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CADTH RAPID RESPONSE REPORT:
SUMMARY WITH CRITICAL APPRAISAL

BRAF Targeted Therapy after Immunotherapy for Patients with Metastatic Melanoma: A Review of Clinical Effectiveness

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Authors: Kelsey Seal, Lorna Adcock

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About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Context and Policy Issues

Melanoma is a cancer of the skin that begins in melanocytes, the cells that produce the pigment melanin that colors the skin, hair, and eyes.[1] Because melanoma can often be seen on the skin, it can be easier to detect in earlier stages. If it is not detected, the cancer can spread to other sites and organs. When melanoma tumors have spread to regional lymph nodes, it is known as stage III.[2] The five-year survival rate for stage III cancer ranges from 40-53% depending on the size of the primary tumor and how far the cancer has spread into the lymph nodes and other organs.[3] For Canadians, once cancer has spread to nearby lymph nodes, the five-year relative survival rate is 62% (the relative survival statistic is derived from other countries that are likely to have similar outcomes as Canada; relative survival examines how likely people with cancer are to survive after their diagnosis compared to the general population who are cancer-free, but share similar characteristics).[4] Once melanoma has spread to distant lymph nodes or other areas of the body, it is known as metastatic, stage IV, cancer and is often very difficult to treat.[1] The five-year survival rate for stage IV melanoma ranges from 15-20%.[5] Once cancer has spread to other parts of the body (distant or metastatic), the five-year relative survival for Canadians is 18%.[4] The Canadian Cancer Society estimates that in 2017, 7,200 Canadians will be diagnosed with melanoma skin cancer and 1,250 Canadians will die from this type of cancer.[4]

There are different treatment options for metastatic melanoma skin cancer, depending on how advanced the cancer is. Surgery may be used in areas where cancer is found on the skin or just under it, in lymph nodes, in the lung, liver, brain, or small intestine.[4] For some patients with stage III melanoma and stage IV metastatic melanoma, metastases in internal organs may be removed with surgery. In certain cases with stage III and stage IV melanoma, metastases cannot be removed with surgery, mostly because cancer may have already spread to distant lymph nodes, and the melanoma may be called unresectable. Chemotherapy maye be used to destroy cancer cells either throughout the body (systemic chemotherapy) or a more concentrated area (regional chemotherapy). Radiation therapy may be used after surgery to lower the risk of the cancer returning or as palliative therapy to control symptoms such as pain in patients with advanced melanoma.[4]

More recently, treatment outcomes have greatly improved with the emergence of several novel agents, including targeted therapy and immunotherapy.[6] Immunotherapy may be used to shrink and control the growth of the melanoma skin cancer; these drugs include ipilimumab (Yervoy), nivolumab (Opdivo), and pembrolizumab (Keytruda). Targeted therapy may be offered in patients who have certain mutations, including mutations in the BRAF gene. This treatment is also used to shrink and control the growth of the melanoma skin cancer; these drugs include vemurafenib (Zelborad), cobimetinib (Cotellic), dabrafenib (Tafinlar), and trametinib (Mekinist).

Based on work by the CADTH pan-Canadian Oncology Drug Review (pCODR), the pCODR Expert Review Committee (pERC) provided recommendations on the use of immunotherapies for the treatment of metastatic melanoma. pERC recommends funding ipilimumab (Yervoy) as a first-line therapy for patients with primary cutaneous unresectable stage IIIV or IV melanoma, regardless of BRAF mutation status, who have Eastern Cooperative Oncology Group (ECOG) performance status s1 and are currently not

receiving immunosuppressive therapy.[7] Nivolumab (Opdivo) is recommended for patients with unresectable or metastatic BRAF wild-type melanoma who were not previously treated, with good performance status and who have stable brain metastases.[8] Pembrolizumab (Keytruda) is recommended for the treatment of patients with unresectable or metastatic melanoma who have not received or failed treatment with ipilimumab, or for patients who have failed BRAF mutation-targeted therapies.[9] All recommendations were conditional on the cost-effectiveness of these drugs being improved to an acceptable level.

pERC has also made recommendations on the use of BRAF mutation-targeted therapies for metastatic melanoma. Vemurafenib (Zelboraf) is recommended for first-line treatment of patients with BRAF V600 mutation-positive unresectable stage IIIC or IV melanoma or for patients who have developed metastatic disease,[10] and dabrafenib (Tafinlar) monotherapy for patients with BRAF V600 mutation-positive unresectable or metastatic melanoma and ECOG performance status of 0 or 1.[11] Dabrafenib (Tafinlar) is also recommended in combination with trametinib (Mekinist) for patients with BRAF V600 mutation-positive, unresectable or metastic melanoma in the first-line setting and who have an ECOG performance status of 0 or 1,[12] and vemurafenib (Zelborad) in combination with cobimetinib (Cotellic) is recommended for patients with previously untreated BRAF V600 mutation-positive unresectable stage III or stage IV melanoma who have good performance status.[13] All recommendations were conditional on the cost-effectiveness of these drug monotherapies and combinations being improved to an acceptable level.

