors such as XL888 and AT13387 can also overcome the onset of BRAF inhibitor resistance, as HSP90 is a chaperone protein involved in resistance mechanisms to BRAF-targeted therapies. [34] A phase 1 trial of the combination of vemurafenib with XL888 has shown similar ORR (75%) to vemurafenib and cobimetinib, with a PFS 9.2 months [35]; clinical trials with triple combinations of BRAF and MEK inhibitors combined with XL888 and AT13387 are ongoing. (NCT02721459, NCT02097225). As anti-apoptotic proteins such as BCL-2 have also been shown to delay the onset of resistance to BRAF-inhibitor therapy [22], studies with the oral BCL-2 inhibitor navitoclax plus dabrafenib and trametinib are also enrolling patients (NCT01989585). CDK4 pathway has likewise been targeted in patients with BRAF-mutant metastatic melanoma, with a phase 1/2 trial conducted of encorafenib and binimetinib with the CDK4/6 inhibitor ribociclib.[36] However, the ORR of 52% and median PFS of 9.2 from 42 patients was lower than observed in studies with encorafenib and binimetinib alone, potentially because of 24% of patients who had to stop therapy due to toxicity. This trial does serve as a cautionary tale in triple-combinations with BRAF and MEK-inhibitors; holding or dose-reducing drugs too often due to toxicities may potentially impact response and PFS and affect pharmacokinetics and

pharmacodynamics with triplet combinations. It is unclear how tolerable triple combinations will be at drug levels needed to maintain pathway inhibition. While the studies above have all included patients with BRAF V600 mutated melanoma, less frequent non-V600 BRAF mutations, such as L597 and K601, along with BRAF fusions have been detected as well. Responses with use of MEK inhibitors in patients with these mutations have been described [37, 38]. A trial is ongoing to evaluate efficacy of trametinib for these patients with advanced non-V600 BRAF-mutated melanoma (NCT02296112).

While early attempts at combinations of targeted therapy and immunotherapies were not successful due to toxicity [39], efforts with anti-PD-1 therapies have shown more promise. The rationale behind the combinations has been the favorable effects of BRAF inhibitors in the tumor microenvironment, such as enhanced infiltration by immune effector cells, along with increased antigen and HLA molecule expression by tumor cells. [40, 41] Preliminary results from a phase 1 trial of the combination of dabrafenib, trametinib and the anti-PD-L1 antibody durvalumab revealed an acceptable toxicity profile with a response rate of 67%; further follow-up will determine whether the tumor responses are more durable than those observed in BRAF/MEK combination therapy alone.[42] In a phase 1 study of 15 patients with BRAF-mutant melanoma treated with pembrolizumab in combination with dabrafenib and trametinib as first-line therapy, ORR of 69% in 13 patients was observed; in an updated analysis, 7 patients had ongoing responses 20 months or longer.[43] In the phase 2 portion of this trial, patients are randomized to the combination of dabrafenib and trametinib with pembrolizumab or dabrafenib and trametinib with placebo (NCT02130466). Vemurafenib and cobimetinib were also combined with the anti-PDL1 antibody atezolizumab in a phase 1 study of 34 patients, with ORR 86% and grade 3/4 AE rate of 44%; a randomized phase 3 trial of this combination compared to vemurafenib and cobimetinib is ongoing (NCT02908672)..[44] A phase 3 trial of dabrafenib and trametinib alone or in combination with the anti-PD-1 antibody PDR001 has also recently completed accrual (NCT02967692). Trials exploring pembrolizumab with intermittent and short-term dosing of dabrafenib and trametinib (NCT02625337), and trials with encorafenib and binimetib with pemrolizumab are also underway (NCT02902042). Nevertheless, it is not yet known whether the rate of durable responses is significantly increased by adding anti-PD-1/L1 antibodies to BRAF and MEK inhibitors, in order to justify the presumably increased toxicity and cost of the triple-combination therapies versus sequential administration of the drugs.

