PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ipilimumab (Yervoy) for First Line Advanced Melanoma

December 22, 2014

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1 GUIDANCE IN BRIEF

1.1 Background

The purpose of this review was to evaluate the effect of ipilimumab, either alone or in combination, on patient outcomes compared to commonly used therapies, placebo, or best supportive care in the treatment of patients with unresectable melanoma (stage III or stage IV) who had no previous systemic therapy.

In 2012, ipilimumab was initially approved by Health Canada for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.[1] In September 2014, it was further approved as first line therapy of unresectable or metastatic melanoma.[2] The Health Canada-recommended dose for ipilimumab, in both previously treated and untreated patients, is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.[1] The funding indication currently being sought by the manufacturer is for ipilimumab 3 mg/kg in the first line treatment of advanced melanoma.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multinational, randomized, double-blind trial was identified that compared the use of ipilimumab 10 mg/kg plus dacarbazine versus dacarbazine plus placebo in patients with previously untreated unresectable stage III or stage IV melanoma (Study CA184-024).[3]

The baseline characteristics were balanced between the treatment groups. The mean age of patients was 57.5 years in the ipilimumab-dacarbazine group and 56.4 years in the dacarbazine-placebo group. Approximately 71% of patients in each group had an Eastern Cooperative Oncology Group (ECOG) performance status of 0 (patients were fully active and able to carry on all pre-disease performance without restriction).

Patients with CNS metastases, ocular or mucosal melanoma, patients on chronic steroids or immune suppressive agents or with a history or autoimmune disease were excluded from the trial.

Efficacy

The CA184-024 study demonstrated a statistically significant improvement in overall survival, its primary outcome, in favour of ipilimumab-dacarbazine (median 11.2 months) compared to dacarbazine-placebo (median 9.1 months); HR 0.72, 95% confidence interval (CI) 0.59 to 0.87.[3] A statistically significant difference was also demonstrated for progression-free survival in favour of ipilimumab-dacarbazine.

Health-related quality of life (HRQOL) results for this trial were reported in abstract form only.[4] Patients in both groups reported a declined average Global Health Status (GHS) score from baseline (ipilimumab-dacarbazine, -6.5; dacarbazine-placebo, -10.0), indicating worsened health status; however, no p-value or 95% CI was reported for this comparison. Given the limited details of the HRQOL data and the methods used to collect the data, as well as the lack of a validated minimal clinically important difference, interpretation of these data is difficult.

Safety

No statistical comparisons of the rates of adverse events between the treatment groups were performed. A similar proportion of patients in both treatment groups experienced at least one adverse event of any Grade. Patients who received ipilimumab-dacarbazine experienced more diarrhea, dermatologic disorders, elevated liver enzymes, pyrexia, and chills.

Grade 3 or higher adverse events occurred in more patients who received ipilimumab-dacarbazine (56.3%) than in patients who received dacarbazine-placebo (27.5%).

Immune-related adverse events occurred in a higher proportion of patients treated with ipilimumab-dacarbazine than in those treated with dacarbazine-placebo, 77.7% versus 38.2%, respectively. The most common immune-related adverse events were dermatologic disorders, diarrhea, and elevated ALT/AST.

Withdrawals due to adverse events occurred in 38.5% of patients treated with ipilimumab-dacarbazine and in 8% of those treated with dacarbazine-placebo.

1.2.2 Additional Evidence

pCODR received input on ipilimumab for the first-line treatment of advanced melanoma from one patient advocacy group, Melanoma Network of Canada (MNC). Provincial Advisory Group input was obtained from all nine provinces participating in pCODR.

pCODR previously reviewed the use of ipilimumab 3 mg/kg in patients with unresectable Stage III or Stage IV melanoma who received prior systemic therapy in 2012. The pCODR Expert Review Committee (pERC) recommended funding ipilimumab, conditional on the cost-effectiveness being improved to an acceptable level, in patients with unresectable Stage III or Stage IV melanoma who have received prior systemic therapy.[5]

In addition, two supplemental questions were identified during development of the review protocol as relevant to the pCODR review of ipilimumab and are discussed as supporting information:

- Comparison of the clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma
    - No evidence was found in the literature on the comparative efficacy and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma.
- The clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose used as first line therapy for patients with unresectable or metastatic melanoma.
    - One pooled analysis of 78 patients demonstrated median overall survival of 13.47 months.[6] Many limitations were identified for this pooled analysis.
    - Two ongoing retrospective observational studies (studies CA184-332 and CA184-338) reported median overall survivals of 11.5 months for 90 patients and 14.3 months for 120 patients, respectively.[7,8] The results from the two observational studies should be interpreted with caution due to the high risk of bias associated with their design.

1.2.3 Interpretation and Guidance

Burden of Illness and Need

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1100 patients will die of melanoma in 2014.[9] Unresectable stage III or IV melanoma carries a poor prognosis with a median survival of 6.2 months and one-year survival of 25%.[10]

Recently, Health Canada has approved the use of ipilimumab 3 mg/kg in the first-line treatment of patients with advanced melanoma.[2] Dacarbazine had been the mainstay of treatment up until 2011 ipilimumab demonstrated an improvement in overall survival in patients with pre-treated unresectable stage III or IV melanoma.[11] There is no evidence that chemotherapy offers any benefit in either quality of life or in overall survival, and as such dacarbazine is felt to be only very modestly effective in inducing responses.[12,13]

Effectiveness

In patients with previously untreated advanced melanoma, there are no randomized trials comparing ipilimumab at 3 mg/kg for four doses versus dacarbazine or versus ipilimumab at 10 mg/kg. Evidence from one pooled analysis of four RCTs and from two retrospective observational studies was used to understand the effectiveness of ipilimumab at 3 mg/kg in this group of patients. Notwithstanding the limitations of making comparisons across trials, the survival curves in advanced melanoma patients who received ipilimumab at 3 mg/kg in the first-line setting are similar to those who receive it as subsequent therapy. Dacarbazine is only very modestly effective in inducing responses in melanoma and there is no evidence that it improves either quality of life or overall survival, with less than 3% of patients getting long-term survival benefit.[14-18] Most patients only receive one or two cycles of dacarbazine and are then switched to ipilimumab as the median PFS of dacarbazine is only 6 weeks (i.e. 1st assessment).

As there remains some uncertainty about the dose effect of ipilimumab, the US FDA, in their approval of ipilimumab in the first-line setting, mandated that the manufacturer perform a randomized trial comparing the 10 mg/kg dose to the 3 mg/kg dose. This study (BMS 169) has been completed and the results are expected in early 2016.[19]

Safety

In the CA184-024 study, 56.3% of patients receiving ipilimumab-dacarbazine experienced a Grade 3 or higher adverse event whereas 27.5% of patients receiving dacarbazine + placebo experienced a Grade 3 or higher adverse event. The most common adverse events are skin related, with the majority being Grade 1 or 2.

Although the CA184-024 study had a higher rate of withdrawal due to adverse events in the group that received ipilimumab + dacarbazine, most of those were immune-related adverse events which are now better understood and are rapidly reversible with the use of treatment algorithms. The exception to rapid reversibility of immune-related adverse events are the endocrine side effects, which generally require several weeks to months to reverse and about 46% of patients will require long-term steroid replacement.

BRAF Mutation-Positive Advanced Melanoma

Most patients with BRAF mutated metastatic melanoma are treated with a BRAF inhibitor as first-line therapy. There are no randomized trials comparing upfront treatment with a BRAF inhibitor (vemurafenib or dabrafenib) versus ipilimumab in treatment-naïve patients. Treatment resistance to a BRAF inhibitor is almost always inevitable and the median duration of response to a BRAF inhibitor is less than seven months, whereas approximately

20% of patients who receive ipilimumab experience long-term survival and do not require further treatment.[3]

Approximately 30% of patients treated with a BRAF inhibitor will experience an explosive recurrence and many of those will not be candidates to receive ipilimumab, due to a rapid decline in performance status or the development of CNS metastases requiring steroid use. There is uncertainty with respect to sequencing BRAF therapy with ipilimumab; however, some researchers are now moving in the direction of ipilimumab as first-line in patients with good performance status and slower progressing tumours, whereas BRAF inhibitors are reserved for patients with poorer performance status and more rapidly progressing tumours.

1.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to ipilimumab monotherapy 3 mg/kg in the first-line treatment of patients with unresectable or metastatic (i.e., Stage III-IV) melanoma with ECOG performance status of 0 or 1 and who are not receiving immunosuppressive therapy. This conclusion was based on several factors:

- One well-conducted randomized controlled trial that demonstrated a clear benefit in overall survival and progression free survival in favour of ipilimumab 10 mg/kg plus dacarbazine compared to dacarbazine plus placebo.
- A pooled data set from four RCTs, as well as two observational studies that provided supporting evidence of the effectiveness of the 3 mg/kg dose in the first-line setting.

The Clinical Guidance Panel also considered that from a clinical perspective:

- The Health Canada approved dose in the first-line setting is 3 mg/kg for four doses, which is based on the second line study of ipilimumab 3 mg/kg versus gp100 vaccine.
- The optimal dose in the first line setting is being addressed by the CA184-169 study which is comparing the 10 mg/kg dose versus the 3 mg/kg dose in the first-line setting. The results of that study are expected in the first quarter of 2016, and until that time, the CGP agreed that there is no reason or evidence to expect that Ipilimumab 3 mg/kg would be any less effective in the first line than in the second line.
- Most Canadian patients treated in the first-line setting with dacarbazine receive ipilimumab in the second line, and the majority of those patients are not receiving an overall survival benefit from dacarbazine.
- Ipilimumab should also be available for the first line treatment of patients with BRAF mutation positive melanoma who have low bulk disease, good performance status and whose disease is not progressing rapidly, as these patients can achieve a long term response from treatment with ipilimumab.

2 CLINICAL GUIDANCE

This Clinical Guidance Report was prepared to assist the pCODR Expert Review Committee (pERC) in making recommendations to guide funding decisions made by the provincial and territorial Ministries of Health and provincial cancer agencies regarding ipilimumab for advanced melanoma. The Clinical Guidance Report is one source of information that is considered in the *pERC Deliberative Framework*. The *pERC Deliberative Framework* is available on the pCODR website, www.pcodr.ca.

This Clinical Guidance is based on: a systematic review of the literature regarding ipilimumab conducted by the pCODR Clinical Guidance Panel (CGP) and the pCODR Methods Team; input from patient advocacy groups; input from the Provincial Advisory Group; and supplemental issues relevant to the implementation of a funding decision.

The systematic review and supplemental issues are fully reported in Sections 6 and 7. Background clinical information provided by the CGP, a summary of submitted Patient Advocacy Group Input on ipilimumab and a summary of submitted Provincial Advisory Group Input on ipilimumab are provided in Sections 3, 4 and 5 respectively.

2.1 Context for the Clinical Guidance

2.1.1 Introduction

Unresectable stage III or stage IV melanoma is an aggressive skin malignancy with poor prognosis, and treatment options for this patient population are limited.[20,21] The currently accepted standard therapy for patients with advanced melanoma include BRAF inhibitors, MEK inhibitors, immunotherapy (e.g. ipilimumab), and dacarbazine- or paclitaxel-based systemic chemotherapy.[21]

Ipilimumab is a monoclonal antibody that binds to and blocks cytotoxic T lymphocyte-associated antigen 4 (CTLA-4), which is located on cytotoxic T lymphocytes, and may play a role in regulating immune response.[2]

In 2012, ipilimumab was approved by Health Canada for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.[1] In September 2014, it was further approved as first line therapy of unresectable or metastatic melanoma.[2] The Health Canada-recommended dose for ipilimumab in both previously treated and untreated patients is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of four doses.[1]

Ipilimumab, at a dose of 3 mg/kg, has been approved as first-line and second-line therapy of patients with advanced unresectable melanoma by the US Food and Drug Administration (FDA) and European Medicine Agency (EMA).[22-24] Currently, the manufacturer is requesting funding for ipilimumab 3 mg/kg as first line treatment of advanced melanoma.

2.1.2 Objectives and Scope of pCODR Review

To evaluate the effect of ipilimumab, either alone or in combination, on patient outcomes compared to commonly used therapies, placebo, or best supportive care in the treatment of patients with unresectable melanoma (stage III or stage IV) who had no previous systemic therapy.