While the current pERC recommendations mainly focus on the use of immunotherapies and BRAF inhibitors (BRAFi) as first-line therapies, the optimal sequencing of BRAF targeted therapy and immunotherapy when both are considered for the treatment of advanced melanoma has yet to be determined. The purpose of this report is to evaluate the clinical effectiveness of BRAF targeted therapy in patients with BRAF mutation positive unresectable or metastatic melanoma who have received immunotherapy as their first-line option.

Research Question

What is the clinical effectiveness of BRAF targeted therapy in patients with BRAF mutation positive unresectable or metastatic melanoma who have received immunotherapy as their first-line option?

Key Findings

Three non-randomized studies were identified regarding the clinical effectiveness of BRAF inhibitor targeted therapy in patients with BRAF mutation positive unresectable or metastatic melanoma who have received immunotherapy as their first-line option. Two of the studies were more favourable to treating with immunotherapy prior to BRAF inhibitor in patients with BRAF mutation positive melanoma. One study reported that the optimal sequencing paradigm has yet to be established. All three studies identified in this report were low-quality; therefore, findings need to be interpreted with caution. Future prospective, randomized studies need to be conducted in order to determine the optimal sequencing of treatment for these patients.

Methods

A limited literature search was conducted on key resources including Ovid Medline, 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. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials and, non-randomized studies. The search was limited to English language documents published between January 1, 2012 and September 19, 2017.

Literature Search Methods

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	Patients with BRAF V600 mutation positive, unresectable or metastatic melanoma (stage III or stage IV)
Intervention	First-line immunotherapy (e.g., nivolumab, pembrolizumab, ipilimumab) followed by BRAFi therapy with: • dabrafenib (Tafinlar) monotherapy • dabrafenib (Tafinlar) and trametinib (Mekinist) in combination • vemurafenib (Zelboraf) monotherapy • vemurafenib (Zelboraf) and cobimetinib (Cotellic) in combination
Comparator	First-line BRAFi therapy with: • dabrafenib (Tafinlar) monotherapy • dabrafenib (Tafinlar) and trametinib (Mekinist) in combination • vemurafenib (Zelboraf) monotherapy • vemurafenib (Zelboraf) and cobimetinib (Cotellic) in combination followed by immunotherapy (e.g., with nivolumab, pembrolizumab, ipilimumab)
Outcomes	Clinical benefits and harms (e.g., response rates, adverse events)
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

BRAFi = BRAF inhibitor.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012.

Critical Appraisal of Individual Studies

The included non-randomized studies were critically appraised using the Downs and Black checklist.[14] 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 619 citations were identified in the literature search. Following screening of titles and abstracts, 607 citations were excluded and 12 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, nine publications were excluded for various reasons, while three publications met the inclusion criteria and were included in this report. Appendix 1 describes the PRISMA flowchart of the study selection.

Summary of Study Characteristics

Study Design

All of the included studies[15-17] were non-randomized, retrospective cohort studies.

Country of Origin

Two of the studies were published in Italy[15,16] and one of the studies was published in the United States of America.[17]

Patient Population

Patients from all three studies[15-17] were all BRAF-mutation positive patients with metastatic melanoma. One study[17] included patients who had required documentation of BRAF V600 mutation, measurable disease, and treatment with dabrafenib, vemurafenib, or the combination of debrafenib and trametinib; patients who had received prior treatment with other BRAF inhibitors (BRAFi) were excluded. In the same study,[17] 2% of patients had stage III melanoma and 98% of patients had stage IV melanoma. Two studies[15,16] included patients who tested positive for the V600 mutation and had sequentially received a BRAFi (vemurafenib or dabrafenib) and ipilimumab, or vice versa. One study[16] did not report on initial melanoma stage, but reported the median age of the patients in the BRAFi group (54 years) and ipilimumab initial group (52 years). One study[15] reported that 89% of patients in the BRAFi group had M1c with a median age of 50 years, whereas 100% of patients in the ipilimumab initial group were stage M1c with a median age of 48 years (Stage M1c defined as metastatic disease to all other visceral organs and normal lactate dehydrogenase [LDH] levels or any distant disease with elevated levels of LDH).

