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CADTH TECHNOLOGY REVIEW

Metastatic Melanoma Gap Analysis: Protocol

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Table of Contents

Rationale and Policy Question

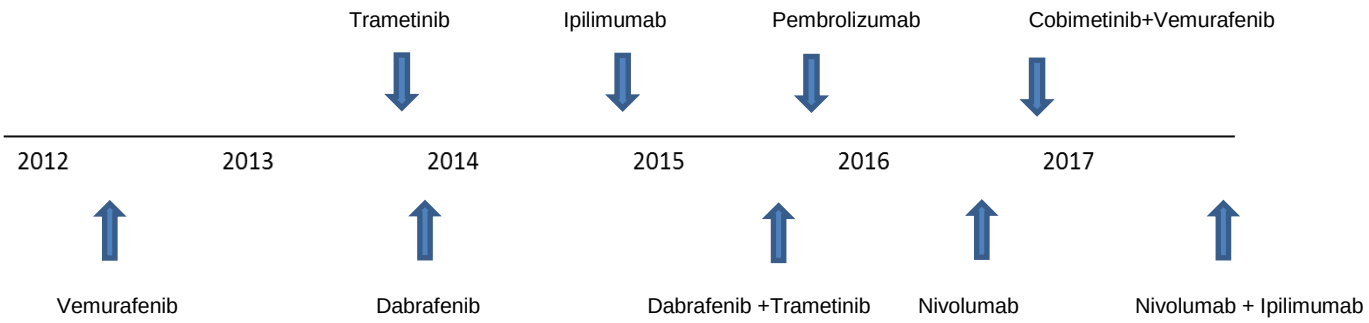
In 2017, 7,200 Canadians were diagnosed with melanoma skin cancer, while 1,250 patients died from it.[1] Unresectable stage III or stage IV melanoma is associated with a poor prognosis. The median survival for these patients is approximately six months and only 25% of patients with late-stage disease survive to one year. The five-year survival rate for stage IV melanoma ranges from 15% to 20%.[2] Once cancer has spread to other parts of the body (distant or metastatic), the five-year relative survival rate for Canadians is 18%.[1]

A wide spectrum of chemotherapeutic and immunological treatment approaches have been explored in patients with metastatic melanoma, with limited to no success until recently. Immunotherapies are now commonly used in the treatment of metastatic melanoma. These drugs include ipilimumab (Yervoy), a monoclonal antibody targeting CTLA-4 and anti-programmed cell death protein 1 (anti-PD-1) checkpoint inhibitors, nivolumab (Opdivo), and pembrolizumab (Keytruda). Furthermore, patients with specific genetic mutations, such as *BRAF*, can be treated with targeted therapies, which include: vemurafenib (Zelboraf), cobimetinib (Cotellic), dabrafenib (Tafinlar), and trametinib (Mekinist).

The CADTH pan-Canadian Oncology Drug Review (pCODR) and the pCODR Expert Review Committee (pERC) have provided reimbursement recommendations on immunotherapies for the treatment of metastatic melanoma since 2012. (See Figure 1.) pERC recommended reimbursement of ipilimumab as a first-line therapy for patients with primary cutaneous, unresectable stage III or stage IV melanoma, regardless of *BRAF* mutation status.[3] Additionally, nivolumab was also recommended for patients with previously untreated, unresectable or metastatic, *BRAF* wild-type melanoma.[4] Pembrolizumab was 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*-targeted therapies.[5] All of these recommendations were conditional on the cost-effectiveness being improved to an acceptable level. More recently, pERC recommended the reimbursement of the combination of nivolumab plus ipilimumab for patients with previously untreated, unresectable metastatic melanoma regardless of *BRAF* status, conditional on the feasibility of adoption being addressed.[6]

In addition to immunotherapies, pERC has also made recommendations on the reimbursement of *BRAF*-targeted therapies for metastatic melanoma in the first-line setting including vemurafenib monotherapy,[7] dabrafenib monotherapy,[8] trametinib monotherapy,[9] dabrafenib in combination with trametinib,[10] and vemurafenib in combination with cobimetinib.[11] These drugs were studied in previously untreated patients. All recommendations were conditional on the cost-effectiveness of these drug monotherapies and combinations being improved to an acceptable level.