See Section 6.2.1 for more details on the pCODR systematic review protocol.

2.1.3 Highlights of Evidence in the Systematic Review

Trial Characteristics

One multinational, randomized, double-blind trial was identified that investigated the use of ipilimumab plus dacarbazine compared to placebo plus dacarbazine in patients with previously untreated unresectable stage III or stage IV melanoma (Study ID: CA184-024). A summary of key trial characteristics can be found in Table 1.

The baseline demographic and disease characteristics of the study population were balanced between the two treatment groups. The mean age was 57.5 years in the intervention group and 56.4 years in the comparison group. The majority of the patients (approximately 71% in both groups) had ECOG performance status of 0 (the patients were fully active and able to carry on all pre-disease performance without restriction).

Out of the 502 patients who started on the trial, 414 (82.5%) had died by the cut-off date for data analysis in March 2011. Eleven patients from the intervention group and six patients from the comparison group were still on treatment. The median follow-up was 54 months.

Progression-free survival (PFS) was the original primary endpoint in this trial, but it was changed to overall survival (OS) in October 2008, before the treatment assignments were revealed. OS was a secondary endpoint prior to the change. The manufacturer indicated that emerging data from other ipilimumab trials suggested that the conventional definitions of disease progression and response incompletely reflect overall survival among patients who appear to have a long-term benefit. This amendment was approved by the FDA in October 2008. There was no change in the pre-determined sample size based on progression-free survival.

Health-related quality of life (HRQOL) data were briefly reported in an abstract.[4] Interpretation of those data was difficult given that insufficient details of the HRQOL data as well as the methods used to collect the data were reported and given the lack of a validated minimal clinically important difference (MCID) to determine the clinical importance of the study results.

Patients with brain metastases was identified as a subgroup of interest for this review; however, in the CA184-024 Study, one of the exclusion criteria was brain metastasis. Therefore, extrapolation of the study results to patients with brain metastases should be done with caution.

The included study evaluated the clinical effectiveness and safety of ipilimumab at 10 mg/kg, while the manufacturer is requesting reimbursement for ipilimumab at 3 mg/kg. The pivotal question is whether the results from one dose are generalizable to another dose.

Table 1. Summary of Trial Characteristics of Study CA184-024[3]

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
Study CA184-024 Multinational study conducted in countries	Age ≥ 18 years, previous untreated (with systemic therapy) stage III or stage IV melanoma,	Ipi 10 mg/kg + DTIC 850 mg/m^2 (n=250) Or	<u>Primary</u> Overall survival <u>Secondary</u>

Trial Design	Key Inclusion Criteria	Intervention and Comparator	Outcomes
in North America and Europe. Patients enrolled from August 2006 to January 2008 Enrolled: n=681 Randomized: n=502 Double-blind, placebo-controlled, phase 3 RCT Randomized in a 1:1 ratio Randomization was stratified by: A) metastasis stage (M0, M1a, M1b, or M1c) B) study site C) ECOG performance status (0 or 1) Funded by: Bristol-Myers Squibb	ECOG PS 0 or 1, life expectancy ≥ 16 weeks. <u>**Exclusion criteria:**</u> Received any prior treatment for metastatic disease, concomitant treatment with immunosuppressive agents or long-term use of systemic glucocorticoids, brain metastasis, primary ocular or mucosal melanoma or autoimmune disease.	Placebo + DTIC 850 mg/m^2 (n=252) Note: study drugs were administered at week-1, 4, 7 and 10 for a total of 4 treatments; After week 10, patients received DTIC alone every 3 weeks till week 22; starting at Week 24, patients with stable disease or had objective response in previous period received Ipi or placebo every 12 weeks until disease progress, development of toxic effects or the end of the study.	Progression-free survival HRQOL Best overall response rate (CP + PR) Disease control rate Time to response Duration of response Safety

CR= complete response; DB= double-blind; DTIC= dacarbazine; ECOG= Eastern Cooperative Oncology Group; HRQOL=health-related quality of life; Ipi= ipilimumab; PR= partial response; PS=performance status; RCT= randomized controlled trial

Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the intention-to-treat (ITT) population, comprised of all randomized patients (n=502). The safety population consisted of all randomized patients who had received at least one dose of their assigned treatment (n=498). A summary of key efficacy and harms outcomes can be found in Table 2 and Table 3 below. Outcomes that were important to patients, based on input from the Melanoma Network of Canada (a patient advocacy group), included OS, HRQOL and safety, in particular immune-related adverse events.

A statistically significant improvement in median OS was observed for ipilimumab plus dacarbazine (11.2 months) compared with placebo plus dacarbazine (9.1 months), with a hazard ratio (HR) of 0.72 (95% confidence interval [CI]: 0.59 to 0.87, $p < 0.001$).

A statistically significant difference in PFS was found for ipilimumab plus dacarbazine compared with placebo plus dacarbazine (Table 2).

HRQOL was assessed using the Global Health Status (GHS) scale and symptom scales of the EORTC-QLQ-C30. The results were reported in an abstract only. Patients in both groups reported a declined average GHS scores from baseline (ipilimumab +

dacarbazine: -6.5; placebo + dacarbazine: -10.0), indicating worsened health status; however, no p-value or 95% CI was reported for this comparison. No further details regarding the HRQOL assessment were provided in this abstract. Interpretation of the QOL data was challenging, due to the limited available data in the abstract and a lack of MCID of the employed HRQOL assessment tool.

The difference in best overall response (complete response + partial response) was not statistically significant between the two groups: 15.2% in the ipilimumab plus dacarbazine group versus 10.3% in the placebo plus dacarbazine group (p=0.09).

Table 2. Summary of Key Efficacy Outcomes from Study CA184-024[3,25]

Efficacy	Intervention	Results	HR (95% CI)	p-value
OS, median (95% CI), months	Ipi + DTIC	11.2 (9.4 - 13.6)	0.72 (0.59 - 0.87)	< 0.001
	PL + DTIC	9.1 (7.8 - 10.5)		
PFS, median (95% CI), months	Ipi + DTIC	2.76 (2.63 - 3.29)	0.76 (0.63 - 0.93)	0.006
	PL + DTIC	2.60 (2.56 - 2.66)		
Best overall response, n (%, 95% CI)	Ipi + DTIC	38 (15.2, 11.0 - 20.3) CR: 4 (1.6) PR: 34 (13.6)	NR	0.09
	PL + DTIC	26 (10.3, 6.9 - 14.8) CR: 2 (0.8) PR: 24 (9.5)		

CI= confidence interval; CR= complete response; DTIC= dacarbazine; HR= hazard ratio; Ipi= ipilimumab; NR= not reported; OS=overall survival; PFS=progression-free survival; PL= placebo; PR= partial response

In safety analyses, statistical comparisons for adverse event rates between the two treatment groups were not performed. A similar proportion of patients in the two treatment groups experienced at least one adverse event of any Grade (Table 3). Patients who received ipilimumab reported more diarrhea, dermatologic disorders, elevated liver enzymes, pyrexia and chills.

More patients treated with ipilimumab plus dacarbazine complained about serious adverse events (≥ Grade 3 toxicities), 56.3% versus 27.5%, respectively.

Immune-related adverse events occurred in a higher proportion of patients treated with ipilimumab plus dacarbazine, 77.7% versus 38.2%, respectively. The most common immune-related adverse events included dermatologic disorders, diarrhea and elevated ALT/AST.

Withdrawals due to adverse events occurred in 38.5% of patients treated with ipilimumab plus dacarbazine and 8% of those treated with placebo plus dacarbazine.

Table 3. Summary of Key Harm Outcomes in Study CA184-024[3,26]

Harms, n (%)	Ipi + DTIC N=247	PL + DTIC N=251
AE	244 (98.8)	236 (94.0)
SAE (Grade ≥3)	139 (56.3)	69 (27.5)
Immune-related AE	192 (77.7)	96 (38.2)
WDAE	95 (38.5)	20 (8.0)
AE=adverse event; DTIC=dacarbazine; Ipi=ipilimumab; PL=placebo; SAE=serious adverse event; WDAE=withdrawal due to adverse event		

2.1.4 Comparison with Other Literature

Relevant literature identified jointly by the pCODR Clinical Guidance Panel and Methods Team and providing supporting information to the systematic review is summarized below. This information has not been systematically reviewed.

The National Institute for Health and Care Excellence (NICE) issued a technology appraisal review on ipilimumab as first line therapy in patients with previously untreated, unresectable melanoma in 2014.[27] Due to a lack of trials directly comparing ipilimumab 3 mg/kg monotherapy with the appropriate comparators, such as dacarbazine or vemurafenib, clinical evidence from RCTs with a different population, different study drugs and different primary endpoints was evaluated. An indirect comparison approach was adopted to assess the effectiveness of ipilimumab 3 mg/kg compared with dacarbaine, vemurafenib or dabrafenib. Furthermore, data from two retrospective, observational trials (investigating ipilimumab 3 mg/kg monotherapy) and one pooled analysis (enrolling 78 chemo-naïve patients treated with ipilimumab 3 mg/kg) were examined.

Ipilimumab 3 mg/kg was compared with ipilimumab 10 mg/kg used as second line therapy or a mix of first/second line therapy (Studies CA184-004 and CA184-022) in 54 chemo-naïve patients, and the results suggested comparable survival benefit between these two doses, while Grade 3 or 4 adverse events were more common with the higher dose. Data from Study CA184-024 was discussed in this review as well, and the long-term safety data showed that the safety profile of ipilimumab was similar in patients during the induction period and in patients having treatment for longer than two years. The NICE review stated that the efficacy of ipilimumab 3 mg/kg alone has been established in patients with previously treated melanoma and the baseline characteristics of the patients included in the pivotal studies in previously treated and previously untreated patients were similar; in addition, there was no biological rationale to suspect a different activity for ipilimumab treatment in the first- or later-line setting.

The NICE report recommends ipilimumab as an option for treating adults with previously untreated unresectable or metastatic melanoma, within its marketing authorisation.

Based on the ESMO guideline, patients with unresectable or metastatic melanoma and BRAF mutation, a BRAF-inhibitor such as vemurafenib is recommended as the first line therapy.[22] However, they noted that the optimal sequencing of antineoplastic agents in this patient population has not been well established. A multicenter study examining the sequential treatment with ipilimumab and vemurafenib was conducted in 855 patients enrolled in an Italian expanded access

programme.[28] These patients either failed prior systemic therapy or were intolerant to at least one systemic treatment. Among the 855 patients, 173 had positive BRAF status and 93 (53.7%) of them were treated sequentially with both treatments: 48 patients received vemurafenib (doses and treatment duration were not specified) upon disease progression with ipilimumab, while 45 patients received ipilimumab (3 mg/kg intravenously every 3 weeks for 4 doses) upon disease progression with vemurafenib. The median overall survival was 14.5 months (95% CI 11.1 to 17.9) for the first group and 9.7 months (95% CI 4.6 to 14.9) for the second group, p = 0.01. These preliminary findings suggested that in patients with unresectable or metastatic melanoma and BRAF mutation, to initiate the sequential treatment with ipilimumab may be associated with better survival compared with the reverse sequence. However, the validity of the study results cannot be assessed due to the nature of the study design (small observational study) and the insufficient details presented in this abstract. Furthermore, the effects of the sequential treatment need to be evaluated in patients without prior systemic therapy, preferably in a larger prospective study.

On April 18, 2012, the pCODR Expert Review Committee (pERC) recommended funding ipilimumab, conditional on the cost-effectiveness being improved to an acceptable level, in patients with unresectable Stage III or Stage IV melanoma who have received prior systemic therapy.[5] pERC determined that there is a net clinical benefit associated with ipilimumab, based on clinically meaningful improvements in both relative and absolute measures of overall survival in favour of ipilimumab. The key evidence was a randomized controlled trial comparing ipilimumab 3 mg/kg plus gp100 vaccine versus ipilimumab 3 mg/kg plus placebo versus gp100 plus placebo. Median overall survival was statistically significantly higher in the ipilimumab plus gp100 group (10.0 months) compared with the gp100 plus placebo group (6.4 months), with a hazard ratio of 0.68 (95% CI 0.55 to 0.85; p<0.001). The median overall survival was 10.1 months in the ipilimumab plus placebo arm, which was similar to the ipilimumab plus gp100 arm. In addition, the proportion of patients alive after one year was similar for the ipilimumab plus gp100 group and for the ipilimumab plus placebo group (43.5% and 45.6%, respectively) and higher than the proportion of patients in the placebo plus gp100 group (25.3%). A similar trend was observed in the proportion of patients surviving at two years (21.6% and 23.5% versus 13.7%, respectively). pERC noted that there were serious immune-related side effects associated with ipilimumab but that these adverse events are manageable by specialists with the support of other therapies directed at these symptoms and close patient monitoring of adverse events. pERC considered that patients receiving ipilimumab should be managed in specialized cancer treatment centres with the medical expertise required to manage these side effects. However, pERC also noted that this could impact the feasibility of implementing ipilimumab treatment as there would likely be additional costs associated with patient management and for adverse event monitoring.