Interventions and Comparators

Two studies[15,16] compared immunotherapy (ipilimumab) followed by a BRAFi (vemurafenib or dabrafenib) with a BRAFi (vemurafenib or dabrafenib), followed by immunotherapy (ipilimumab). The other study[17] compared immunotherapy followed by BRAFi (vemurafenib, dabrafenib, or dabarafenib/trametinib) with BRAFi (vemurafenib, dabrafenib, or dabarafenib/trametinib), followed by immunotherapy. In this study, immunotherapy could have included commercial high-dose IL-2, ipilimumab, clinical trials of PD-1 antibodies (nivolumab, pembrolizumab, and CT-011), anti-PDL1 antibody (MPDL-3280A), or adoptive T-cell therapy, as per clinical trial or commercial use.

Two studies[15,16] described the dosing for ipilimumab at 3 mg/kg intravenously over 90 minutes, every three weeks for four doses. For BRAFi, patients could have received vemurafenib 960 mg twice daily or dabarafenib 150 mg twice daily.

Outcomes

One study[17] measured objective response rate as defined by Response Evaluation Criteria in Solid Tumors (RECIST) 1.0. Progression-free survival and overall survival were also measured from the start of BRAFi until progression as defined by RECIST, death, or last documented contact.

Another study[16] measured overall survival from first treatment and progression-free survival was also measured. Tumor response was measured using tumor assessments were performed at baseline, prior to starting ipilimumab, and after completion of ipilimumab therapy, according to immune-related response criteria.

Another study[15] measured overall survival, and specified that analysis was performed using Kaplan-Meier. Progression-free survival was also measured. Tumor response was measured using tumor assessments performed according to immune-related response criteria.

Summary of Critical Appraisal

One study[17] clearly described the intervention and comparator and the overall aims of the study. The main outcomes were described a priori and were described in detail in the results section. The study did have some major limitations. Some of the patient characteristics were not described including age, comorbidities, and sex. There was no evidence of stratification being performed, which would have decreased the possibility of confounding. Moreover, the two cohorts differed significantly in some of the baseline characteristics. For example, in the cohort that received immunotherapy first, 97% of patients had normal levels of LDH, whereas 62% of patients in the BRAFi cohort had normal levels, meaning 38% of patients had elevated levels. This is potentially important as elevated LDH levels have emerged as a negative prognostic indicator.[15] Having vastly different baseline characteristics could skew the outcome data, as patients may have been in different health states prior to treatment. The number of patients in each cohort also varied substantially; the cohort who was initially treated with immunotherapy had 32 patients, whereas the cohort was treated with BRAFi initially had 242 patients (no power calculation was performed). The study also may have not been a proper representation of all patients with BRAF-mutant metastatic melanoma, due to potential variation in institutions across different countries. Access to different drugs (both BRAFi and ipilimumab) also varied over the different institutions throughout the years, which may have influenced what treatment was selected and what sequence of treatment was implemented. There was strong potential for confounders that would have been difficult to control for as this was not a randomized study. It was also unclear if outcomes assessors were blinded to treatment.

Another study[16] clearly described patient characteristics, intervention and comparator, and outcomes. However, main outcomes were not clearly described a priori. There may have also been potential confounders in baseline characteristics. For example, more patients who received BRAFi initially had elevated lactate dehydrogenase or brain metastases at baseline than patients who were treated with immunotherapy first. These baseline factors are associated with poor prognosis and may have contributed to worse survival outcomes in these patients. Patients in the study were unlikely to be representative for the entire population of patients with BRAF-mutant metastatic melanoma as the sample was limited to 90 patients from an Italian cohort, leading to potential issues with external validity. Choice of initial therapy was not based on uniform criteria. Some of the patients who received BRAFi first discontinued treatment and it is unknown why these patients discontinued

treatment; patients who discontinued treatment due to toxicity may have had a better prognosis than people who discontinued treatment due to disease progression. Discontinuation rates for all study groups were not reported; therefore it is unclear whether there was a difference in this outcome based on choice of initial treatment. Moreover, data were not available for patients who did not cross over to another treatment (patients who discontinued first-line therapy for unknown reasons), which means patients may have not completed a treatment regimen. It was also unclear if outcome assessors were blinded.

