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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

BRAF Targeted Therapy for Patients with Melanoma and Active Brain Metastases: A Review of Clinical Effectiveness

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Context and Policy Issues

Skin cancer is the most common cancer in Canada, with about 6,500 new cases of skin malignant melanoma reported in 2014, and 1250 Canadians expected to die from it in 2017.[1,2] Approximately 40-60% of melanomas contain a mutation in the gene that encodes BRAF, which leads to constitutive activation of downstream signaling in the MAP (mitogen-activated protein) kinase pathway. In 80-90% of these cases, the activating mutation consists of the substitution of glutamic acid for valine at amino acid 600 (V600E); the other less common BRAF mutations include V600D, K and R.[3,4] Approximately 20% of patients with BRAF-mutated advanced melanoma have brain metastases which are difficult to treat, and carry a poor prognosis.[5,6]Targeted therapies with BRAF inhibitors (dabrafenib, vemurafenib), MEK inhibitors (trametinib, cobimetinib), or immunotherapy alone or in combination have been used with clinical benefits for patients with metastatic melanoma.[6-13] Oncologic patients' performance status are often measured using the Eastern Cooperative Oncology Group (ECOG) Scale that describes a patient's level of functioning in terms of their ability to care for themselves, daily activity, and physical ability on a scale of 0 (fully active, able to carry on all pre-disease activities without restriction) to 5 (deceased).[14]

The pan-Canadian Oncologic Drug Review (pCODR) expert review committee (pERC) has recommended combination therapies of dabrafenib plus trametinib or cobimetinib plus vemurafenib, and monotherapies of dabrafenib, vemurafenib, or trametinib for previously untreated patients with BRAF mutation positive unresectable or metastatic melanoma[15-19] based on evidence that excluded patients with active or symptomatic brain metastases.[20-22] Brain metastases are considered active when tumour growth has been shown on sequential CT scans; active brain metastases can be symptomatic or asymptomatic. The effectiveness of these treatments in patients with active brain metastases remains unclear.

This Rapid Response report aims to review the clinical effectiveness and safety of dabrafenib plus trametinib and cobimetinib plus vemurafenib for patients with BRAF mutation positive metastatic melanoma with active brain metastasis.

Research Questions

1. What is the clinical effectiveness of dabrafenib and trametinib for patients with BRAF mutation positive metastatic melanoma with active or symptomatic brain metastasis?
2. What is the clinical effectiveness of cobimetinib and vemurafenib for patients with BRAF mutation positive metastatic melanoma with active or symptomatic brain metastasis?

Key Findings

Data from a non-randomized, no control, open-label phase 2 study suggested that the clinical benefit and tolerability of dabrafenib plus trametinib, as measured by intracranial response and adverse event rate, were found in patients with melanoma and active brain metastasis with BRAF V600E mutation after a median 8.5 months follow-up.

Methods

Literature Search Methods

A limited literature search was conducted on key resources including Ovid Medline, Ovid Embase, PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. No methodological filters were applied to limit retrieval by publication type. The search was limited to English language documents published between January 01, 2012 and September 20, 2017.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Adult patients with BRAF V600 mutation-positive unresectable stage III or stage IV melanoma who have active brain metastases
Intervention	Q1: Dabrafenib (Tafinlar) and trametinib (Mekinist) in combination Q2: Cobimetinib (Cotellic) and vemurafenib (Zelboraf) in combination
Comparator	No treatment or placebo BRAF monotherapy (single agent vemurafenib, single agent dabrafenib, single agent trametinib); Immunotherapy (e.g, pembrolizumab, ipilimumab, nivolumab)
Outcomes	Clinical effectiveness, safety
Study Designs	Heath technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), non-RCTs

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications were already reported in the included SRs, or were published prior to 2012. Articles will also be excluded if the population was not clearly defined as having active brain metastasis.

Critical Appraisal of Individual Studies

The included clinical studies were assessed using the Downs and Black checklist.[23]

Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described narratively.