2.1.5 Summary of Supplemental Questions

Question 1: Comparison of the clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma.

No evidence was found in the literature on the comparative efficacy and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma.

See section 7.1 for more information.

Question 2: The clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose used as first line therapy for patients with unresectable or metastatic melanoma.

A pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients who were included in four RCTs (MDX010-20, MDX010-08, CA184-004, and CA184-022) and two ongoing retrospective observational studies (CA184-332, and CA184-338) investigated the use of 3mg/kg ipilimumab monotherapy in patients with unresectable or metastatic melanoma. The pooled analysis included 78 patients while studies CA184-332 and CA184-338 included 90 and 120 patients respectively. There were some clinically relevant differences in the baseline characteristics (such as ECOG performance status, presence of brain metastases, disease stage and duration of melanoma) between the three studies. Median overall survival was 13.47 months in the pooled analysis, while it was 11.5 and 14.3 in studies CA184-332 and CA184-338 respectively. The one year survival rate was 54.1%, 49.4%, and 59.5% in the pooled analysis, study CA184-332, and study CA184-338, respectively. The two and three year survival rates in the pooled analysis were 31.6% and 23.7%, respectively. The adverse events were reported only in the pooled analysis and study CA184-338. Immune-related adverse events of any grade occurred in 84% and 52.5% of patients included in the pooled analysis and study CA184-338, respectively, with Grade 3 or higher immune-related adverse events occurred 8.0% and 13.3% of patients in the pooled analysis and study CA184-338, respectively. Results reported in the pooled analysis might be unreliable due to the many limitations in that analysis. In addition, results from the two observational studies should be interpreted with caution due to the high risk of bias associated with their design.

See section 7.2 for more information.

2.1.6 Other Considerations

Patient Advocacy Group Input

From a patient perspective, first line access to ipilimumab would be beneficial to patients as response rates for current therapies remain limited. According to a survey, 26% of respondents indicated that they had some regression or stabilization of disease for less than 3 months with current therapies. However, none of the respondents indicated a durable response beyond 6 months before they were switched to another therapy. According to the Melanoma Network of Canada, 94% of respondents who received the full course of treatment with ipilimumab reported durable response, and specifically 83% respondents reported having a durable response over two (2) years. While ipilimumab has been known to cause significant adverse side effects (e.g., rash, potentially deadly colitis, fatigue, headaches), most of the respondents stated they would be willing to take all the necessary steps to manage those side-effects given that other current therapies often have severe and lasting side effects as well, including liver failure.

PAG Input

Input on the ipilimumab review was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. PAG identified that providing a more effective treatment upfront in the first-line setting eliminates the use of dacarbazine (generally ineffective), as the patients

eventually are treated with ipilimumab in the second line setting. From a PAG perspective, dosing issues with ipilimumab would be of greatest importance. PAG requires clarity on clinical effectiveness of ipilimumab 3 mg/kg for first-line therapy over the 10 mg/kg dose where there is data. Doses of 3 mg/kg versus 10 mg/kg, drug wastage and the number of patients requiring re-inductions could have an impact on the overall cost-effectiveness of ipilimumab and would need to be considered in the economic analysis.

Other

The final Health Canada product monograph for ipilimumab (Yervoy) provided by the manufacturer (Bristol-Myers Squibb [BMS] Canada) provides the following warnings:[2]

Yervoy can cause severe and fatal immune-mediated adverse reactions, including enterocolitis, intestinal perforation, hepatitis, dermatitis, neuropathy, endocrinopathy, as well as toxcities in other organ systems. While most of these reactions occurred during the induction period, onset months after the last dose has been reported.

For severe immune-mediated adverse reactions, Yervoy should be permanently discontinued; systemic high-dose corticosteroids with or without additional immunosuppressive therapy may be required for treatment.

The monograph provides specific advice on managing the above adverse events. That advice includes when to discontinue ipilimumab and the administration of corticosteroids. The monograph notes that some patients with moderate to severe immune-mediated enterocolitis received infliximab following an inadequate response to corticosteroids.

2.2 Interpretation and Guidance

Burden of Illness

It is estimated that 6,500 Canadians will be diagnosed with melanoma in 2014, and approximately 1050 patients will die of melanoma in 2014. The majority of patients will present with early stage disease and be cured by surgery but those who present with advanced disease or who subsequently relapse, the prognosis remains poor. Although the number of patients developing melanoma is small compared to breast cancer or lung cancer, melanoma remains the number one cause of cancer death in women age 25 to 35, and causes a disproportionate number of years of life lost. Unresectable stage III or stage IV melanoma carries a poor prognosis with a median survival of 6.2 months and only 25.5% of patients surviving to one year, although recently new therapies have improved the prognosis and a small proportion are experiencing long term survival.

Effectiveness

One multinational, randomized, double-blind trial was identified that investigated the use of ipilimumab plus dacarbazine compared to placebo plus dacarbazine in patients with previously untreated unresectable stage III or stage IV melanoma (the CA184-024 study).[3] The trial population excluded patients with CNS metastases, ocular or mucosal melanoma,

patients on chronic steroids or immune suppressive agents or with a history of autoimmune disease. The patient demographics were well balanced between the two arms. Patients were accrued between August 2006 and January 2008. At a median follow up of 54 months 82.5% of the patients had died as of the data cutoff in March of 2011. Overall survival was statistically significantly higher in the dacarbazine + ipilimumab arm (median 11.2 months) versus the dacarbazine + placebo arm (median 9.1 months; p<0.001). In addition, PFS was also statistically significantly higher in the ipilimumab + dacarbazine group versus the dacarbazine + placebo group (2.76 months. versus 2.6 months, p = 0.006). The one, two, three and four year survivals were 47.5, 28.8, 21.2 and 19 percent in the ipilimumab containing arm respectively versus 36.4, 17.5, 12.1, and 9.6 percent for the dacarbazine + placebo arm respectively. The study met its primary endpoint of improving overall survival. More importantly the survival curve separated early and at 3-years was 20.8% in the ipilimumab plus dacarbazine arm compared with 12.2% in the dacarbazine plus placebo arm. As immuno-oncology has become more mainstream it has become apparent that clinical endpoints have to change and classic chemotherapy response criteria have to be modified. Thus the immune-related response criteria (irRC) and 1, 2 and 3 year survivals have become accepted as more meaningful endpoints in immune checkpoint inhibitor therapy. PFS is not a good surrogate endpoint and thus the primary endpoint of the trial was changed based on emerging evidence during the trial period. Some patients can progress with either pseudo-progression or true progression, and still experience a later response and long term survival.

The choice of dose in the CA184-024 study was due to the fact that most of the earlier trials of ipilimumab in metastatic melanoma patients had used a dose of 10 mg/kg for four induction doses followed by a maintenance period. Therefore, the first-line registration trial (CA184-024), which is the primary study in this review, used a dose of 10 mg/kg of ipilimumab, in combination with dacarbazine which was the standard of care in the first-line treatment of metastatic melanoma at that time. The FDA approval mandated that the manufacturer conduct a trial of ipilimumab 10 mg/kg versus 3 mg/kg until disease progression in patients with previously untreated or previously treated advanced melanoma to see if dose had an effect on outcome. This trial has completed accrual and results are expected in early 2016. More recently the European Union and subsequently Health Canada approved ipilimumab in untreated metastatic melanoma patients at a dose of 3 mg/kg for four doses.

There are no randomized studies comparing ipilimumab at a dose of 3 mg/kg for four doses versus dacarbazine in untreated metastatic melanoma patients or versus ipilimumab at 10 mg/kg. Evidence from one pooled analysis of four RCTs and from two retrospective observational studies was used to understand the effectiveness of ipilimumab at 3 mg/kg in this group of patients.[6-8] Notwithstanding the limitations of making comparisons across studies, the survival curves in untreated melanoma patients for patients who received ipilimumab at 3 mg/kg in the 1st-line setting are similar to those who receive it as subsequent therapy. Dacarbazine is largely felt to be only very modestly effective in inducing responses in melanoma, as response rates have ranged from 7 to 10% in randomized studies.[14-18] There is no evidence that it improves either quality of life or overall survival, and less than 3% of patients getting long-term survival benefit.[14-18] Most patients only receive one or two cycles of dacarbazine and are then switched to ipilimumab as the median PFS of Dacarbazine is only 6 weeks (i.e. 1st assessment). In fact, many melanoma oncologists consider dacarbazine an ineffective treatment with respect to overall survival.

Safety

Ipilimumab is associated with well-defined immune related adverse events. In the CA184-024 study, ipilimumab + dacarbazine was associated with a higher rate of adverse events that led to withdrawal than dacarbazine + placebo (38.5% versus 8.0%, respectively), with most being immune-related. Colitis is the most frequent grade III/IV immune-related AE, ranging from 5 to 7% at a dose of 3 mg/kg. Rarely, colitis/diarrhea will be refractory to high dose steroids and will require infliximab at a dose of 5 mg/kg. Usually one dose suffices. Rare patients will require a colectomy (<1%). In the CA184-024 study when dacarbazine was combined with ipilimumab there was a 20% incidence of hepatotoxity as opposed to the previously reported rate of 2% when ipilimumab was given as a single agent at a dose of 3 mg kg. There were no patient deaths from hepatotoxicity and all cases reversed with either cessation of therapy or with the use of immunosuppressive therapy such as high dose glucocorticoids. 77.7% of patients on the CA184-024 study reported an immune-related adverse event on the ipilimumab + DTIC arm with 41.7% reporting an immune-related adverse event of grade III or greater versus an immune-related adverse event rate of 38.2% in the DTIC + placebo arm (6% with an immune-related adverse event of grade III or greater). The most common adverse event is skin with the majority being Grade I/II. Although the CA184-024 study had a higher rate of withdrawal due to adverse events in the group that received ipilimumab +dacarbazine, most of those were immune-related adverse events which are now better understood and are rapidly reversible with the use of treatment algorithms. The exception to rapid reversibility of immune-related adverse events are the endocrine side effects, which generally require several weeks to months to reverse and about 46% of patients will require long term steroid replacement.

Dacarbazine has a higher incidence of nausea, vomiting and myelosuppression than ipilimumab.

Need

The survival of metastatic melanoma patients had not changed for several decades, and prior to 2010 there was no evidence that any systemic treatment had any impact on overall survival. Dacarbazine remained the mainstay of treatment up until 2011, with select centres offering high dose IL-2. The first drug trial to report an improvement in overall survival was the MDX-020 trial of ipilimumab +/- gp100 versus gp100 alone in pre-treated unresectable stage III/IV melanoma patients. This led to the approval of ipilimumab in either the 1st line or subsequent line of therapy by the FDA in metastatic melanoma patients, at a dose of 3 mg/kg every 3 weeks for four doses. Both Health Canada and the European Medicines Agency (EMA) subsequently approved Ipilimumab 3 mg/kg in patients who had failed a prior treatment regimen in metastatic melanoma. pERC recommended the funding of ipilimumab at 3 mg/kg in the 2nd-line setting, conditional on the cost-effectiveness being improved to an acceptable level.[5]

There is no randomized evidence that chemotherapy offers any benefits in either quality of life or in overall survival, with more modern response rates ranging from 7 to 10%, and less than 2% five year survival.[12,14-18] Dacarbazine is felt to be only very modestly effective in inducing responses.