Figure 1: Timeline of pERC Recommendations for Metastatic Melanoma Treatments



Although the current pERC recommendations specify the use of immunotherapies and *BRAF*-targeted therapies in specific patient populations, implementation issues and gaps not addressed in the recommendations or which were out of scope at the time of the pERC recommendation have been identified by the Provincial Advisory Group (PAG). Thus, the optimal use of immunotherapies and *BRAF*-targeted therapies for patients with metastatic melanoma is unknown. There are several benefits to proceeding with this gap analysis. First, to our knowledge, there have not been any systematic reviews evaluating this issue. Second, a review of the current evidence may inform implementation gaps identified by PAG. Third, a systematic review will help produce evidence that may be incorporated into implementing an evidence-informed reimbursement algorithm for metastatic melanoma therapy in Canada.

Objectives

Identify evidence that may inform and address the implementation gaps identified by PAG. Specifically:

- evidence informing the sequencing of *BRAF*-targeted therapies and immunotherapies for previously untreated *BRAF*-mutated metastatic melanoma patients
- evidence informing the use of ipilimumab monotherapy x 4 doses after progression on first-line treatment with pembrolizumab or nivolumab for metastatic melanoma patients, regardless of BRAF status
- evidence informing the use of nivolumab monotherapy as a first-line treatment option for *BRAF*-mutated metastatic melanoma patients.

Assess the strength and quality of the evidence identified for each implementation gap.

Deliverables

The following deliverables are planned:

- a CADTH Technology Review report.

Research Questions

The proposed CADTH Technology Review will address the following research questions. Details on the specific interventions and outcomes are included in Tables 1 to 3 that follow.

1. What evidence is available to inform the sequencing of *BRAF*-targeted therapies (i.e., dabrafenib plus trametinib, dabrafenib, vemurafenib, vemurafenib plus cobimetinib) and immunotherapies (i.e., nivolumab, pembrolizumab, ipilimumab, nivolumab plus ipilimumab) for the treatment of previously untreated *BRAF*-mutated metastatic melanoma patients?
    a) What is the clinical efficacy and safety of treatment with *BRAF*-targeted therapies as a second-line option for *BRAF*-mutated patients who have previously been treated with either: i) single agent immunotherapy or ii) combination immunotherapy?
    b) What is the clinical efficacy and safety of treatment with either i) single-agent immunotherapy, or ii) combination immunotherapy, as a second-line option for *BRAF*-mutated patients who have been previously treated with *BRAF*-targeted therapy?
2. What is the clinical efficacy and safety of treatment with ipilimumab monotherapy x 4 doses after progression on pembrolizumab or nivolumab for metastatic melanoma patients regardless of *BRAF* status?
3. What is the clinical efficacy and safety of nivolumab monotherapy as a first-line option for *BRAF*-mutated metastatic melanoma patients?

Methods

Literature Search Methods

The literature search will be performed by an information specialist, using a peer-reviewed search strategy. The complete search strategy is presented in Appendix 1.

Published literature will be identified by searching the following databases: MEDLINE (1946–) with In-Process records and daily updates, via Ovid; Embase (1974–) via Ovid; and PubMed. The search strategy will comprise both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts will be nivolumab, ipilimumab, dabrafenib, trametinib, pembrolizumab, cobimetinib, vemurafenib, *BRAF* inhibitor, PD-1 inhibitor, CTLA-4 inhibitor, and melanoma.

Methodological filters will be applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials (RCTs), and non-randomized studies. Where possible, retrieval will be limited to the human population. The search will also be limited to English-language documents. No date limit will be applied. A search for conference abstracts will also be conducted and a methodological filter will be applied to limit the retrieval to RCTs. The search will be limited to English-language documents. No date limit will be applied.

The initial searches will be completed in February and March of 2018. Regular alerts will be established to update the searches until the publication of the final report. Regular search updates will be performed on databases that do not provide alert services.