Summary of Evidence

Quantity of Research Available

A total of 351 citations were identified in the literature search. Following screening of titles and abstracts, 342citations were excluded and nine potentially relevant reports from the electronic search were retrieved for full-text review. Two potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, ten publications were excluded for various reasons, while one publication met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

The literature search identified one open-label, phase 2 study in 125 patients with BRAF V600- mutant melanoma with active brain metastasis.[24] There were four cohorts: A) BRAF V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy and ECOG- performance status of 0 or 1; B) BRAF V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy and ECOG- performance status of 0 or 1; C) BRAF V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy and ECOG- performance status of 0 or 1; and D) BRAF V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy and ECOG- performance status of 0, 1 or 2. After a median 8.5 months follow-up, the outcomes measured were intracranial response and duration of response, extracranial response and duration of response, overall response and duration of response, progression-free survival, overall survival, and adverse events. The primary endpoint was intracranial response (percentage of patients with a confirmed intracranial complete or partial response assessed by the investigator using modified RECIST [Response Evaluation Criteria in Solid Tumours] version 1.1 criteria) in cohort A. Findings from the other three cohorts with small sample sizes were considered exploratory and hypothesis generating. The study was conducted in North America, Europe and Australia.

Characteristics of the included study are detailed in Appendix 2.

Summary of Critical Appraisal

The included study clearly described hypotheses, method of selection from the source population and representation of the study population, main outcomes, interventions, patient characteristics, loss to follow-up, and main findings. Estimates of random variability and actual probability values were provided. The study had an a priori determined primary endpoint. The study was a non-randomized open-label, phase 2 study which increases the potential risk of bias due to lack of randomization or blinding. Based on a power calculation, the study had sufficient power to detect a clinically important effect in the primary endpoint in cohort A, but did not have sufficient power to detect a clinically important effect in the three remaining cohorts where sample sizes were small.

Details of the critical appraisal of the included study are presented in Appendix 3.

Summary of Findings

The main findings of the included study are presented in Appendix 4 and summarized in Table 2.

What is the clinical effectiveness of dabrafenib and trametinib for patients with BRAF mutation positive metastatic melanoma with active or symptomatic brain metastasis?

Data from a multi-centre, multi-cohort, open-label, phase 2 trial on 125 patients with BRAF V600- mutation-positive melanoma with active brain metastasis[24] showed that after a median follow-up of 8.5 months, an intracranial response was found in 58% of patients (44/76 patients) in cohort A (BRAF V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, and an ECOG performance status of 0 or 1) achieved an intracranial response (primary endpoint). Intracranial response was also achieved in 56% of patients (9/16 patients) in cohort B (BRAF V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOG performance status of 0 or 1), 44% of patients (7/16 patients) in cohort C (BRAF V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0 or 1), and 59% of patients (10/17 patients) in cohort D (BRAF V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2). The median duration of response was 6.5 months, 7.3 months, 8.3 months and 4.5 months, in cohorts A, B, C, and D, respectively.

Extracranial response (percentage of patients with a confirmed extracranial complete or partial response assessed by the investigator using modified RECIST version 1.1 criteria) was found in 55% of patients in cohort A with median duration of response of 10.2 months, 44% of patients in cohort B with median duration of response not estimable, 75% of patients in cohort C with median duration of response of 4.9 months, and 41% of patients in cohort D with median duration of response of 5.9 months.

Overall response was found in 58% of patients in cohort A with median duration of response of 6.5 months, 56% of patients in cohort B with median duration of response of 12.5 months, 44% of patients in cohort C with median duration of response of 6.6 months, and 65% of patients in cohort D with median duration of response of 4.5 months.

Progression-free survival (the median interval between the first dose of study treatment and the earliest date of disease progression or death from any cause) was 5.6 months, 7.2 months, 4.2 months and 5.5 months, in cohorts A, B, C, and D, respectively. Overall survival (the median time from first dose until death due to any cause) was 10.8 months, 24.3 months, 10.1 months and 11.5 months, in cohorts A, B, C, and D, respectively.