BRAF Mutation-Positive Advanced Melanoma

Most patients with BRAF mutated metastatic melanoma are now being treated with a BRAF inhibitor as 1st line therapy. There are no randomized studies comparing upfront treatment of a BRAF inhibitor such as vemurafenib or dabrafenib versus ipilimumab in treatment naïve patients. Treatment resistance to a BRAF inhibitor is almost always inevitable and

the median duration of response to a BRAF inhibitor is less than 7 months. BRAF inhibitor therapy is given as an oral medication twice a day and is associated with significant toxicities including but not limited to pyrexia, arthralgias, skin rash, photosensitivity, fatigue and nausea. Currently the recommended treatment using a BRAF inhibitor is to treat until disease progression or until unacceptable toxicity. Ipilimumab is given as four 90 minute infusions over a period of 12 weeks and approximately 20% of patients experience long term survival and do not require further treatment. 38% of patients versus 8% of patients withdrew from the CA184-024 study due to adverse events, but adverse events are almost always reversible (most reversing fully within 4 to 8 weeks).

Approximately 30 per cent of patients treated with a BRAF inhibitor will experience an explosive recurrence and many will not be candidates to receive ipilimumab, due to a rapid decline in performance status or the development of CNS metastases requiring steroid use. There is much debate on how to sequence BRAF therapy with ipilimumab and many researchers are now moving in the direction of ipilimumab in patients with good performance status and slower progressing tumors, while BRAF inhibitors are reserved for those patients with a poorer performance status and more rapidly progressing tumors. A retrospective review in 855 patients treated on the EAP program in Italy suggested improved survival in patients who received ipilimumab prior to a BRAF inhibitor as opposed to ipilimumab after a BRAF inhibitor (45 patients versus 48 patients).[28] Again this was a retrospective review and numbers were small.

There are ongoing studies examining the appropriate sequencing of therapy for patients with advanced melanoma who have a BRAF mutation. Results are not expected for two years.

2.3 Conclusions

The Clinical Guidance Panel concluded that there is an overall net clinical benefit to ipilimumab monotherapy 3 mg/kg in the first-line treatment of patients with unresectable or metastatic (i.e., Stage III-IV) melanoma with ECOG performance status of 0 or 1 and who are not receiving immunosuppressive therapy. This conclusion was based on several factors:

- One well-conducted randomized controlled trial that demonstrated a clear benefit in overall survival and progression free survival in favour of ipilimumab 10 mg/kg plus dacarbazine compared to dacarbazine plus placebo.
- A pooled data set from four RCTs, as well as two observational studies that provided supporting evidence of the effectiveness of the 3 mg/kg dose in the first-line setting.

The Clinical Guidance Panel also considered that from a clinical perspective:

- The Health Canada approved dose in the first-line setting is 3 mg/kg for four doses, which is based on the second line study of ipilimumab 3 mg/kg versus gp100 vaccine.
- The optimal dose in the first line setting is being addressed by the CA184-169 study which is comparing the 10 mg/kg dose versus the 3 mg/kg dose in the first-line setting. The results of that study are expected in the first quarter of 2016, and until that time, the CGP agreed that there is no reason or evidence to expect that Ipilimumab 3 mg/kg would be any less effective in the first line than in the second line.

- Most Canadian patients treated in the first-line setting with dacarbazine receive ipilimumab in the second line, and the majority of those patients are not receiving an overall survival benefit from dacarbazine.
- Ipilimumab should also be available for the first line treatment of patients with BRAF mutation positive melanoma who have low bulk disease, good performance status and whose disease is not progressing rapidly, as these patients can achieve a long term response from treatment with ipilimumab.

3 BACKGROUND CLINICAL INFORMATION

This section was prepared by the pCODR Melanoma Clinical Guidance Panel. It is not based on a systematic review of the relevant literature.

1.1 Description of the Condition

Melanoma is a malignancy of melanocytes which are distributed throughout the body. Although primary melanoma can occur in a variety of sites, skin is the most common, comprising 95% of cases. In Canada 6500 new cases of primary melanoma were diagnosed in 2014 and approximately 1100 individuals will die from melanoma each year.[9] The incidence of melanoma has been steadily increasing over the past 60 years. Currently the lifetime probability of developing melanoma for women is 1 in 85 and for men is 1 in 67.[29]

Staging of melanoma is based on the current American Joint Committee on Cancer (AJCC) 7th edition classification.[30] The tumour characteristics principally involve the Breslow height, presence or absence of ulceration, and mitotic rate. The detection of microscopic and macroscopic lymph node involvement, lactate dehydrogenase (LDH) and sites of metastatic disease are also incorporated in the staging classification. All of these prognostic factors have important impact upon patient outcomes and also serve to guide management decisions.

1.2 Accepted Clinical Practice

In early stage melanoma, cures are commonly achieved with surgery alone. The primary site is excised with appropriate surgical margins. Depending upon the T stage and location of the primary, a sentinel node biopsy (SNB) may be performed to assess regional nodal status. If the sentinel node contains metastatic disease, then a completion lymph node dissection of the regional basin is often performed. This additional procedure has been shown to reduce the risk of regional occurrence.[31]

Although only 5% of patients present with metastatic disease, the majority of patients who ultimately die from melanoma will have developed recurrent and/or distant disease. About 1/3 of patients with early stage melanoma will develop metastasis; however, 1/2 of the patients with nodal disease will recur and likely die from metastatic disease.[32] Brain metastases are common and occur in up to 75% of patients with overt metastatic disease. In highly selected patients with metastatic disease, clinical benefit may occur from surgical resection of known sites of disease and may result in long term survival. Unfortunately, most metastatic patients are not candidates for surgical resection and systemic treatment is the only alternative. The prognosis for these patients remains poor. The median survival has been 6-9 months with 5 year survival of approximately 6%.[10] With the more recent introduction of new and effective treatments, a significant improvement in survival is being realized.

Over the past 30 years, standard first-line systemic treatment has been dacarbazine.[31,33] Although this alkylating agent is generally well tolerated, response rates are low and complete responses are rare.[34] In comparative studies the use of dacarbazine has not been shown to improve survival in metastatic melanoma.[14-18] Temozolomide, an oral imidazole

tetrazene derivative of dacarbazine, is activated to the active metabolite of dacarbazine, and has also been commonly used. In phase III trials comparing temozolomide directly to dacarbazine, similar progression free and overall survival rates were observed.[35-37] In the early 1990s the FDA approved the use of high dose Interleukin-2 based on phase II data showing a response rate of 16% and a durable complete response of 5%.[38,39] Unfortunately, high dose Interleukin-2 is associated with severe toxicity and requires intense cardiac monitoring and hemodynamic support. Interleukin-2 is largely unavailable in Canada.

A wide spectrum of chemotherapeutic and immunological treatments has been explored in patients with metastatic melanoma. Until recently limited to no success has been achieved. It has become increasingly apparent that melanoma represents a heterogeneous group of diseases. A variety of genetic abnormalities exists within primary melanomas and their respective metastases and influence both cellular proliferation and ultimately response to therapy.[40-42] The MAP kinase signaling pathway appears to be a key regulatory mechanism for cell growth and differentiation in melanoma.[43] Mutations in the BRAF protein within this pathway can result in uncontrolled cellular proliferation and increased potential for metastatic spread.[44] Approximately 50% of human melanomas appear to have an activated mutation in BRAF which has become a key target for inhibition and potential therapeutic site.[45]

Vemurafenib is a BRAF inhibitor that selectively targets the V600E mutation approved by Health Canada in February 2012.[46-48] In a randomized phase III study, vemurafenib use led to a relative reduction of 63% in risk of death and 74% reduction in the risk of tumor progression. The overall response rate was 48%.[12] Vemurafenib has become the first-line treatment of advanced unresectable melanoma in patients harboring the V600 BRAF mutation. Dabrafenib is a similar targeted oral BRAF inhibitor which has a slightly different toxicity profile and which is similarly efficacious in the therapy of patients with BRAF mutant metastatic melanoma.[49-52] Unfortunately, for those patients who are BRAF positive, resistance to the BRAF inhibitors ultimately develops and they experience rapid and often unrelenting disease progression. In the remaining 50% of the patients who do not have BRAF mutation, the BRAF inhibitors are uniformly ineffective and additional therapies are needed.

1.3 Evidence-Based Considerations for a Funding Population

Ipilimumab is a monoclonal antibody that binds to and blocks the cytotoxic T-lymphocyte associated antigen 4 (CTLA4) located on cytotoxic T-lymphocytes. CTLA4 appears to play an important role in the regulation of the immune response.[53,54] In 2012, Ipilimumab received a Health Canada indication for treatment of unresectable or metastatic melanoma in patients who have failed or did not tolerate other systemic therapy for advanced disease. Since that time it has been widely used across Canada as second line therapy given at a dose of 3 mg per kg given every 3 weeks for a total of 4 doses. Provision for re-induction has been provided in patients who progress following a response to ipilimumab treatment.

The initial approval was principally based upon the findings of a multi-center, double blind placebo controlled trial consisting of three treatment arms randomly assigned 3:1:1: ipilimumab 3 mg/kg + cancer vaccine GP100, ipilimumab alone, GP100 alone.[11] The study

demonstrated an improvement on overall survival (HR 0.66) in the two ipilimumab containing arms compared to GP100 alone. Median overall survival for ipilimumab arms was 10 months compared to 6.4 months in GP100 alone arm. Adverse events were primarily immune related which included diarrhea/colitis, and endocrine problems. Fatigue, rash and anorexia were common but were seldom grade 3 or greater. The study represents the first randomized controlled trial which demonstrated an improvement in survival in patients with metastatic disease. In 2011, Robert and colleagues reported on a randomized controlled trial comparing Ipilimumab 10 mg/kg + dacarbazine 850 mg/m2 versus dacarbazine alone in patients who were previously untreated.[3] Overall survival was improved in the Ipilimumab containing arm (HR 0.72) and appeared to extend out to 3 years. The median survival was 11.2 months in the Ipilimumab arm compared to 9.1 months in the dacarbazine arm. Immune related events were observed in the Ipilimumab arm and grade 3 or 4 adverse events were more common (56.3% vs 27.5%). Rates of elevated liver enzymes appeared to be higher than observed in other studies in which Ipilimumab was used alone. Although the progression free survival and overall survival were similar in these trials, the relative impact of the 3 and 10 mg doses of ipilimumab which were used cannot be directly assessed. Furthermore the positive or negative effect on outcomes and toxicity which the GP100 or dacarbazine had within the combination arms of each trial also remains uncertain.

1.4 Other Patient Populations in Whom the Drug May Be Used

A multi-centre randomized trial study which compares ipilimumab at 3 mg/kg versus 10 mg/kg in patients with unresectable/metastatic disease has completed accrual and the results have not yet been reported. There are also on-going studies specifically addressing the impact on patients with brain metastases and include combination with radiotherapy. Ipilimumab is currently being evaluated in patients who are at high risk for recurrence and is being compared to alpha-interferon, as well as in combination with other immunotherapies.

Potential indications for ipilimumab are also being explored in other malignancies such as lung, head and neck, prostate, colon and pancreas.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

One patient advocacy group, Melanoma Network of Canada (MNC), provided input on ipilimumab (Yervoy) for the first-line treatment of adult patients with advanced (unresectable or metastatic) melanoma, and their input is summarized below.

MNC conducted an online survey of patients from across Canada through a confidential online survey. Patients were recruited through a generic eblast requesting input from those patients that had been specifically treated with ipilimumab. The survey had a combination of multiple choice, rating and comment open ended questions. MNC reported a total of 18 patients who responded to the survey from 7 different provinces.

From a patient perspective, first line access to ipilimumab would be beneficial to patients as response rates for current therapies remain limited. According to the survey, 26% of respondents indicated that they had some regression or stabilization of disease for less than 3 months with current therapies. However, none of the respondents indicated a durable response beyond 6 months, before they were switched to another therapy. According to MNC, 94% of respondents who received the full course of treatment with ipilimumab reported durable response, and specifically 83% respondents reported having a durable response over two (2) years. While ipilimumab has been known to cause significant adverse side effects (e.g., rash, potentially deadly colitis, fatigue, headaches), most of the respondents stated they would be willing to take all the necessary steps to manage those side-effects given that other current therapies often have severe and lasting side effects as well, including liver failure.