Grey literature (literature that is not commercially published) will be identified by searching relevant sections of the *Grey Matters* checklist (https://www.cadth.ca/grey-matters). Google and other Internet search engines will be used to search for additional Web-based materials. These searches will be supplemented by reviewing the bibliographies of key papers and through contacts with appropriate experts and industry.

Selection and Eligibility Criteria

Two reviewers (KC and SM) will independently screen the titles and abstracts of all citations received from the literature search using DistillerSR. In the first round of screening, titles and abstracts will be screened for inclusion based on the selection criteria. At the title and abstract screening level, consensus must be reached with both reviewers in order to exclude an article. Following preliminary screening, eligibility will be assessed through full-text screening. Eligibility for the inclusion of articles will be assessed independently and in duplicate. During full-text screening, disagreements will require resolution through consensus. If consensus cannot be achieved, a third reviewer will be called to make a decision. The study selection process will be presented in a Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart.[12]

Criteria for Inclusion

This review will include literature published in electronic databases, conference abstracts (limited to RCTs only), and grey literature.

Table 1: Selection Criteria for Research Question 1

Population(s)	**Patients aged 18 years or older with metastatic (stage III or stage IV) melanoma, with *BRAF* mutation status**
Intervention(s)	a) First-line: Immunotherapies (i.e., pembrolizumab, nivolumab, ipilimumab, nivolumab plus ipilimumab) Second-Line: *BRAF*-targeted therapies (i.e., dabrafenib plus trametinib, dabrafenib, trametinib, vemurafenib, vemurafenib plus cobimetinib) b) First-line*: BRAF*-targeted therapies (i.e., dabrafenib plus trametinib, dabrafenib, trametinib, vemurafenib, vemurafenib plus cobimetinib) Second-line: Immunotherapies (i.e., pembrolizumab, nivolumab, ipilimumab, nivolumab plus ipilimumab)
Comparator(s)	Randomized studies: Opposite sequence of the intervention (as previously described) Non-randomized studies: Not applicable
Outcome(s)	Clinical benefits and harms: Overall survival, progression-free survival, response rates, duration of response, disease control rate, quality of life, safety (Grade 3 to 4 adverse events, immune-related adverse events)
Study Design(s)	Health technology assessments, indirect treatment comparisons, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Table 2: Selection Criteria for Research Question 2

Population(s)	**Patients aged 18 years or older with metastatic (stage III or stage IV) melanoma regardless of *BRAF* status**
Intervention(s)	ipilimumab monotherapy x 4 doses after progression on pembrolizumab or nivolumab
Comparator(s)	Randomized studies: Treatment other than ipilimumab monotherapy x 4 doses after progression on nivolumab or pembrolizumab, or no treatment after progression on nivolumab or pembrolizumab Non-randomized studies: Not applicable
Outcome(s)	Clinical benefits and harms: Overall survival, progression-free survival, response rates, duration of response, disease control rate, quality of life, safety (Grade 3 to 4 adverse events, immune-related adverse events)
Study Design(s)	Health technology assessments, indirect treatment comparisons, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Table 3: Selection Criteria for Research Question 3

Population(s)	**Patients aged 18 years or older with metastatic (stage III or stage IV) melanoma, with *BRAF* mutation status**
Intervention(s)	First-line: nivolumab monotherapy
Comparator(s)	Randomized studies: First-line: *BRAF*-targeted therapies (i.e., dabrafenib plus trametinib, dabrafenib, trametinib, vemurafenib, vemurafenib plus cobimetinib) or immunotherapies (i.e., pembrolizumab, ipilimumab, nivolumab plus ipilimumab) Non-randomized studies: Not applicable
Outcome(s)	Clinical benefits and harms: Overall survival, progression-free survival, response rates, duration of response, disease control rate, quality of life, safety (Grade 3 to 4 adverse events, immune-related adverse events)
Study Design(s)	Health technology assessments, indirect treatment comparisons, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Study Exclusion Criteria

- Studies will be excluded that are:
- not available in English
- case series
- case reports
- cross-sectional
- editorials
- letters
- comments
- phase I dose escalation trials (mixed design clinical trials [i.e., trials with a dose escalation phase followed by an efficacy-determining phase in which the intervention is administered at the same dose and schedule to all patients] will be included if data were reported separately for the two phases of the trial) and sample size n < 30 for non-randomized studies.[13]