Table 2: Summary of Study Findings

	Intracranial response (%, median duration)	Extracranial response (%, median duration)	Overall response (%, median duration)	Progression-free survival (median duration)	Overall survival (median duration)
Cohort A	58%, 6.5 months	55%, 10.2 months	58%, 6.5 months	5.6 months	10.8 months
Cohort B	56%, 7.3 months	44%, (not estimable)	56%, 12.5 months	7.2 months	24.3 months
Cohort C	44%, 8.3 months	75%, 4.9 months	44%, 6.6 months	4.2 months	10.1 months
Cohort D	59%, 4.5 months	41%, 5.9 months	65%, 4.5 months	5.5 months	11.5 months

The most common serious adverse events related to study treatment were pyrexia for dabrafenib (8/125 patients [6%]) and decreased ejection fraction (5/125 patients [4%]) for trametinib. The most common grade 3 or worse adverse events, regardless of study drug relationship, were pyrexia (3/125 patients [3%]) and headache (3/125 patients [2%]).

The authors recognized the non-randomized design with small sample size and no control group was a limitation of the study but suggested that the clinical benefit and tolerability of dabrafenib plus trametinib was achieved in patients with melanoma and active brain metastases.

What is the clinical effectiveness of cobimetinib and vemurafenib for patients with BRAF mutation positive metastatic melanoma with active or symptomatic brain metastasis?

There was no evidence found on the clinical effectiveness of cobimetinib and vemurafenib for patients with BRAF mutation positive metastatic melanoma with active or symptomatic brain metastasis.

Limitations

Evidence is from a non-randomized phase 2 study lacking a control group. Findings from three out of four cohorts with small sample sizes are considered exploratory and hypothesis generating.

Conclusions and Implications for Decision or Policy Making

Data from a phase 2 study suggested that the clinical benefit and manageable tolerability of dabrafenib plus trametinib were found in patients with melanoma and active brain metastasis with BRAF V600E mutation, as measured by intracranial response and adverse event rate after a median 8.5 months follow-up. There was no evidence found on the clinical effectiveness of cobimetinib and vemurafenib for patients with BRAF mutation positive metastatic melanoma with active brain metastasis.