Please see below for a summary of specific input received from the patient advocacy group. Quotes are reproduced as they appeared in the survey, with no modifications made for spelling, punctuation or grammar. The statistical data that was reported have also been reproduced as is according to the submission and have not been corrected.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Advanced Melanoma

According to MNC, 100% of survey respondents experienced pain and fatigue; 94% experienced loss of appetite, with 83% indicating some depression and loss of regular sleep. Based on prior surveys that were submitted to pCODR in the past, MNC found that key experiences for patients with melanoma included detrimental impact on their quality of life, loss of employment income, as well as negative impacts on caregiver and family related stresses. Below is a summary table of the key adverse physical effect or symptoms that respondents reported in the online survey.

Adverse physical effect or symptom related to melanoma	% of Respondents indicating symptom	N (# of Respondents who responded)
pain	100	18
nausea	61	11
loss of appetite	94	17
headaches	78	14
loss of mobility or immobility	50	9
neuropathy	61	11
fatigue	100	18
depression, anxiety or post-traumatic stress	83	15

Adverse physical effect or symptom related to melanoma	% of Respondents indicating symptom	N (# of Respondents who responded)
sleep deprivation	83	15
cognitive impairment	39	7
general weakness	56	10

4.1.2 Patients' Experiences with Current Therapy for Advanced Melanoma

MNC reported that there have been several drug therapies approved in the last two years for metastatic melanoma. According to the online survey, 100% of respondents had been treated with some other form of therapy, prior to receiving ipilimumab. Of the 18 respondents, 78% of respondents had been treated with dacarbazine; 67% with interferon. When asked if they had had a positive response to the therapy, in terms of regression of disease or stabilization, it was reported that 26% of respondents indicated that they had some regression or stabilization of disease for less than 3 months. However, none of the respondents indicated a durable response beyond 6 months, before they were switched to another therapy. Below is a summary table that sets out the current therapy that the respondents reported receiving.

Therapy Name:	# of respondents indicating treatment (total=18)	% of respondents
Dacarbazine	14	78
Interferon	12	67
Zelboraf	2	11
Mekinist	0	0
Tafinlar	1	5
Docetaxel	1	5

According to MNC, 78% of the respondents indicated that the therapies listed above had done little to alleviate adverse symptoms and in the case of chemotherapy, had created more adverse side effects of fatigue, nausea, cognitive impairment, and hair loss. In particular, respondents who received Zelboraf and Tafinlar indicated almost immediate regression of disease, but also experienced rash, fatigue, sun sensitivity and intolerance or progression of disease that required them to stop that therapy.

MNC asserted that oncologists are required to use a first line therapy that has been proven to be highly ineffective for most melanoma patients. As an example, MNC found that response rates for current therapies such as dacarbazine have generally been under 15%. While treatment options for some melanoma patients are improving, MNC believes that they remain limited, and for some types of melanoma, almost non-existent.

4.1.3 Impact of Advanced Melanoma and Current Therapy on Caregivers

MNC reported that they did not include caregivers in this survey. MNC noted that they specifically focussed on the experiences of the patient after receiving treatment with ipilimumab as an approved second-line therapy, versus the patient experience with the approved first-line therapy.

MNC believes that previous submission to pCODR have included sufficient information from caregivers on the benefits and disadvantages of ipilimumab as treatment for melanoma, and the experiences and side effects with other therapies to demonstrate the impact of advanced melanoma on caregivers.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences To Date with Ipilimumab

As part of the survey questions on patients' expectation with using ipilimumab as a treatment, MNC asked respondents if they felt that having ipilimumab available as a first line therapy would be of benefit for patients and to describe what they felt are the key benefits or disadvantages with this therapy.

94% of respondents reported that access to ipilimumab as a first line therapy would benefit patients. 1 respondent did not know. None of the respondents indicated a disadvantage. Below are some of the comments that were received:

> "*I ended up on Yervoy twice. The first time I made it through ok, but it took a few months to see any improvement. I was worried that I was out of options. It worked and most of my tumours were gone. There were only a few small ones that were showing on scans. After about 8 months, those ones started to grow again. I went through a second round of treatment with Yervoy and have been basically cancer free for the last two years. I think it would benefit us to go directly to these new therapies instead of wasting time on old ones that don't work. I got sicker and sicker on my chemo, and just watched as my tumours burst through my skin, in my lungs and ruin my spine and liver. My wife was panicked, I was panicked and I thought I was going to die. Clearly we need more effective treatments sooner. Why do they put us through that, if they have something better? That to me is torture*."
>
> "*Yervoy wasn't easy. I don't know if I could do it again if I had to. Steroids helped. I had a lot of headaches and diarrhea. I had a big rash too. But maybe having it right up front would have given me a shorter treatment time – getting me back to work earlier. I missed a lot of time with having to go through chemo and then this, and it almost cost me my job and my house. I am lucky to be alive though and thankful for that*."
>
> "*The big benefit I found is life – I am here! What better benefit is that? Yervoy should be made available for doctors for first line therapy. Why sit there and try other drugs that don't work? I would guess that the government wouldn't sit back and do that if it was their own lives on the line. Why do the doctors have to jump through hoops when we have effective therapies? It is criminal in my mind. Yes to this as a front line therapy. There is no debating that*."
>
> "*I have just been through treatment and am seeing good results. I am really tired and I am hoping that I start to feel better soon. The results make me feel hopeful, but I have been there before. I don't know if this will be a cure for me, but at least it may get me enough time to try something else. I am really glad that I don't have to continue to take more drugs for the moment. I think it should be available for all patients if their doctors feel it is right for them*."

According to MNC, while most patients surveyed have direct experience with the adverse side effects of therapies currently available, the survey results indicate that 100% of the respondents are still willing to accept side effects and the serious risks associated with ipilimumab if they know those side-effects can be effectively managed. Most notably, 88% of respondents stated they would be willing to take all the necessary steps to manage those side-effects. MNC noted that other therapies like dacarbazine and interferon have often very severe and lasting side effects –

including liver failure, nausea, debilitating depression, headaches, loss of memory, rheumatoid arthritis, diarrhea, hair loss, fatigue, confusion, rigors and other flu like symptoms.
MNC stated that first line access would allow patients access to a drug therapy that has proven results with over 30% of melanoma patients. MNC believes that ipilimumab will improve their recovery from the disease and allow them to return to a more normal existence; return to work in many cases and alleviate the stress - emotional, financial and physical, on patients and importantly, minimize long term heath impact of delayed treatment or treatment with therapies with long term adverse side effects.

Based on the findings of the survey, MNC reported that respondents who have experienced with ipilimumab stated the following positive benefits:

- Ease of administration through IV and relatively short administration window (only 4 intravenous treatments spaced over several weeks).
- 17 of 18 (94%) respondents who received the full course of treatment reported durable response with ipilimumab.
- 15 of 18 (83%) respondents have had a durable response over two (2) years.

According to the survey, short term side effects are the most widely acceptable. Side effects that continue to last and affect quality of life are sometimes unacceptable. Respondents indicated fatigue and nausea as the most common side effects, followed by colitis and rash.

Side Effect Experienced	# Patients Reporting Side Effect (total=18)
nausea	11
colitis	7
neuropathy	4
fatigue	14
rash or blisters	5
stomach pain	3

One respondent indicated that she had to be removed from the therapy as her side effects, coupled with an existing health issue made it too difficult to tolerate.

While ipilimumab has been known to cause significant adverse side effects - rash, potentially deadly colitis, fatigue, headaches, MNC noted that as physicians have become more familiar with the drug, it appears that side effects in most cases are being managed effectively.

MNC noted that patients are content to be alive after achieving a durable response with ipilimumab. With the exception of minor symptoms such as ongoing fatigue, respondents reported to have responded well to ipilimumab and are happy to be alive; and for the most part, able to return to a good quality of life.

4.3 Additional Information

MNC submits that if provided as a first line therapy, ipilimumab may hasten positive responses to treatment and may shorten periods of debilitation or long term health effects due to other less effective therapies.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group (PAG) as factors that could affect the feasibility of implementing a funding recommendation for ipilimumab (Yervoy) for the treatment of advanced melanoma. The Provincial Advisory Group includes representatives from provincial cancer agencies and provincial and territorial Ministries of Health participating in pCODR. The complete list of PAG members is available on the pCODR website (www.pcodr.ca).

Overall Summary

Input on the ipilimumab (Yervoy) review was obtained from all of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, key enablers to implementation include the familiarity with the use of ipilimumab and not requiring BRAF testing. PAG indicated that providing a more effective treatment upfront in the first-line setting eliminates the use of dacarbazine, a generally ineffective treatment, as these patients eventually are treated with ipilimumab in the second line setting. PAG identified that the uncertainty in the data for the 3mg/kg dose in the first line setting and in the use of ipilimumab over vemurafenib for BRAF mutation positive patients are potential barriers. Other key barriers PAG noted are the drug wastage and the high cost of ipilimumab.

Please see below for more detailed PAG input on individual parameters.

5.1 Factors Related to Comparators

PAG identified that the current standard of practice in the first-line treatment of patients with metastatic melanoma is vemuarfenib for patients with BRAF mutation positive metastatic melanoma and dacarbazine for BRAF negative patients. PAG noted that dacarbazine is not very effective and not well tolerated, thus, the majority of patients generally receive ipilimumab second-line.

PAG noted that there may be no randomized controlled trial data available for ipilimumab in the first-line treatment at the 3mg/kg dose and would like clarity on clinical effectiveness of this dose for first-line treatment over the 10mg/kg dose where there is data.

5.2 Factors Related to Patient Population

The number of patients with metastatic melanoma is relatively small. PAG noted that using ipilimumab in first-line instead of second-line would provide an option to dacarbazine, particulary for patients who are not BRAF mutation positive. As dacarbazine is considered to be ineffective and has significant toxicities, PAG noted that ipilimumab would replace dacarbazine and dacarbazine would no longer be considered for first-line treatment. Since patients eventually receive ipilimumab second-line and ipilimumab is currently funded in all provinces only for second-line, using ipilimumab in the first-line setting would eliminate the need to treat with dacarbazine first and provide access to a more effective treatment for patients upfront. This is an enabler to implementation as clinicians and patients are requesting use of ipilimumab in first-line.

5.3 Factors Related to Accessibility

Ipilimumab, being an intravenous drug, would be administered in an outpatient chemotherapy center for appropriate administration and monitoring of toxicities. Intravenous chemotherapy drugs would be fully funded (i.e. no co-payments for patients) in all jurisdictions for eligible patients, which is an enabler for patients.

As ipilimumab is a high cost drug and requires monitoring of immune-mediated reactions post-infusion, PAG noted that smaller outpatient cancer centres may not have the resources to administer ipilimumab. This is a barrier as some patients will need to travel to larger cancer centres that have the resources and expertise to administer ipilimumab.

5.4 Factors Related to Dosing

In the funding request and the Health Canada submission, the proposed dosing is 3mg/kg given every three weeks for first-line, which is the same as for second-line treatment. This is considered an enabler as there would be no confusion with dosing in the first-line versus second-line setting. However, PAG noted that there is a trial using 10mg/kg in first-line and has concerns regarding dose-creep and the costs of the higher dose, which are barriers. PAG would like pERC to address the optimal dose in the first-line setting to achieve clinical benefits.

PAG has concerns for incremental costs due to drug wastage, specifically in centers where vial sharing would be difficult because there would be only one patient in the day. As dose is based on weight and there are two vial sizes (50mg and 200mg), a dose of 210mg (3mg/kg x 70kg) would result in significant wastage given that any unused portion would be discarded.

PAG noted that only four doses for induction are required and the defined number of doses is an enabler. However, PAG also noted that in the real-world experience, a higher percentage of patients require re-induction than indicated in trial data for second-line treatment.

Doses of 10mg/kg, drug wastage and the number of patients requiring re-inductions are barriers to implementation and PAG would like these factors incorporated into the economic analysis.

5.5 Factors Related to Implementation Costs

As dacarbazine is considered to be ineffective and not well tolerated, PAG noted that ipilimumab would replace dacarbazine for first-line treatment and the resources needed to treat with dacarbazine and its toxicities would be eliminated. Ipilimumab for first-line treatment would provide access to a more effective treatment upfront, particularly for patients who are not BRAF mutation positive. PAG indicated that the number of patients receiving ipilimumab would not be significantly more in first-line than in second-line and the costs of ipilimumab would just be shifted. This is an enabler to implementation as patients would not need to use dacarbazine first.