Data Extraction and Critical Appraisal

A data extraction form for the review will be designed a priori to document and tabulate relevant study characteristics. One reviewer will independently extract data from the included studies using standardized data collection forms and will be checked by a second reviewer. When methodological information cannot not be obtained from a publication, the author will be contacted for further comment. A preliminary synthesis will develop an initial description of the included study results, incorporating outcome statistics against research questions, where possible. The narrative synthesis of evidence is expected to be reported in a table format, highlighting the key outcomes and addressing the research questions. In order to avoid potential biases, key points of difference between studies will be identified.

Data Items and Data Abstraction Process

The following information will be extracted from each included trial:

- characteristics of the study participants (including inclusion and exclusion criteria)
- characteristics of the study design (including study design, sample size, median follow-up period, analysis strategy)
- characteristics of the intervention and control (including timing of the intervention, dose of the intervention, and frequency of the intervention)
- characteristics of the outcome measures. (See Tables 1 to 3).

Risk of Bias Appraisal

Risk of bias in individual studies: At minimum, the methodological validity of included RCTs will be assessed using the Cochrane risk of bias assessment,[14] while non-randomized studies will be assessed using the Downs and Black checklist.[15] Quality assessment will be done by the lead researcher, and verified by a second researcher. A review of the strength and limitations of each included study will be described narratively.

Risk of bias across studies: Publication bias will be evaluated using a funnel plot, with both graphical and statistical representations. However, a small number of publications are anticipated for each outcome, so the presence of publication bias by visual inspection may be indiscernible.

Summary of Evidence

For each question, a narrative summary will be undertaken to describe the design, intervention, comparator, settings, and outcome measures, where applicable. Tables will accompany the narrative summary, to ensure the consistency of the presented information across all studies and to facilitate study comparisons by the reader. This approach will be used to synthesize the evidence relevant to the research questions, summarizing and explaining the findings of included studies.

A narrative summary of the results of the methodological assessments will be presented separately for each research question, including an overall impression of the quality of included studies. Tables outlining the strengths and limitations of each study will accompany the narrative summary to ensure consistency of presented information across all studies and to facilitate study comparisons by the reader. Separate tables will be created for each study design, or tabulated data will be separated within the same table by the use of subheadings.

Results will be presented using outcomes statistics, where possible, to address each research question. For time-to-event outcomes, the treatment effect will be expressed as a hazard ratio with the 95% confidence intervals and *P* value as a measure of uncertainty. For continuous outcomes, the treatment effect will be expressed as a mean with the standard deviation, or a median with the range, as well as the corresponding *P* values as a measure of uncertainty.

Meta-analysis and pooling of statistical results will not be undertaken.

Areas for Potential Amendments

If amendments are required at any time during the study, reasons for changes will be recorded in a study file and subsequently reported within the final study report. If necessary, a rescreening of the previous literature search or an updated literature search will be performed to capture additional data according to the amendments.