Another study[15] clearly described the intervention and comparator, overall aims of the study, and patient characteristics. Main outcomes were also described a priori. However, there were several limitations within this study. Cohorts varied substantially in the number of patients. For example, the cohort that was treated with immunotherapy first had eight patients, whereas the cohort that was treated with BRAFi first had 28 patients; there is no indication that a power calculation was performed. There were also differences in baseline characteristics between patient groups. For example, ECOG performance status was measured as 0 in 100% of the patients in one of the cohorts, whereas 54% of the other cohort was measured as 0; patients in ECOG performance status grade 0 are considered fully active and able to carry on all pre-disease performance without restriction, meaning patients would have started in a better health state than a patient in a higher grade. The study did not discuss these and other potential confounders. Moreover, patients in the study were unlikely to be representative for the entire population of patients with BRAF-mutant metastatic melanoma, as the sample was limited to 34 patients from a single Italian institution. It was unclear if outcome assessors were blinded and if initial therapy was a uniform process (for example, it was unclear whether the choice of treatment sequence was the same for all patients or different depending on the state of the patient).

Summary of Findings

Two studies[16,17] were more favourable to the use of immunotherapy prior to BRAFi in patients. One study[17] concluded that being treated with BRAF after immunotherapy was just as effective as being treated with BRAFi prior to immunotherapy (no statistical difference was found in overall survival and progression-free survival). The first study[17] stated that immunotherapy should be considered first-line if the patient is deemed to be an appropriate candidate for immunotherapy. The second study[16] found that median overall survival was significantly longer in patients who completed immunotherapy prior to BRAFi than those who received BRAFi first, but these results should be interpreted with caution. One study[15] concluded that the optimal sequencing paradigm has not yet been fully determined because no statistically significant findings were reported between the two treatment sequences. Statistical significance was not reported for tumor response outcomes in any study. Tumor response data is available in Appendix 4.

Limitations

All of the studies[15-17] had significant limitations. The studies were retrospective in nature, which could have led to issues in selection and recall bias (some of the health records were incomplete as data were not prospectively collected). The studies likely had major issues with confounding due to differences in baseline characteristics and the potential confounding because of the non-randomized study design. The study populations were not stratified in an attempt to control for confounding, though the ability to stratify may have been limited due to the sample sizes in some groups. Two of the studies also had differences in the number of patients in the different cohorts. Because of all these major

limitations and other possible issues, including the lack of power calculations, the results of all the studies need to be interpreted with caution when drawing conclusions.

Conclusions and Implications for Decision or Policy Making

Three non-randomized, retrospective studies were identified regarding the clinical effectiveness of BRAFi targeted therapy in patients with BRAF mutation positive metastatic melanoma who have received immunotherapy as their first-line option. Two of the studies[16,17] were more favourable to treating with immunotherapy prior to BRAFi in patients with BRAF mutation positive melanoma. One study[15] reported that the optimal sequencing paradigm has yet to be established. All three studies[15-17] identified in this report were low-quality, so findings need to be interpreted with caution.

Due to the significant limitations of the included studies, prospective, randomized studies need to be conducted in order to determine the clinical effectiveness of BRAF targeted therapy in patients with BRAF mutation positive unresectable or metastatic melanoma who have received immunotherapy as their first-line option.