PAG estimates that each treatment session would require up to 3 hours (90 minutes for the infusion and 1 hour for monitoring time for immune-related reactions post infusion) of chair time, which is a barrier. Since ipilimumab is already being used in the second-line

setting, PAG noted that health care professionals are already familiar with the preparation, administration and monitoring of ipilimumab, which is an enabler.

BRAF testing is not required for the use of ipilimumab and this is an enabler. PAG is requesting advice around the use of ipilimumab versus vemurafenib for patients with BRAF mutation positive melanoma in the first-line setting. PAG noted that ipilimumab would provide an option and is seeking information on the use of ipilimumab instead of vemurafenib for BRAF mutation positive patients. However, vemuarfenib is currently only funded for first-line treatment and not funded for second-line treatment. For patients who have used vemurafenib in the first-line setting, ipilimumab is currently funded in the second line setting. PAG is also requesting for information around using vemurafenib after ipilimumab to guide treatment sequence should ipilimumab be used in patients with BRAF mutation positive patients in the first-line treatment over vemurafenib.

5.6 Other Factors

None identified.

6 SYSTEMATIC REVIEW

6.1 Objectives

To evaluate the effect of ipilimumab as first line therapy on patient outcomes compared to standard therapies, placebo, or best supportive care in the treatment of patients with unresectable or metastatic melanoma (stage III or IV) (see Table 4 in Section 6.2.1 for outcomes of interest and comparators).

Note: Two supplemental questions relevant to the pCODR review and to the Provincial Advisory Group were identified while developing the review protocol and are outlined in Section 7.

- Comparison of the clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma
- The clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose used as first line therapy for patients with unresectable or metastatic melanoma

6.2 Methods

6.2.1 Review Protocol and Study Selection Criteria

The systematic review protocol was developed jointly by the Clinical Guidance Panel and the pCODR Methods Team. Studies were chosen for inclusion in the review based on the criteria in the table below. Outcomes considered most relevant to patients, based on input from patient advocacy groups are those in bold.

Table 4. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCTs	Patients with unresectable or metastatic melanoma Subgroups: • Patients with or without brain metastases • BRAF mutation status	Ipilimumab as 1st line therapy, alone or in combination with chemo-therapy	BRAF inhibitor (e.g. vemurafenib, dabrafenib) MEK inhibitor (e.g. trametinib, alone or combined with dabrafenib) Immunotherapy (e.g. interleukin-2) Chemotherapy (e.g. dacarbazine, paclitaxel) Best supportive care Placebo	• **OS** • PFS • **HRQOL** • Response rate (CR, PR) • % of patients required ipilimumab re-induction • **AE** • **SAE** • WDAE • **Immune-related SAE**
AE=adverse events; **CR**=complete response; **HRQOL**=health-related quality of life; **OS**=overall survival; **PFS**=progression-free survival; **PR**=partial response; **RCT**=randomized controlled trial; **SAE**=serious adverse event; **WDAE**=withdrawals due to adverse event				

** Standard and/or relevant therapies available in Canada (may include drug and non-drug interventions)*

6.2.2 Literature Search Methods

The literature search was performed by the pCODR Methods Team using the search strategy provided in Appendix A.

Published literature was identified by searching the following bibliographic databases: MEDLINE (1946-) with in-process records & daily updates via Ovid; Embase (1974-) via Ovid; The Cochrane Central Register of Controlled Trials (July 2014) via Ovid; and PubMed. The search strategy was comprised of both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were ipilimumab and Yervoy.

Methodological filters were applied to limit retrieval to randomized controlled trials or controlled clinical trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents, but not limited by publication year. The search is considered up to date as of November 5, 2014.

Grey literature (literature that is not commercially published) was identified by searching the websites of regulatory agencies (Food and Drug Administration and European Medicines Agency), clinical trial registries (U.S. National Institutes of Health – clinicaltrials.gov and Canadian Partnership Against Cancer – Canadian Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) were limited to the last five years. Searches were supplemented by reviewing the bibliographies of key papers and through contacts with the Clinical Guidance Panel. In addition, the manufacturer of the drug was contacted for additional information as required by the pCODR Review Team.

6.2.3 Study Selection

One member of the pCODR Methods Team selected studies for inclusion in the review according to the predetermined protocol. All articles considered potentially relevant were acquired from library sources. Two members of the pCODR Methods Team independently made the final selection of studies to be included in the review and differences were resolved through discussion.

Included and excluded studies (with reasons for exclusion) are identified in section 6.3.1.

6.2.4 Quality Assessment

Assessment of study bias was performed by one member of the pCODR Methods Team with input provided by the Clinical Guidance Panel and other members of the pCODR Review Team. SIGN-50 Checklists were applied as a minimum standard. Additional limitations and sources of bias were identified by the pCODR Review Team.

6.2.5 Data Analysis

No additional data analyses were conducted as part of the pCODR review.

6.2.6 Writing of the Review Report

This report was written by the Methods Team, the Clinical Guidance Panel and the pCODR Secretariat:

- The Methods Team wrote a systematic review of the evidence and summaries of evidence for supplemental questions.

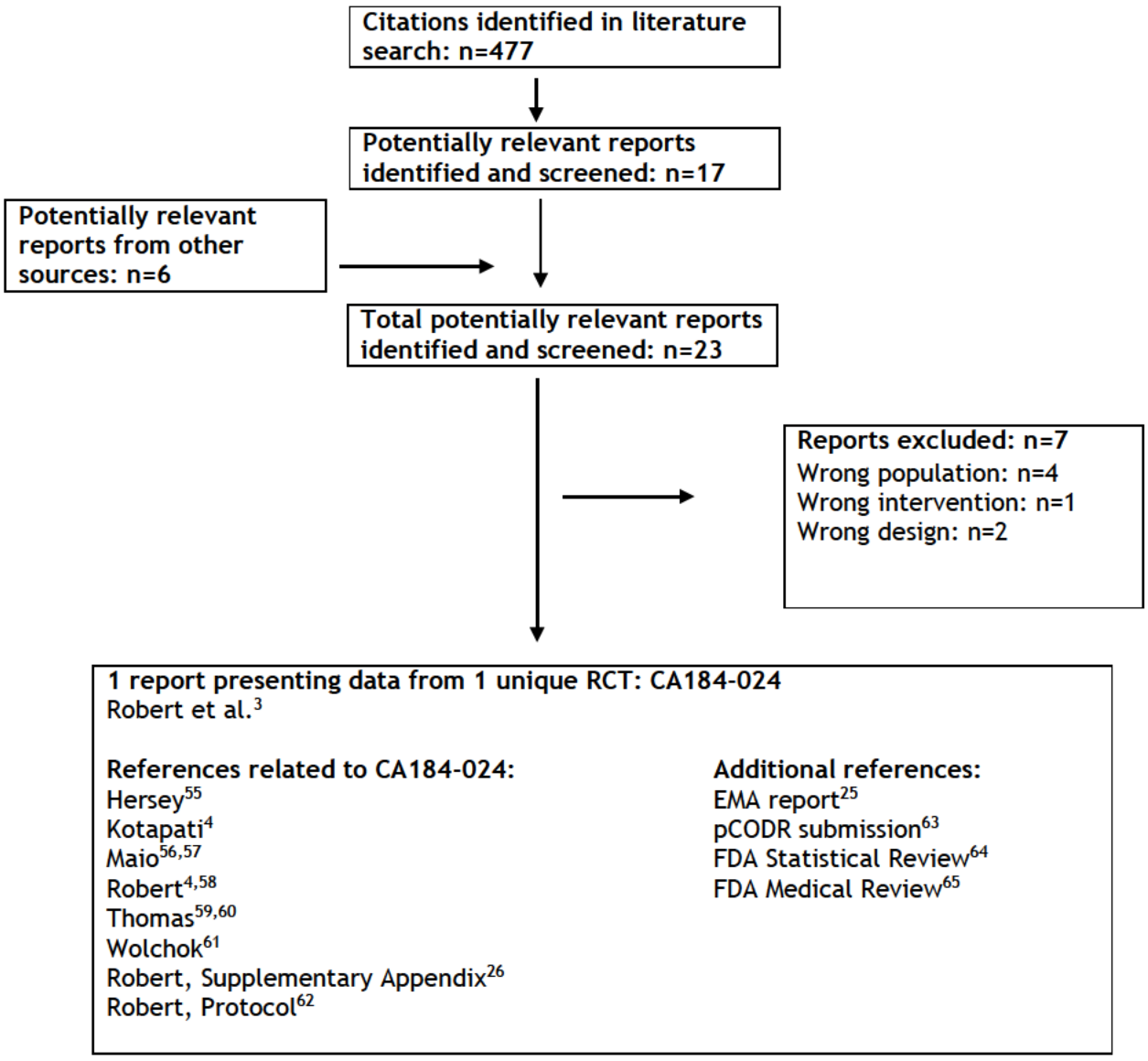
- The pCODR Clinical Guidance Panel wrote a summary of background clinical information and the interpretation of the systematic review. The Panel provided guidance and developed conclusions on the net overall clinical benefit of the drug.
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 477 potentially relevant reports identified, one study was included in the pCODR systematic review[3] and seven studies were excluded (see Figure 1 for study selection). Studies were excluded because they were with inappropriate patient population, inappropriate intervention or inappropriate study design.

Figure 1. QUOROM Flow Diagram for Inclusion and Exclusion of studies



6.3.2 Summary of Included Studies

One double-blind RCT (Study CA184-024) was identified that met the eligibility criteria. The study compared ipilimumab plus dacarbazine versus placebo plus dacarbazine in patients with previously untreated unresectable or metastatic melanoma.

6.3.2.1 Detailed Trial Characteristics

a) Trials

One double-blind randomized controlled trial (CA184-024) was included in this review (Table 1).[3] The study was conducted in different countries in North America (including Canada) and Europe. It was sponsored by the manufacturer, and the manufacturer was involved in the study design, data collection, data analysis and report writing. A total of 502 patients were randomized in a 1:1 ratio to ipilimumab plus dacarbazine or placebo plus dacarbazine. Randomization was stratified by baseline metastasis stage (M0, M1a, M1b or M1c), study site and ECOG performance status. A centralized randomization scheme was used to assign patients to one of the two treatment groups. The sponsor, patients, investigator and site staff were blinded with respect to the patient's treatment assignment (ipilimumab or placebo). Local pharmacists and the CRO pharmacy monitors were unblinded. An Independent Data Monitoring Committee had the possibility to access unblinded data in order to enable review of emerging safety data. The dacarbazine dose was open-label.[62]

The original primary outcome was progression-free survival (PFS). Because the emerging data from other ipilimumab trials suggested that conventional definitions of disease progression and response incompletely reflect overall survival among patients who appear to have a long-term benefit, the primary outcome was changed to overall survival (OS, defined as the time from randomization until death from any cause), and this was approved by the FDA in October 2008. A total of 500 patients were required in the initial study design, and there was no change in the size of the study population. In the protocol of this study, the authors estimated that 416 deaths among a total of 500 patients (250 patients in each treatment arm) would have 90% power to detect a 38% improvement in median OS to 11 months with ipilimumab plus dacarbazine versus 8 months with placebo plus dacarbazine, with a corresponding hazard ratio (HR) for death of 0.727 at a two-sided alpha of 0.05.[62] The secondary outcomes included PFS, the rate of best overall response, the rate of disease control (defined as a complete response, a partial response or stable disease), time to response, the duration of the response, HRQOL and safety, in particular, immune-mediated adverse events. The efficacy outcomes in CA184-024 were assessed by local investigators as well as an Independent Review Committee (IRC), whose members were not aware of the treatment assignments. Because the primary outcome was overall survival, the IRC assessments are considered to be consistent with the investigator assessment. The IRC-reviewed outcomes are presented in this report.