References

1. Canadian Cancer Society. Melanoma skin cancer statistics. 2017; http://www.cancer.ca/en/cancer-information/cancer-type/skin-melanoma/statistics/?region=on. Accessed March 1 2018.
2. American Cancer Society. Survival rates for melanoma skin cancer, by stage. 2017; https://www.cancer.org/cancer/melanoma-skin-cancer/detection-diagnosis-staging/survival-rates-for-melanoma-skin-cancer-by-stage.html Accessed March 1 2018.
3. pCODR Expert Review Committee (pERC) final recommendation: ipilimumab (Yervoy). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2012: https://cadth.ca/sites/default/files/pcodr/pcodr-yervoy-adv-mel-fn-rec.pdf. Accessed March 1 2018.
4. pCODR Expert Review Committee (pERC) final recommendation: nivolumab (Opdivo). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2016: https://cadth.ca/sites/default/files/pcodr/nivolumab_opdivo_mm_fn_rec.pdf. Accessed March 1 2018.
5. pCODR Expert Review Committee (pERC) final recommendation: pembrolizumab (Keytruda). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2015: https://cadth.ca/sites/default/files/pcodr/pcodr_pembrolizumab_keytruda_mm_fn_rec.pd. Accessed March 1 2018.
6. pCODR Expert Review Committee (pERC) final recommendation: nivolumab (Opdivo) plus ipilimumab (Yervoy). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2017: https://cadth.ca/sites/default/files/pcodr/pcodr_opdivo_yervoy_metmela_fn_rec.pdf. Accessed March 1 2018.
7. pCODR Expert Review Committee (pERC) final recommendation: vemurafenib (Zelboraf). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2012: https://cadth.ca/sites/default/files/pcodr/pcodr-zelboraf-adv-mel-fn-rec.pdf. Accessed March 1 2018.
8. pCODR Expert Review Committee (pERC) final recommendation: dabrafenib (Tafinlar). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2013: https://www.cadth.ca/sites/default/files/pcodr/pcodr-tafinlar-metmla-fn-rec.pdf. Accessed March 1 2018.
9. pCODR Expert Review Committee (pERC) final recommendation: trametinib (Mekinist). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2013: https://cadth.ca/sites/default/files/pcodr/pcodr-mekinist-mm-fn-rec.pdf. Accessed March 1 2018.
10. pCODR Expert Review Committee (pERC) final recommendation: dabrafenib (Taflinar) in combination with trametinib (Mekinist). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2015: https://www.cadth.ca/sites/default/files/pcodr/pcodr_tafinlar_mekinist_metmelanoma_fn_rec.pdf. Accessed March 1 2018.
11. pCODR Expert Review Committee (pERC) final recommendation: cobimetinib (Cotelic) and vemurafenib (Zelboraf). Ottawa: Canadian Agency for Drugs and Technologies in Health (CADTH); 2016: https://www.cadth.ca/sites/default/files/pcodr/pcodr_cobimetinib_cotellic_metmela_fn_rec.pdf. Accessed March 1 2018.
12. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6(7):e1000100.
13. Springate SD. The effect of sample size and bias on the reliability of estimates of error: a comparative study of Dahlberg's formula. *Eur J Orthod.* 2012;34(2):158-163.
14. Higgins JPT, Altman DG, Gøtzsche PC, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ.* 2011;343.
15. Downs SH, Black N. The feasibility of creating a checklist for the assessment of the methodological quality both of randomised and non-randomised studies of health care interventions. *J Epidemiol Community Health.* 1998;52(6):377-384.

Appendix 1: Literature Search Strategy

OVERVIEW	
Interface:	Ovid
Databases:	Embase 1974 to 2018 February 22 Ovid MEDLINE(R) ALL 1946 to February 22, 2018 **Note:** Subject headings have been customized for each database. Duplicates between databases were removed in Ovid.
Date of Search:	February 23, 2018: Randomized controlled trials, non-randomized studies March 9, 2018: Health technology assessments, systematic reviews, meta-analyses
Alerts:	Monthly search updates until project completion
Study Types:	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies
Limits:	English Humans

SYNTAX GUIDE	
/	At the end of a phrase, searches the phrase as a subject heading
MeSH	Medical Subject Heading
exp	Explode a subject heading
*	Before a word, indicates that the marked subject heading is a primary topic; or, after a word, a truncation symbol (wildcard) to retrieve plurals or varying endings
adj#	Adjacency within # number of words (in any order)
.ti	Title
.ab	Abstract
.kf	Author keyword heading word (MEDLINE)
.kw	Keyword heading (MEDLINE)
.dq	Candidate term (Embase)
.kw	Author keyword (Embase)
medall	Ovid database code; Medline ALL
oemezd	Ovid database cose; Embase 1974 to present

MULTI-DATABASE STRATEGY	
#	**Searches**
1	(Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,ot,kf,hw,rn,nm.
2	Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666).ti,ab,ot,kf,hw,rn,nm.
3	(dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436* or QGP4HA4G1B).ti,ab,ot,kf,hw,rn,nm.
4	(trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN).ti,ab,ot,kf,hw,rn,nm.