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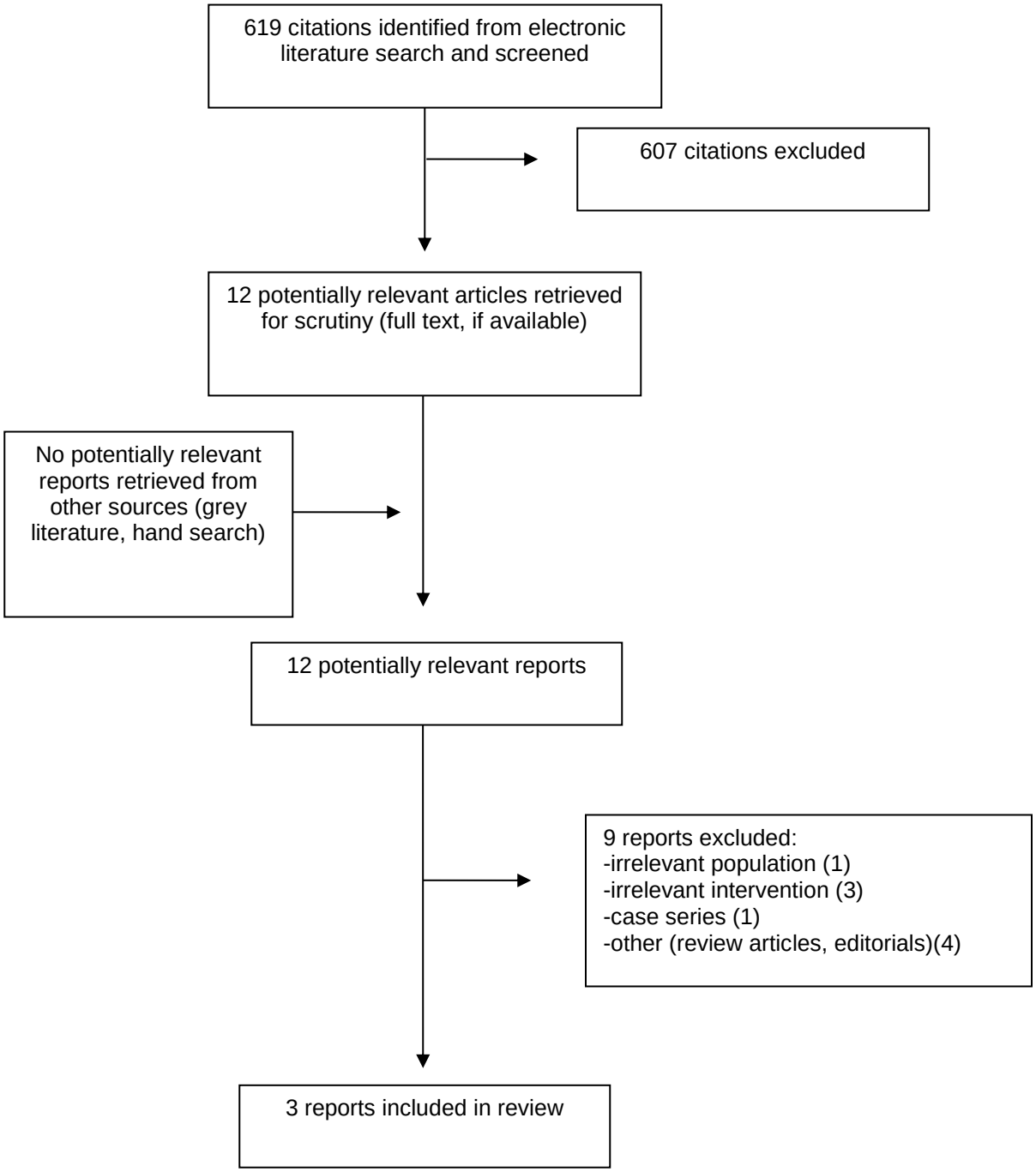
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Clinical Studies

First Author, Publication Year, Country	Study Design	Patient Characteristics	Intervention	Comparator(s)	Clinical Outcomes
Ackerman, 2014, United States of America[17]	Retrospective cohort	Patients who BRAF-mutant metastatic melanoma, N = 274 Patients with BRAFi initially, N = 242 Patients with Immunotherapy initially, N = 32	BRAFi (vemurafenib, dabrafenib, or dabarafenib/trametinib) Followed by: Immunotherapy, which could have included: • Commercial high-dose IL-2 ipilimumab • Clinical trials of PD-1 antibodies (nivolumab, prembrolizumab, and pidilizumab) • Anti-PDL1 antibody (atezolizumab) • Adoptive T-cell therapy	Immunotherapy, which could have included: • Commercial high-dose IL-2 ipilimumab • Clinical trials of PD-1 antibodies (nivolumab, pembrolizumab, and pidilizumab) • Anti-PDL1 antibody (atezolizumab) • Adoptive T-cell therapy Followed by: BRAFi (vemurafenib, dabrafenib, or dabarafenib/trametinib)	• Overall survival • Progression-free survival • Tumor response (as defined by Response Evaluation Criteria in Solid Tumors)
Ascierto, 2014, Italy[16]	Retrospective cohort	Patients who tested positive for the $BRAF^{V600}$ mutation, N = 93 Patients with BRAFi initially, N = 45 Patients with Immunotherapy (Ipilimumab) initially, N = 48	BRAFi (vemurafenib or dabrafenib) followed by Ipilimumab	Ipilimumab followed by a BRAFi (vemurafenib or dabrafenib)	• Overall survival • Progression-free survival • Tumor response (measured by immune-related response criteria)
Ascierto, 2012, Italy[15]	Retrospective cohort	Patients who tested positive for the $BRAF^{V600}$ mutation, N = 34 Patients with BRAFi initially, N = 28 Patients with Immunotherapy (Ipilimumab) initially, N = 6	BRAFi (vemurafenib or dabrafenib) followed by Ipilimumab	Ipilimumab followed by a BRAFi (vemurafenib or dabrafenib)	• Overall survival • Progression-free survival • Tumor response (measured by immune-related response criteria)

BRAFi = BRAF inihibtors; PD = programmed cell death protein; PDL = programmed death ligand.