Intention-to-treat (ITT) approach was adopted in analyses of baseline characteristics and efficacy endpoints. All randomized patients were taken into account. The safety population was defined as all treated patients who received at least one dose of ipilimumab or placebo and/or dacarbazine.[25] A log-rank test was performed for the analysis of OS. A stratified Cox proportional-hazards model was

used to calculate hazard ratios for OS and PFS. The Kaplan-Meier method was used to analyze the survival outcomes between the two treatment groups.

b) Populations

The baseline demographic and disease characteristics were balanced between the two treatment arms. The mean age (range) was 57.5 years in the ipilimumab plus dacarbazine group and 56.4 years in the placebo plus dacarbazine group. There were more males (approximately 60%) in the trial than females (40%). More patients had an ECOG performance status of 0 (approximately 71%) than 1 (29%). Patients who received any prior treatment for metastatic disease or concomitant therapy with immunosuppressive agents (including long-term corticosteroids), or those with brain metastasis, primary ocular or mucosal melanoma or autoimmune disease were excluded from the study. In both treatment groups, 26% of patients received prior adjuvant therapy.

c) Interventions

This phase III study evaluated the efficacy and safety of ipilimumab combined with dacarbazine versus placebo plus dacarbazine. Ipilimumab was administered at 10 mg/kg/dose via a 90-minute intravenous infusion, while dacarbazine was administered at a dose of 850 mg/m^2. The study consisted of two phases: 1) Induction phase: patients were randomly assigned to treatment with ipilimumab plus dacarbazine or placebo plus dacarbazine at weeks 1, 4, 7 and 10, followed by dacarbazine alone every 3 weeks through week 22; treatment in this phase would be terminated if toxic effects associated with the drug or progressive disease was noted. 2) Maintenance phase: starting at week 24, patients with stable disease or an objective response during the induction phase who did not have a dose-limiting adverse event received placebo or ipilimumab every 12 weeks until disease progression, unacceptable toxic effects, withdrawal of consent, or the end of the study.[3]

A total of 92 patients (36.8%) in the ipilimumab + dacarbazine group and 165 (65.5%) in the dacarbazine + placebo group received all four doses of ipilimumab or placebo.

d) Patient Disposition

A total of 502 patients started on the study and 95.8% of the participants discontinued the study prematurely. Higher risks of disease progression were observed in the placebo plus dacarbazine group, while more study drug-related adverse events were reported in the ipilimumab plus dacarbazine group. The follow-up time between the start of the study (the first visit of the first enrolled patient) and the end of the study (the last visit of the last enrolled patient) was 54 months, and the follow-up time between the time the last patient underwent randomization and the end of the study was 36.6 months. Details of patient disposition are presented in Table 5.

Table 5. Patient Disposition in Study CA184-024[3,25,26]

	Ipi + DTIC	PL + DTIC	Total
Randomized	250	252	502
Not treated (n, %)	3 (1.2)	1 (0.4)	4 (0.8)
Treated (n, %)	247 (98.8)	251 (99.6)	498 (99.2)
Discontinued study (n, %)	236 (94.4)	245 (97.2)	481 (95.8)
Disease progression	114 (45.6)	194 (77.0)	308 (61.4)
Adverse events	95 (38.0)	20 (7.9)	115 (22.9)
Other	27 (10.8)	31 (12.3)	58 (11.6)
Death	196 (78.4)	218 (86.5)	414 (82.5)
Still on treatment (n, %)	11 (4.4)	6 (2.4)	17 (3.4)
Treatment during maintenance phase (n, %)	43 (17.2)	53 (21.0)	96 (19.1)
Intention-to-treat population (n, %)	250 (100)	252 (100)	502 (100)
Safety population (n, %)	247 (98.8)	251 (99.6)	498 (99.2)

DTIC=dacarbazine; Ipi=ipilimumab

Data sources: Robert 2011,[3] Robert supplementary appendix[26] and EMA report 2013.[25] Data in this table were collected at the database lock in March 2011.

e) Limitations/Sources of Bias

According to the study design, a genuine randomized analysis population was from week 1 to week 12. After week 12, patients discontinued treatment if deemed lack of efficacy or toxic effect, due either to ipilimumab or dacarbazine. It is likely that patients who responded to the treatments during the initial induction phase would continue benefit from the maintenance treatment (receiving ipilimumab or placebo) every 12 weeks, and were more likely to stay in the study throughout the follow up period up to 54 months. This study design feature may help portray a benefit-risk profile in favor of ilipimumab, as it is possible that patients in the two treatment groups might have dropped out disproportionately.

HRQOL data were briefly reported in an abstract. Interpretation of those data was difficult given that insufficient details of the HRQOL data as well as the methods used to collect the data were reported and given the lack of a validated MCID to determine the clinical importance of the study results.

The current study evaluated the clinical efficacy and safety of ipilimumab at 10 mg/kg. The manufacturer is requesting reimbursement for ipilimumab at 3 mg/kg. It is uncertain whether the results from this study can be generalized to patients who will be receiving a lower dose of ipilimumab for the first-line treatment of unresectable or metastatic melanoma.

Patients with brain metastases was identified as a subgroup of interest for this review; however, in the CA184-024 study, one of the exclusion criteria was brain metastasis. Therefore, extrapolation of the study results to patients with brain metastases should be done with caution. In addition, only patients with ECOG

performance status of 0 and 1 were included limiting the generalizability of the study findings.

CA184-024 was sponsored by the manufacturer, and the manufacturer was involved in study design, data collection, data analysis and report writing.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

Efficacy Outcomes

Overall survival

The primary endpoint of Study CA184-024 was OS between ipilimumab plus dacarbazine and placebo plus dacarbazine. It was defined as the time from randomization to death from any cause and was analyzed using the ITT population.

The median OS was statistically significantly longer in patients treated with ipilimumab plus dacarbazine (11.2 months [95% CI: 9.4, 13.6]) compared with those treated with placebo plus dacarbazine (9.1 months [95% CI: 7.8, 10.5]) (Figure 2). The survival curves were similar through the first three months of treatment, after which the ipilimumab curve separated from the placebo curve, and the separation was sustained over time. The hazard ratio (HR) for the between-group comparison of OS was 0.72 (95% CI 0.59 to 0.87, $p < 0.001$), indicating a 28% risk reduction in OS for ipilimumab plus dacarbazine compared with placebo plus dacarbazine. Subgroup analyses of OS were conducted. A trend in improved OS was observed for the ipilimumab plus dacarbazine group compared with the placebo plus dacarbazine group across various patient subgroups; however, statistical significance was not always achieved (Figure 3).

Figure 2. Kaplan-Meier survival curves in CA184-024 (data source: Robert 2011[3])

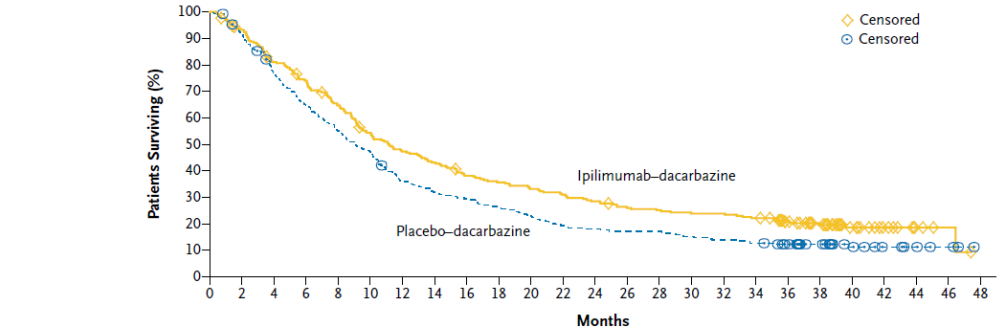
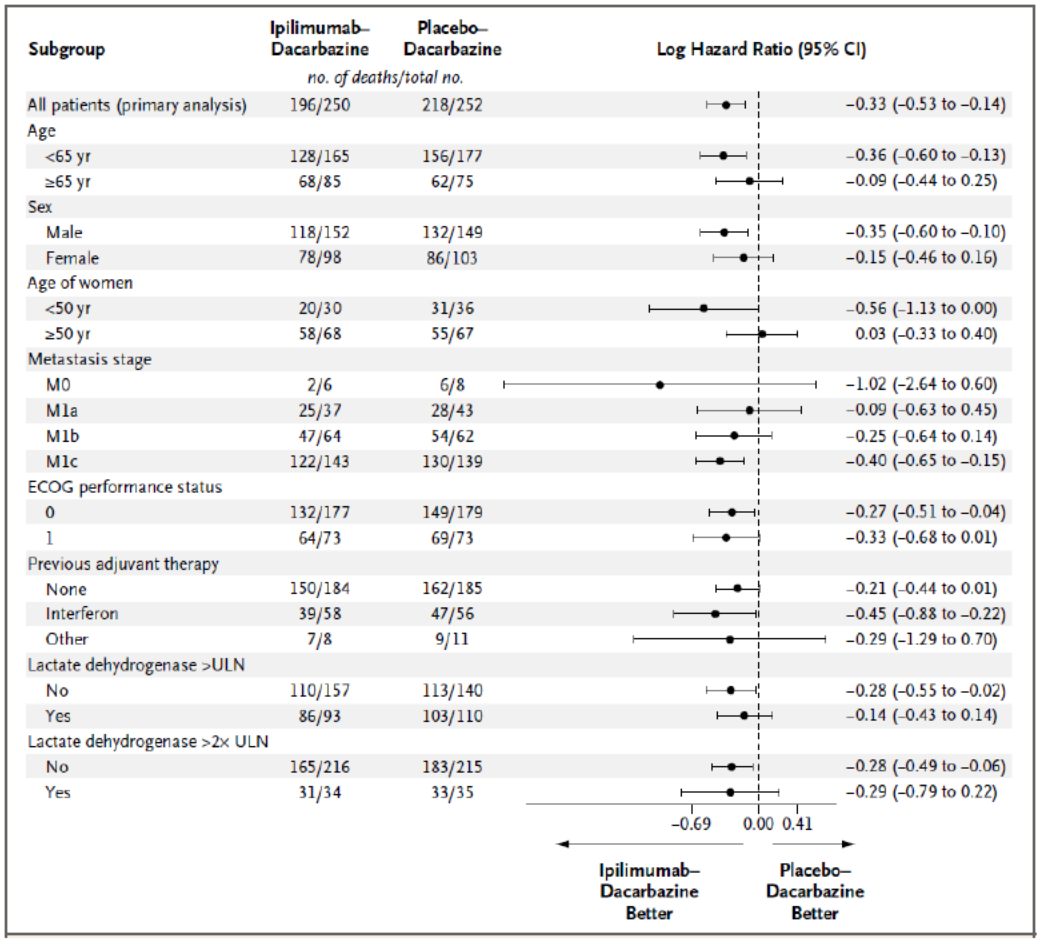


Figure 3. Subgroup Analyses of Overall Survival in Study CA184-024 (data source: Robert 2011[3])



Overall survival rates at Year 1, 2 and 3 can be found in

Table 6. The survival rates were consistently higher in the ipilimumab plus dacarbazine group than in the placebo plus dacarbazine group throughout these three years: Year-1, 47.3% versus 36.3%; Year-2, 28.5% versus 17.9%; Year-3, 20.8% versus 12.2%, respectively.

Table 6. Survival Rates at Year-1, 2 and 3 in Study CA184-024[3]

Intervention	N	1-year OS, % (95% CI)	2-year OS, % (95% CI)	3-year OS, % (95% CI)
Ipi + DTIC	250	47.3 (41.0 - 53.6)	28.5 (22.9 - 34.2)	20.8 (15.7 - 26.1)
DTIC + PL	252	36.3 (30.4 - 42.4)	17.9 (13.3 - 22.8)	12.2 (8.2 - 16.5)

CI=confidence interval; DTIC=dacarbazine; Ipi=ipilimumab; OS=overall survival; PL=placebo

Progression-free survival

This was a secondary endpoint in the current study. The analysis of PFS was conducted on a database that was locked after 416 events had been documented (March 2011). The survival curves were similar through the first three months of treatment, after which the ipilimumab curve separated from the placebo curve. A statistically significant difference in median PFS was reported in favour of ipilimumab plus dacarbazine (2.76 months [2.63, 3.29]) compared to placebo plus dacarbazine (2.60 months [2.56, 2.66]), although the results were numerically similar between the two groups. The HR for disease progression or death in the ipilimumab plus dacarbazine group as compared with the dacarbazine monotherapy group was 0.76 (95% CI 0.63 - 0.93, p = 0.006), indicating a 24% reduction in the risk of progression or death in the former (Table 2).