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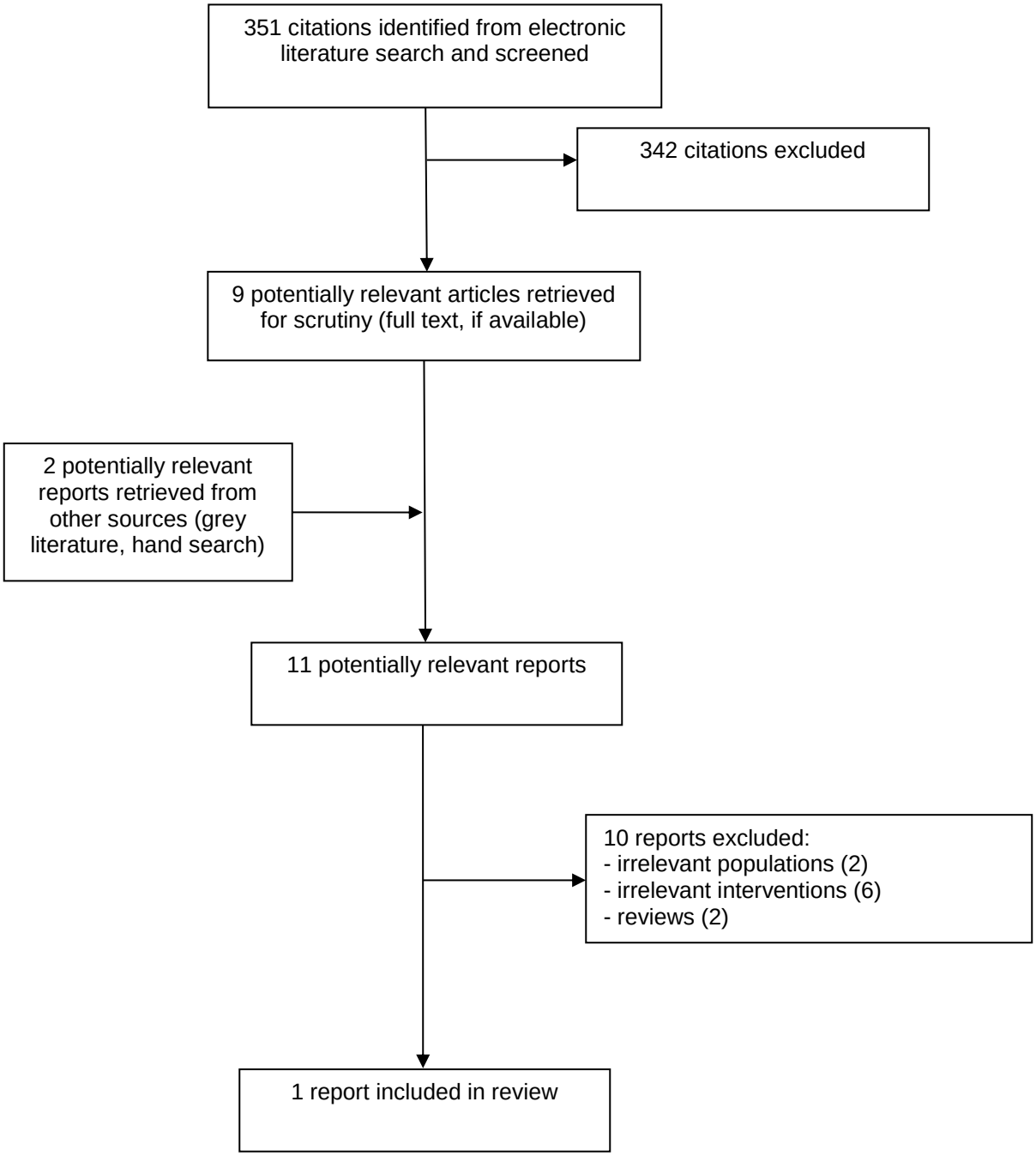
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 3: Characteristics of Included Clinical Studies

First Author, Year, Country	Study Design Study Objectives	Interventions/ Comparators	Patients	Main Outcomes
Davies,[24] 2017, Europe, North America, Australia	Open-label, phase 2 study *"the activity of dabrafenib plus trametinib has not been studied in active melanoma brain metastases. Here, we report results from the phase 2 COMBI-MB trial. Our aim was to build on the current body of evidence of targeted therapy in melanoma brain metastases through an evaluation of dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases."* (p 863)	dabrafenib plus trametinib	Patients with BRAFV600-mutant melanoma with active brain metastasis in 4 cohorts (total 125 patients): (A - 76 patients) *BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy, and an Eastern Cooperative Oncology Group (ECOG) performance status* of 0 or 1 (B – 16 patients) *BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy, and an ECOG performance status of 0 or 1 (C – 16 patients) *BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0 or 1 (D – 17 patients)*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy, and an ECOG performance status of 0, 1, or 2.	After median 8.5 months follow-up Intracranial response Intracranial duration of response Extracranial response Extracranial duration of response Overall response Overall duration of response Progression-free survival Overall survival Adverse events (primary endpoint was intracranial response in cohort A)

*ECOG performance status = grade 0: fully active, able to carry on all pre-disease performance without restriction; grade 1: restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work; grade 2: ambulatory and capable of all self-care but unable to carry out any work activities, up and about more than 50% of waking hours

Appendix 3: Critical Appraisal of Included Publications

Table 4: Summary of Critical Appraisal of Included Studies

First Author, Publication Year	Strengths	Limitations
Critical appraisal of included clinical trials (Downs and Black[23])		
Davies[24]	• hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• non-randomized, open-label, one-arm study • study had insufficient power to detect a clinically important effect in 3 out of 4 cohorts