Appendix 3: Critical Appraisal of Included Publications

Table 3: Strengths and Limitations of Non-Randomized Studies using Downs and Black

Strengths	Limitations
Ackerman, 2014[17]	

• Intervention and comparator were clearly described
• Overall aims of the study were clearly described
• Main outcomes were described a priori
• Outcomes were described in detail
	• Some patient characteristics were not described including, age, comorbidities, and sex
	• Cohorts varied in some of the described baseline characteristics:
	  ○ e.g., lactate dehydrogenase: 97% in immunotherapy initial cohort vs. 62% in BRAFi initial cohort
	• Cohorts varied substantially in number of patients
	  ○ Immunotherapy initial cohort = 32 vs. BRAFi initial cohort = 242
	• Retrospective in design
	  ○ Possible recall and selection bias
	• Possible issues with external validity (the sample may not be a proper representation of all patients with BRAF-mutant metastatic melanoma)
	• Availabilities of certain treatments that are included in the study may not be accessible depending on a patient's specific treatment location; Access to the different treatments varied between the multiple institutions in which the patients were drawn from which could have influenced the bias in selecting certain treatment over another
	• There may have been potential confounders that were difficult to control for, as this was not a randomized controlled trial
	• Unclear if outcomes assessors were blinded

Ascierto, 2014[16]	
• Patient characteristics were clearly described • Intervention and comparator were clearly described • Outcomes were described in detail	• Main outcomes were not clearly described a priori • Potential confounders in baseline characteristics ○ Patients who received BRAFi initially had a higher prevalence with elevated lactate dehydrogenase or brain metastasis; These baseline factors are associated with poor prognosis; therefore, these may have contributed to the worse survival outcomes in patients who received BRAFi first • Study does not discuss potential confounders • Some patients who received BRAFi first discontinued treatment; it is unknown why these patients discontinued treatment • Data was not available on the number of patients who did not cross over to another treatment • Choice of initial therapy was not based on uniform criteria • Patients in the study were unlikely be representative for the entire population with BRAF-mutant metastatic melanoma (issues with external validity) • Unclear if outcomes assessors were blinded

Strengths	Limitations
Ascierto, 2012[15]	

• Intervention and comparator were clearly described
• Overall aims of the study were clearly described
• Main outcomes were described a priori
• Patient characteristics were described
	• Cohorts varied substantially in number of patients
	  ○ Immunotherapy initial cohort = 8 vs. BRAFi initial cohort = 28
	• There were differences in baseline characteristics between patient groups
	  ○ For example, one of the baseline characteristics was Eastern Cooperative Oncology Group performance status
	  ▪ Immunotherapy initial cohort = 100% of patients were “0”
	  ▪ BRAFi initial cohort = 54% were “0”
	• Study did not discuss potential confounders
	• Unclear if outcomes assessors were blinded
	• Unclear if initial therapy was a uniform process