MULTI-DATABASE STRATEGY	
#	**Searches**
5	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,hw,rn,nm.
6	(Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518 or ER29L26N1X).ti,ab,ot,kf,hw,rn,nm.
7	(Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or R7204 or R 7204 or RO 51 85426 or RO 5185426 or 207SMY3FQT).ti,ab,ot,kf,hw,rn,nm.
8	or/1-7
9	exp Melanoma/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kf.
10	8 and 9
11	10 use medall
12	*Nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538).ti,ab,kw.
13	*Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016).ti,ab,kw.
14	*dabrafenib/ or (dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436).ti,ab,kw.
15	*tametinib/ or (trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057).ti,ab,kw.
16	*pembrolizumab/ or (pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.
17	*Cotellic/ or (Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518).ti,ab,kw.
18	*Vemurafenib/ or (Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or R7204 or R 7204 or RO 51 85426 or RO 5185426).ti,ab,kw.
19	or/12-18
20	exp melanoma/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kw,dq.
21	19 and 20
22	21 use oemezd
23	11 or 22
24	limit 23 to english language
25	(Randomized Controlled Trial or Controlled Clinical Trial or Pragmatic Clinical Trial or Clinical Study or Adaptive Clinical Trial or Equivalence Trial).pt.
26	(Clinical Trial or Clinical Trial, Phase I or Clinical Trial, Phase II or Clinical Trial, Phase III or Clinical Trial, Phase IV).pt.
27	Multicenter Study.pt.
28	Clinical Studies as Topic/
29	exp Clinical Trial/ or exp Clinical Trials as Topic/ or exp "Clinical Trial (topic)"/
30	Multicenter Study/ or Multicenter Studies as Topic/ or "Multicenter Study (topic)"/
31	Randomization/
32	Random Allocation/
33	Double-Blind Method/
34	Double Blind Procedure/
35	Double-Blind Studies/
36	Single-Blind Method/
37	Single Blind Procedure/
38	Single-Blind Studies/
39	Placebos/
40	Placebo/
41	Control Groups/
42	Control Group/
43	Cross-Over Studies/ or Crossover Procedure/

MULTI-DATABASE STRATEGY	
#	**Searches**
44	(random* or sham or placebo*).ti,ab,hw,kf,kw.
45	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
46	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kf,kw.
47	(control* adj3 (study or studies or trial* or group*)).ti,ab,hw,kf,kw.
48	(clinical adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
49	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw,kf,kw.
50	(phase adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
51	((crossover or cross-over) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
52	((multicent* or multi-cent*) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
53	allocated.ti,ab,hw.
54	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw,kf,kw.
55	((equivalence or superiority or non-inferiority or noninferiority) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
56	(pragmatic study or pragmatic studies).ti,ab,hw,kf,kw.
57	((pragmatic or practical) adj3 trial*).ti,ab,hw,kf,kw.
58	((quasiexperimental or quasi-experimental) adj3 (study or studies or trial*)).ti,ab,hw,kf,kw.
59	trial.ti,kf,kw.
60	or/25-59
61	epidemiologic methods.sh.
62	epidemiologic studies.sh.
63	observational study/
64	observational studies as topic/
65	clinical studies as topic/
66	controlled before-after studies/
67	historically controlled study/
68	interrupted time series analysis/
69	exp seroepidemiologic studies/
70	national longitudinal study of adolescent health/
71	cohort studies/
72	cohort analysis/
73	longitudinal studies/
74	longitudinal study/
75	prospective studies/
76	prospective study/
77	follow-up studies/
78	follow up/
79	followup studies/
80	retrospective studies/
81	retrospective study/
82	case-control studies/
83	exp case control study/
84	observational study/
85	quasi experimental methods/
86	quasi experimental study/
87	(observational study or validation studies or clinical study).pt.
88	(observational adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
89	cohort*.ti,ab,kf,kw.
90	(prospective adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
91	((follow up or followup) adj7 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.