Appendix 4: Main Study Findings and Author's Conclusions

Table 5: Main Study Findings and Authors' Conclusions

Main Study Findings	Authors' Conclusions
Davies[24]	
Intracranial response (percentage of patients with a confirmed intracranial complete or partial response assessed by the investigator using modified RECIST – Response Evaluation Criteria in Solid Tumours version 1.1) (% of patients; 95% confidence interval – CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 44/76 patients (58%; 46–69; 3 patients with complete response and 41 with partial response) (primary endpoint) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 9/16patients (56%; 30–80) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 7/16patients (44%; 20–70) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 10/17patients (59%; 33–82) **Duration of intracranial response** (median months; 95% CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 6.5 (4.9–10.3) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 7.3 (95% CI 3.6–12.6) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 8.3 (1.3–15.0) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 4.5 (2.8–5.9) **Extracranial response** (percentage of patients with a confirmed extracranial complete or partial response assessed by the investigator using modified RECIST – Response Evaluation Criteria in Solid Tumours version 1.1) (% of patients; 95% confidence interval – CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 42/76 patients (55%; 43–67)	*"Dabrafenib plus trametinib was active with a manageable safety profile in this melanoma population that was consistent with previous dabrafenib plus trametinib studies in patients with BRAFV600-mutant melanoma without brain metastases, but the median duration of response was relatively short. These results provide evidence of clinical benefit with dabrafenib plus trametinib and support the need for additional research to further improve outcomes in patients with melanoma brain metastases"* (p 863)

Main Study Findings	Authors' Conclusions
Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 7/16patients (44%; 20–70) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 12/16patients (75%; 48–93) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 7/17patients (41%; 18–67) **Duration of extracranial response** (median months; 95% CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 10.2 (5.8–NE) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) NE (NE–NE) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 4.9 (3.0–NE) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 5.9 (1.8–NE**)** **Overall response** (percentage of patients with a confirmed complete or partial intracranial or extracranial response assessed by the investigator using modified RECIST – Response Evaluation Criteria in Solid Tumours version 1.1) (% of patients; 95% confidence interval – CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 44/76 patients (58%; 46–69) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 9/16patients (56%; 30–80) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 7/16patients (44%; 20–70) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 11/17patients (65%; 38–86) **Duration of overall response** (median months; 95% CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain	

Main Study Findings	Authors' Conclusions
metastases, with no previous local brain therapy 6.5 (4.9–10.3) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 12.5 (5.3–NE) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 6.6 (1.3–16.3) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 4.5 (2.8–11.2) **Progression-free survival** (interim)(the interval between the first dose of study treatment and the earliest date of disease progression or death from any cause) (median months; 95% CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 5.6 (5.3–7.4) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 7.2 (4.7–14.6) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 4.2 (1.7–6.5) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 5.5(2.8–7.3) **Overall survival** (interim)(the time from first dose until death due to any cause) (median months; 95% CI) Cohort A (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with no previous local brain therapy 10.8 (8.7–19.6) Cohort B (*BRAF*V600E-positive, asymptomatic melanoma brain metastases, with previous local brain therapy) 24.3 (7.9–NE) Cohort C (*BRAF*V600D/K/R-positive, asymptomatic melanoma brain metastases, with or without previous local brain therapy 10.1 (4.6–17.6) Cohort D (*BRAF*V600D/E/K/R-positive, symptomatic melanoma brain metastases, with or without previous local brain therapy 11.5 (6.8–22.4) **Adverse events** Any grade regardless of study drug relationship: 123/125 patients	

Main Study Findings	Authors' Conclusions
(98%) Any grade related to study drug relationship: 108/125 patients (86%) Serious adverse events: 44/125 patients (35%) The most common serious adverse events related to study treatment: pyrexia (8/125 patients [6%]) for dabrafenib and decreased ejection fraction (5/125 patients [4%]) for trametinib. The most common grade 3 or worse adverse events, regardless of study drug relationship, were pyrexia (4/125 patients [3%]) and headache (3/125 patients [2%]).	

CI = confidence interval; NE = non-estimable