Appendix 4: Main Study Findings and Author's Conclusions

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Ackerman, 2014[17]	
Outcomes to BRAFis (BRAFi) *Patients who received BRAFi* **Response (RECIST Criteria)** • Complete Response *Defined as disappearance of all target lesions* ○ BRAFi initially: 9/233 (4%) ○ IT Initially: 0/32 (0%) • Partial Response *Defined as at least a 30% decrease in the sum of longest diameter of target lesions* ○ BRAFi initially: 144/233 (62%) ○ IT Initially: 17/32 (22%) • Stable Disease *Neither sufficient shrinkage to qualify for partial response nor sufficient to quality for progressive disease* ○ BRAFi initially: 54/233 (23%) ○ IT Initially: 7/32 (22%) • Progressive Disease *At least a 20% increase in the sum of the longest diameter of target lesions* ○ BRAFi initially: 26/233 (11%) ○ IT Initially: 6/32 (19%) **Progression** • No ○ BRAFi initially: 57/242 (24%) ○ IT Initially: 11/32 (34%) • Yes ○ BRAFi initially: 185/242 (76%) ○ IT Initially: 21/32 (66%) **Discontinuation** • No ○ BRAFi initially: 68/242 (28%) ○ IT Initially: 13/32 (41%) • Yes ○ BRAFi initially: 174/242 (72%) ○ IT Initially: 19/32 (59%) **Death** • No ○ BRAFi initially: 113/242 (47%) ○ IT Initially: 17/32 (53%) • Yes ○ BRAFi initially: 129/242 (53%) ○ IT Initially: 15/32 (47%) ***Cox Proportional Hazards Model for PFS and OS*** **Progression Free Survival** • BRAFi vs IT initially ○ HR: 0.94 ○ CI: 0.5-1.9	BRAFis are as effective after immunotherapy as they are prior to immunotherapy; immunotherapy should be considered first-line if it is appropriate for the patient.

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
○ *P:* 0.86 • PFS was 6.7 months (95% CI 4.7-9.1 months) for patients with IT initially versus 5.6 months (95% CI 4.7-6.8) BRAFi initially (*P* = 0.43) • Prior IT was associated with non-significant improvement in PFS (*P* = 0.39) • Median PFS for post-BRAFi ipilimumab therapy was 2.7 months (95% CI 1.8-3.1 months) **Overall Survival** • BRAFi vs IT initially ○ HR: 0.78 ○ CI: 0.4-1.4 ○ *P:* 0.39 • OS was 19.6 months (95% CI 10.0-undefined months) for patients with IT initially versus 13.4 months (95% CI 10.1-17.0) BRAFi initially (*P* = 0.40) • Prior IT was associated with non-significant improvement in OS (*P* = 0.86) • Median OS for post-BRAFi ipilimumab therapy was 5.0 months (95% CI 3.0-8.8 months) ***Post-BRAFi Ipilimumab Outcomes*** *Patients who received ipilimumab following BRAFi*[a] **Response** • Complete Response ○ Patients: 0/36 (0%) • Partial Response ○ Patients: 0/26 (0%) • Stable Disease ○ Patients: 2/36 (6%) • Progressive Disease ○ Patients: 34/36 (94%) **Progression** • No ○ Patients: 4/40 (10%) • Yes ○ Patients: 36/40 (90%) **Number of Doses Received** • 1 ○ Patients: 6/40 (15%) • 2 ○ Patients: 8/40 (20%) • 3 ○ Patients: 6/40 (15%) • 4 ○ Patients: 20/40 (50%) **Death** • No ○ Patients: 16/40 (40%) • Yes ○ Patients: 24/40 (60%)	

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Additional Outcome • Following discontinuation of BRAFi, median time to death was 3.0 months (95% CI = 2.1-4.8)	
Ascierto, 2014[16]	

Median OS, months (95% CI)
• All patients
  ○ BRAFi initially: 9.9 (5.8-14.0)
  ○ Ipilimumab initially: 14.5 (11.1-17.9)
  ○ *P* = 0.04
• Elevated lactate dehydrogenase
  ○ BRAFi initially: 7.5 (3.6-11.4)
  ○ Ipilimumab initially: 14.0 (13.4-14.6)
  ○ *P* = 0.12
• Brain metastases
  ○ BRAFi initially: 7.5 (5.6-9.4)
  ○ Ipilimumab initially: 12.3 (7.9-16.7)
  ○ *P* = 0.02
• Females
  ○ BRAFi initially: 8.6 (4.8-12.4)
  ○ Ipilimumab initially: 13.1 (10.7-15.5)
  ○ *P* = 0.19
• Males
  ○ BRAFi initially: 9.9 (5.8-14.0)
  ○ Ipilimumab initially: 14.5 (11.1-17.9)
  ○ *P* = 0.11
• One previous therapy
  ○ BRAFi initially: 9.7 (2.4-17.1)
  ○ Ipilimumab initially: 14.3 (13.5-15.1)
  ○ *P* = 0.41
• Two or more previous therapies
  ○ BRAFi initially: 6.0 (5.7-6.3)
  ○ Ipilimumab initially: 16.0 (9.8-24.8)
  ○ *P* < 0.001
 	
Tumor Responses to Ipilimumab
• Complete Response
  ○ BRAFi initially: 2/44 (5%)
  ○ Ipilimumab initially: 1/47 (2%)
• Partial Response
  ○ BRAFi Initially: 2/44 (5%)
  ○ Ipilimumab initially: 4/42 (9%)
• Stable Disease
  ○ BRAFi Initially: 8/44 (18%)
  ○ Ipilimumab initially: 9/42 (19%)
• Progressive Disease
  ○ BRAFi Initially: 32/44 (72%)
  ○ Ipilimumab initially: 33/42 (70%)
 	
• Median follow-up of 11 months (1-34 months)
• For patients that were treated with BRAF first:
	Median OS was significantly longer in patients who completed induction therapy with ipilimumab prior to BRAFi than those who received BRAFi first, but these results should be interpreted with caution.