5. Expert opinion

The combination of BRAF and MEK inhibitors have shown significant improvement in response rates, progression-free and overall survival as compared to single-agent targeted therapy, and further follow-up of these trials have demonstrated durability of responses in a subset of patients, with comparable survival rates so far to anti-PD-1 therapies. However, development of acquired resistance and subsequent progression on therapy is still the norm for a majority of patients, with median PFS approximately a year; for patients with brain metastases, PFS appears to be about half of that length. Ongoing trials are exploring a variety of avenues including triple-combinations with other targeted therapy agents, altered dosing schedules, and combinations with immunotherapeutics in an attempt to prolong durability of tumor response and ultimately survival of patients with BRAFV600 mutant

melanoma. Additionally for patients with brain metastases, how radiation fits in with systemic treatments is also under exploration. The use of BRAF and MEK inhibitors has also moved past unresectable/metastatic melanoma, showing significant activity in both the stage 3 adjuvant and neoadjuvant setting as well and moving in to the treatment paradigms for earlier stage disease. To keep in mind, comparing treatments from different trials should be done carefully due to differences in baseline characteristics between trial patients and the period of time during which studies were conducted, which can influence the drugs that were available for subsequent treatments.

There is no available trial data yet on how to appropriately sequence BRAF-targeted therapies in patients, and whether outcomes are better if patients start on immunotherapy or targeted therapy. There is an ongoing randomized phase 3 trial of dabrafenib and trametinib followed by the ipilimumab and nivolumab after progression, and vice versa; this trial has an estimated completion date of 2019. (NCT02224781) Another phase 3 trial examining the sequencing of encorafenib and binimetinib with ipilimumab and nivolumab is also enrolling patients, and includes a third arm with combination targeted therapy for 8 weeks followed by combination immunotherapy until disease progression, then combination targeted therapy again until disease progression. (NCT02631447) These questions are now relevant in earlier stage melanoma as well, in regards to how to sequence BRAF/MEK-inhibitor therapies and immunotherapy drugs, and the role of combination treatments. Questions also remain with regards to appropriate use of neoadjuvant BRAF and MEK inhibitor therapy, and whether there is utility of adjuvant treatments in stage 2 melanoma. Ultimately, robust predictive biomarkers will be essential in selecting patients for therapy that will best suit their tumors. Trials exploring molecularly targeted therapies for other mutational subtypes of melanomas will continue as well.

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Article highlights

- BRAF inhibitors (vemurafenib, dabrafenib, encorafenib) and MEK inhibitors (cobimetinib, trametinib, binimetinib) are targeted therapy agent for treatment of BRAFV600-mutated advanced melanoma. The combination of BRAF and MEK inhibitors have shown significant improvement in response rates, progression-free survival and overall survival as compared to single-agent targeted therapy, and this combination therapy is the standard of care targeted therapy in patients with BRAFV600-mutated advanced melanoma.
- BRAF and MEK inhibitors are also now FDA-approved in earlier stage melanoma in the adjuvant setting and have shown promising results in the neoadjuvant setting as well.
- Trials utilizing BRAF and MEK inhibitors with different dosing regimens, in combinations with the other targeted therapy agents and immunotherapy agents are ongoing.

Table 1.
Results of phase 3 trials with combination of BRAF and MEK-inhibitors in advanced melanoma.

Treatment regimen	COMBI-d	COMBI-v	coBRIM	COLUMBUS part1	COLUMBUS part 2
	Phase 3 (n = 423) dabrafenib + trametinib vs dabrafenib	Phase 3 (n = 352) dabrafenib + trametinib vs. vemurafenib	Phase 3 (n = 495) vemurafenib + cobimetinib vs. vemurafenib	Phase 3 (n = 577) encorafenib (450qday) + binimetinib vs encorafenib vs. vemurafenib	Phase 3 (n = 344) encorafenib (300qday) + binimetinib vs encorafenib
Median PFS	11.1 months with combo vs. 8.8 months with dabrafenib	12.6 months with combo vs. 7.3 months with vemurafenib	12.3 months with combo vs. 7.2 months with vemurafenib	14.9 months with combo vs. 9.6 months with encorafenib vs. 7.3 months with vemurafenib	12.9 months with combo vs. 9.2 months with encorafenib (part 1 + 2)
Median OS	25.1 months with combo vs. 18.7 months with dabrafenib	25.6 months with combo vs. 18 months with vemurafenib	22.3 months with combo vs. 17.4 months with vemurafenib	33.6 months with combo vs. 16.9 with vemurafenib	NA
Tumor response rate	68% with combo vs. 53% with dabrafenib	66% with combo vs. 53% with vemurafenib	70% with combo vs. 50% with vemurafenib	63% with combo vs. 51% with encorafenib vs. 40% with vemurafenib	66% with combo vs 50% with encorafenib (part 1 + 2)