MULTI-DATABASE STRATEGY

#	Searches
92	((longitudinal or longterm or (long adj term)) adj7 (study or studies or design or analysis or analyses or data)).ti,ab,kf,kw.
93	(retrospective adj7 (study or studies or design or analysis or analyses or data or review)).ti,ab,kf,kw.
94	((case adj control) or (case adj comparison) or (case adj controlled)).ti,ab,kf,kw.
95	(case-referent adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
96	(population adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
97	(descriptive adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
98	((multidimensional or (multi adj dimensional)) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
99	((natural adj experiment) or (natural adj experiments)).ti,ab,kf,kw.
100	(quasi adj (experiment or experiments or experimental)).ti,ab,kf,kw.
101	((non experiment or nonexperiment or non experimental or nonexperimental) adj3 (study or studies or design or analysis or analyses)).ti,ab,kf,kw.
102	(prevalence adj3 (study or studies or analysis or analyses)).ti,ab,kf,kw.
103	or/61-102
104	60 or 103
105	24 and 104
106	105 not conference abstract.pt.
107	exp animals/
108	exp animal experimentation/ or exp animal experiment/
109	exp models animal/
110	nonhuman/
111	exp vertebrate/ or exp vertebrates/
112	or/107-111
113	exp humans/
114	exp human experimentation/ or exp human experiment/
115	or/113-114
116	112 not 115
117	106 not 116
118	**remove duplicates from 117 - RCT and nonrandomized studies results**
119	(Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538 or 31YO63LBSN).ti,ab,ot,kf,hw,rn,nm.
120	Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016 or 6T8C155666).ti,ab,ot,kf,hw,rn,nm.
121	(dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436* or QGP4HA4G1B).ti,ab,ot,kf,hw,rn,nm.
122	(trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057 or 33E86K87QN).ti,ab,ot,kf,hw,rn,nm.
123	(pembrolizumab* or lambrolizumab* or Keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475 or DPT0O3T46P).ti,ab,ot,kf,hw,rn,nm.
124	(Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518 or ER29L26N1X).ti,ab,ot,kf,hw,rn,nm.
125	(Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or R7204 or R 7204 or RO 51 85426 or RO 5185426 or 207SMY3FQT).ti,ab,ot,kf,hw,rn,nm.
126	or/119-125
127	exp Melanoma/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kf.
128	126 and 127
129	128 use medall
130	*Nivolumab/ or (Opdivo* or nivolumab* or MDX 1106 or MDX1106 or BMS936558 or BMS 936558 or ONO4538 or ONO 4538).ti,ab,kw.