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
○ Median OS from the cessation of treatment with BRAFi was 1.2 months (95% CI 0.5-1.9) ○ Median OS from the end of BRAFi was significantly longer (12.7 months, 95% CI 0.6-24.8, *P* < 0.001)	
Ascierto, 2012[15]	
Tumor Responses to Ipilimumab • Objective tumor response ○ BRAFi (either vemurafenib OR debrafenib) initially, N = 28: ▪ Vemurafenib first: n = 4/12 (33%) ▪ Dabrafenib first: n = 10/16 (63%) ▪ Ipilumumab second: n = 7/28 (25%) ○ Ipilimumab initially, N = 6: ▪ Ipilumumab first: n = 1/6 (17%) ▪ Vemurafenib second: n = 3/4 (75%) ▪ Dabrafenib second: n = 2/2 (100%) • Complete Response ○ BRAFi (either vemurafenib OR debrafenib) initially, N = 28: ▪ Vemurafenib first: n = 0/12 (0%) ▪ Dabrafenib first: n = 1/16 (6%) ▪ Ipilumumab second: n = 0/28 (0%) ○ Ipilimumab initially, N = 6: ▪ Ipilumumab first: n = 0/6 (0%) ▪ Vemurafenib second: n = 0/4 (0%) ▪ Dabrafenib second: n = 0/2 (0%) • Partial Response ○ BRAFi (either vemurafenib OR debrafenib) initially, N = 28: ▪ Vemurafenib first: 4/12 (33%) ▪ Dabrafenib first: 9/16 (56%) ▪ Ipilumumab second: 7/28 (25%) ○ Ipilimumab initially, N = 6: ▪ Ipilumumab first: 1/6 (17%) ▪ Vemurafenib second: 3/4 (75%) ▪ Dabrafenib second: 2/2 (100%) • Stable Disease ○ BRAFi (either vemurafenib OR debrafenib) initially, N = 28: ▪ Vemurafenib first: 4/12 (33%) ▪ Dabrafenib first: 1/16 (6%) ▪ Ipilumumab second: 7/28 (25%) ○ Ipilimumab initially, N = 6: ▪ Ipilumumab first: 2/6 (33%) ▪ Vemurafenib second: 1/4 (25%) ▪ Dabrafenib second: 0/2 (100%) • Progressive Disease ○ BRAFi (either vemurafenib OR debrafenib) initially, N = 28: ▪ Vemurafenib first: 4/12 (33%) ▪ Dabrafenib first: 5/16 (31%)	The optimal sequencing paradigm has not yet been fully determined, but it may be possible to determine the optimal sequence of treatments in these patients based on presence of certain risk factors.

Table 4: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
▪ Ipilumumab second: 7/28 (25%) ○ Ipilimumab initially, N =6: ▪ Ipilumumab first: 3/6 (50%) ▪ Vemurafenib second: 0/4 (0%) ▪ Dabrafenib second: 0/2 (0%) **Median Time to Disease Progression** ○ BRAFi (either vemurafenib OR debrafenib) initially, months (95% CI): ▪ Vemurafenib first: 3.6 (3.3-3.8) ▪ Dabrafenib first: 4.0 (2.1-5.9) ○ Ipilimumab initially, months (95% CI): ▪ Ipilumumab first: 3.4 (2.8-4.1) **Overall Survival** • Median OS ○ BRAFi initially: 14.3 months (95% CI 4.8-23.8) ○ Ipilumumab initially: NR	

CI = confidence interval; HR = hazard ratio; IT = immunotherapy; NR = not reported; OS = overall survival; PFS = progression-free survival; RECIST = Response Evaluation Criteria in Solid Tumors.

[a] This is a subset of the patients initially treated with BRAFi who discontinued BRAFi and were subsequently treated with ipilimumab (n = 40; 33 patients with second-line, 7 patients with third-line). This subset was not statistically compared to the larger cohort.