MULTI-DATABASE STRATEGY	
#	**Searches**
131	*Ipilimumab/ or (Yervoy* or ipilimumab* or strentarga* or Winglore* or MDX-CTLA 4 or MDX-CTLA4 or MDXCTLA-4 or MDXCTLA4 or MDX-010 or MDX010 or MDX101 or MDX 101 or BMS734016 or BMS 734016).ti,ab,kw.
132	*dabrafenib/ or (dabrafenib or Tafinlar* or GSK 2118436* or GSK2118436).ti,ab,kw.
133	*tametinib/ or (trametinib or Mekinist* or GSK 1120212* or GSK1120212* or JTP 74057 or JTP74057).ti,ab,kw.
134	*pembrolizumab/ or (pembrolizumab* or lambrolizumab* or keytruda* or MK-3475 or MK3475 or Merck3475 or Merck-3475 or Sch-900475 or Sch900475).ti,ab,kw.
135	*Cotellic/ or (Cotellic* or cobimetinib* or GDC-0973 or GDC0973 or RG 7420 or RG7420 or XL 518 or XL518).ti,ab,kw.
136	*Vemurafenib/ or (Zelboraf* or vemurafenib* or HSDB 8143 or HSD8143 or PLX 4032 or PLX4023 or RG 7204 or RG7024 or R7204 or R 7204 or RO 51 85426 or RO 5185426).ti,ab,kw.
137	or/130-136
138	exp melanoma/ or (melanoma* or melanotic or melanocarcinoma* or melanomalignoma* or naevocarcinoma* or nevocarcinoma* or pigmentary cancer* or skin cancer*).ti,ab,kw,dq.
139	137 and 138
140	139 use oemezd
141	129 or 140
142	limit 141 to english language
143	CTLA-4 Antigen/ai
144	Programmed Cell Death 1 Receptor/ai
145	Proto-Oncogene Proteins B-raf/ai
146	(BRAF or B-raf).ti,ab,kf.
147	(PD-1 antibod* or antiprogrammed cell death or anti-programmed cell death or anti PD-1 or monoclonal antibody or immunotherap*).ti,ab,kf.
148	(CTLA-4 antibod* or CTLA4 antibod* or monoclonal antibod* or CD152 antibod*).ti,ab,kf.
149	or/143-148
150	149 and 127
151	150 use medall
152	B Raf kinase/
153	PD 1 antibody/
154	programmed death 1 receptor antibody/
155	cytotoxic T lymphocyte antigen 4 antibody/
156	(BRAF or B-raf).ti,ab,kw,dq.
157	(PD-1 antibod* or antiprogrammed cell death or anti-programmed cell death or anti PD-1 or monoclonal antibody or immunotherap*).ti,ab,kw,dq.
158	(CTLA-4 antibod* or CTLA4 antibod* or monoclonal antibod* or CD152 antibod*).ti,ab,kw,dq.
159	or/152-158
160	138 and 159
161	160 use oemezd
162	151 or 161
163	limit 162 to english language
164	meta-analysis.pt.
165	meta-analysis/ or systematic review/ or meta-analysis as topic/ or "meta analysis (topic)"/ or "systematic review (topic)"/ or exp technology assessment, biomedical/ or network meta-analysis/
166	((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kf,kw.
167	((quantitative adj3 (review* or overview* or synthes*)) or (research adj3 (integrati* or overview*))).ti,ab,kf,kw.
168	((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kf,kw.
169	(data synthes* or data extraction* or data abstraction*).ti,ab,kf,kw.
170	(handsearch* or hand search*).ti,ab,kf,kw.
171	(mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kf,kw.
171	(met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology

MULTI-DATABASE STRATEGY	
#	**Searches**
	appraisal*).ti,ab,kf,kw.
172	(PD-1 antibod* or antiprogrammed cell death or anti-programmed cell death or anti PD-1 or monoclonal antibody or immunotherap*).ti,ab,kf.
173	(meta regression* or metaregression*).ti,ab,kf,kw.
174	(meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or bio-medical technology assessment*).mp,hw.
175	(medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw.
176	(cochrane or (health adj2 technology assessment) or evidence report).jw.
177	(comparative adj3 (efficacy or effectiveness)).ti,ab,kf,kw.
178	(outcomes research or relative effectiveness).ti,ab,kf,kw.
179	((indirect or indirect treatment or mixed-treatment or bayesian) adj3 comparison*).ti,ab,kf,kw.
180	(meta-analysis or systematic review).md.
181	(multi* adj3 treatment adj3 comparison*).ti,ab,kf,kw.
182	(mixed adj3 treatment adj3 (meta-analy* or metaanaly*)).ti,ab,kf,kw.
183	umbrella review*.ti,ab,kf,kw.
184	(multi* adj2 paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
185	(multiparamet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
186	(multi-paramet* adj2 evidence adj2 synthesis).ti,ab,kw,kf.
187	or/164-186
188	163 and 187
189	142 and 187
190	188 or 189
191	190 not conference abstract.pt.
192	**remove duplicates from 191 - HTA, systematic review, meta-analysis results**

OTHER DATABASES		
PubMed	A limited PubMed search was performed to capture records not found in MEDLINE. Same MeSH, keywords, limits, and study types used as per MEDLINE search, with appropriate syntax used.	

Grey Literature

Dates for Search:	February 2018
Keywords:	nivolumab, ipilimumab, dabrafenib, trametinib, pembrolizumab, cobimetinib, vemurafenib, *BRAF* inhibitor, PD-1 inhibitor, CTLA-4 inhibitor, and melanoma
Limits:	Human, English

Relevant websites from the following sections of the CADTH grey literature checklist *Grey Matters: a practical tool for searching health-related grey literature* (https://www.cadth.ca/grey-matters) were searched:

- Health Technology Assessment Agencies
- Clinical Practice Guidelines
- Databases (free)
- Internet Search
- Open Access Journals.