Health-related quality of life

In Study CA184-024, patient's HRQOL was examined using the Global Health Status (GHS) scale and the symptom scales of the EORTC-QLQ-C30. The raw scale scores are transformed to scores ranging from 0 to 100. A higher GHS score indicates a better health status, while a higher symptom score indicates more severe symptoms.[66] An MCID for this instrument has not been established yet. The scores were assessed at baseline, week 4, 7, 12 and then every 12 weeks until disease progression. Changes in scores were categorized as "no change" (0 to 5), "a little" (5 to 10 points), "moderate" (10 to 20 points) and "very much" (> 20).

The results of HRQOL assessment were reported in an abstract only.[4] At the end of the double-blind period of this study (week 12), unadjusted mean changes from baseline in both groups were "no change" to "moderate" for all HRQOL domains in this scale including symptom scores. Patients in both groups reported declined average GHS scores (ipilimumab + dacarbazine: -6.5; placebo + dacarbazine: -10.0), indicating worsened health status. The 95% CIs or p-value was not reported for this comparison. The authors concluded that during the first 12 weeks of treatment, most scales and symptom scores were similar to baseline. No further details regarding the HRQOL assessment were provided in this abstract.

Response rate

The rate of best overall response was defined as the proportion of all randomly assigned patients who had a complete (CR) or partial response (PR). This was a secondary endpoint in CA184-024. Patients in the ipilimumab plus dacarbazine group were more likely to respond to the treatment compared with the placebo plus dacarbazine group. CR or PR were achieved in 38 patients (15.2%) and 26 patients (10.3%) in the respective groups. However, the between-group difference in the best overall response rate was not statistically significant, p > 0.05 (Table 2).

Proportion of patients requiring ipilimumab re-induction

Re-induction with ipilimumab following Maintenance was not permitted within Study CA184-024.

Harms Outcomes

A total of 498 patients comprised the safety population, which consisted of randomized patients who had received at least one dose of the assigned study drug. In safety analyses, statistical comparisons for adverse event rates between the two treatment groups were not performed.

Adverse events

The proportion of patients who experienced at least one adverse event of any Grade was comparable in the two treatment groups (98.8% in the ipilimumab plus dacarbazine group versus 94.0% in the placebo plus dacarbazine group), except that patients who received ipilimumab reported more diarrhea, dermatologic disorders, elevated liver enzymes, pyrexia and chills (Table 7).

Table 7. Adverse Events of Any Grade Reported in More than 10% of Patients in Study CA184-024[3,26]

Event, n (%)	Ipi + DTIC N=247	PL + DTIC N=251	Total N=498
Any	244 (98.8)	236 (94.0)	480 (96.4)
Gastrointestinal			
Nausea	120 (48.6)	122 (48.6)	242 (48.6)
Diarrhea	90 (36.4)	62 (24.7)	152 (30.5)
Vomiting	78 (31.6)	70 (27.9)	148 (29.7)
Constipation	70 (28.3)	70 (27.9)	140 (28.1)
Abdominal pain	30 (12.1)	30 (12.0)	60 (12.0)
Dermatologic			
Pruritis	73 (29.6)	22 (8.8)	95 (19.1)
Rash	61 (24.7)	17 (6.8)	78 (15.7)
Fatigue	103 (41.7)	98 (39.0)	201 (40.4)
Pyrexia	91 (36.8)	23 (9.2)	114 (22.9)
Asthenia	29 (11.7)	32 (12.7)	61 (12.2)
Chills	28 (11.3)	10 (4.0)	38 (7.6)
Weight loss	27 (10.9)	13 (5.2)	40 (8.0)
Back pain	28 (11.3)	25 (10.0)	53 (10.6)
Headache	40 (16.2)	33 (13.1)	73 (14.7)
Decreased appetite	54 (21.9)	47 (18.7)	101 (20.3)
Dyspnea	25 (10.1)	31 (12.4)	56 (11.2)
Cough	25 (10.1)	25 (10.0)	50 (10.0)
Hepatic			
Increased ALT	82 (33.2)	14 (5.6)	96 (19.3)
Increased AST	72 (29.1)	14 (5.6)	86 (17.3)

AE= adverse event; ALT= alanine aminotransferase; AST= aspartate aminotransferase; DTIC= dacarbazine; Ipi= ipilimumab; PL= placebo

Serious adverse events

SAE was defined as "any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability/incapacity, is a congenital anomaly, is an important medical event" in the study protocol.[62] In spite of this definition, SAE was reported as Grade 3 or 4 adverse events in the published study (Table 8). More SAEs were reported in the ipilimumab plus dacarbazine group (56.3%) compared with the placebo plus dacarbazine group (27.5%). Overall, the risks of SAEs were low (< 4%), except for increased liver enzymes and fatigue. Patients in the ipilimumab plus dacarbazine group were more likely to observe elevated ALT and AST than those in the placebo plus dacarbazine group (21.9% versus 0.8% for ALT and 18.2% versus 1.2% for AST, respectively).

Table 8. Serious Adverse Events (Grade 3 and 4) Reported in Study CA184-024[3,26]

Event, n (%)	Ipi + DTIC N=247	PL + DTIC N=251
Any	139 (56.3)	69 (27.5)
Gastrointestinal		
Nausea	4 (1.6)	3 (1.2)
Diarrhea	10 (4.0)	0
Vomiting	8 (3.2)	4 (1.6)
Constipation	0	0
Abdominal pain	3 (1.2)	7 (2.8)
Dermatologic		
Pruritis	5 (2.0)	0
Rash	3 (1.2)	0
Fatigue	27 (10.9)	12 (4.8)
Pyrexia	0	0
Asthenia	1 (0.4)	6 (2.4)
Chills	0	0
Weight loss	1 (0.4)	1 (0.4)
Back pain	5 (2.0)	3 (1.2)
Headache	4 (1.6)	1 (0.4)
Decreased appetite	3 (1.2)	4 (1.6)
Dyspnea	8 (3.2)	0
Cough	1 (0.4)	0
Hepatic		
Increased ALT	54 (21.9)	2 (0.8)
Increased AST	45 (18.2)	3 (1.2)

AE= adverse event; DTIC= dacarbazine; Ipi= ipilimumab; PL= placebo

Withdrawal due to adverse events

Of a total of 498 patients in the safety population, 95 of 247 patients (38.5%) with ipilimumab plus dacarbazine withdrew from the study due to adverse events compared to 20 of 251 patients (8.0%) with placebo plus dacarbazine. The common adverse events leading to early study discontinuation were not reported in the published article. During the induction phase, there were 85 patients and 10 patients who discontinued the study in the two groups, respectively, due to an adverse event.[3] According to the additional information provided by the submitter in the checkpoint meeting, in the ipilimumab plus dacarbacine group, the most common adverse events leading to discontinuation was elevated AST/ALT followed by gastrointestinal disorders and hepatobiliary disorders; in the placebo plus dacarbazine group, the most common adverse event leading to discontinuation was neutropenia.[67]

Immune-related serious adverse events

Table 9 presents data on the immune-related adverse events reported in Study CA184-024. Grade 3 or 4 immune-related adverse events occurred in a higher proportion of patients in the ipilimumab plus dacarbazine group (41.7% of 247 patients) as compared to the placebo plus dacarbazine group (6.0% of 251 patients). The most common immune-related adverse events included dermatologic disorders, diarrhea and elevated ALT/AST.

Table 9. Immune-related Adverse Events Reported in Study CA184-024[3,26]

Event, n (%)	Ipi + DTIC N=247		PL + DTIC N=251	
	Total	Grade 3 or 4	Total	Grade 3 or 4
Any	192 (77.7)	103 (41.7)	96 (38.2)	15 (6.0)
Dermatologic				
Pruritus	66 (26.7)	5 (2.0)	15 (6.0)	0
Rash	55 (22.3)	3 (1.2)	12 (4.8)	0
Gastrointestinal				
Diarrhea	81 (32.8)	10 (4.0)	40 (15.9)	0
Colitis	11 (4.5)	5 (2.0)	0	0
Endocrine				
Hypothyroidism	4 (1.6)	0	1 (0.4)	0
Autoimmune thyroiditis	2 (0.8)	0	0	0
Hyperthyroidism	1 (0.4)	0	0	0
Hepatic				
Increased ALT	72 (29.1)	51 (20.6)	11 (4.4)	2 (0.8)
Increased AST	66 (26.7)	43 (17.4)	8 (3.2)	1 (0.4)
Hepatitis	4 (1.6)	3 (1.2)	0	0
Autoimmune hepatitis	4 (1.6)	4 (1.6)	0	0

ALT= alanine aminotransferase; AST= aspartate aminotransferase; DTIC= dacarbazine; Ipi= ipilimumab; PL= placebo

6.4 Ongoing Trials

One phase 3, double-blind RCT (CA184-169 or NCT015151) is ongoing.[19] This study was designed to determine whether ipilimumab at 10 mg/kg will have survival benefits compared with ipilimumab at 3 mg/kg, for patients with previously treated or untreated, unresectable or metastatic melanoma. Patients, caregivers, investigators and outcome assessors will be blinded to the treatment assignments. The primary outcome measure is overall survival. Approximately 700 patients will be enrolled. The study started recruiting patients in February 2012, and the estimated study completion date is in December 2016. It is sponsored by Bristol-Myers Squibb.

7 SUPPLEMENTAL QUESTIONS

The following supplemental questions were identified during development of the review protocol as relevant to the pCODR review of ipilimumab in patients with unresectable stage III or IV melanoma who had no previous systemic therapy:

- Comparison of the clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma
- The clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose used as first line therapy for patients with unresectable or metastatic melanoma

Topics considered in this section are provided as supporting information. The information has not been systematically reviewed.

7.1 Comparison of the clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma

7.1.1 Objective

The objective is to report on the efficacy and harms of ipilimumab at 3 mg/kg dose when compared with ipilimumab at 10 mg/kg in first line therapy for patients with unresectable or metastatic melanoma.

7.1.2 Findings

A literature search was conducted to identify RCTs and non RCTs that compared ipilimumab 3mg/kg dose with 10mg/kg dose in the first-line therapy of unresectable stage III or IV melanoma. The Methods Team identified one study which was randomized, double-blind, phase II biomarker study. Patients included were pretreated or treatment-naïve with unresectable stage III/IV melanoma and were randomized to receive either 3 or 10 mg/kg ipilimumab every 3 weeks for 4 doses, Study CA184-004.[68] Only twenty patients who were treatment naïve were included in this study, however it is not reported how many of those received 3 mg/kg or 10 mg/kg. Also results were not reported for the treatment naïve patient group. Finally, chemotherapy naïve patients who were included in Study CA184-004 were also included in the pooled analyses summarized in the supplemental issue below.

7.1.3 Summary

No evidence was found in the literature on the comparative efficacy and safety of ipilimumab at 3 mg/kg/dose versus 10 mg/kg/dose as first line therapy for patients with unresectable or metastatic melanoma.

7.2 The clinical effectiveness and safety of ipilimumab at 3 mg/kg/dose used as first line therapy for patients with unresectable or metastatic melanoma

7.2.1 Objective

Due to the unavailability of evidence of the comparison of ipilimumab 3 mg/kg when compared with 10 mg/kg dose, there is a need to report the efficacy and safety of 3 mg/kg dose. The objective is to report on the efficacy and harms of ipilimumab when used as first line therapy for patients with unresectable or metastatic melanoma.

7.2.2 Findings

A literature search was conducted to identify RCTs and non-RCTs of ipilimumab in the first line therapy for patients with unresectable or metastatic melanoma. The Methods Team identified two posters which included interim results from two ongoing retrospective observational studies (CA184-332 and CA184-338)[7,8] of first line treatment of ipilimumab 3mg/kg monotherapy for the treatment of patients with unresectable or metastatic melanoma. In addition to the posters the manufacturer submitted a pooled analysis of treatment-naïve or chemotherapy naïve advance melanoma patients who were included in four RCTs (MDX010-20, MDX010-08, CA184-004, and CA184-022) and were randomized to 3mg/kg ipilimumab monotherapy.[6] Details of the study design and participant baseline characteristics can be found in Table 10. The pooled analysis included 78 patients while studies CA184-332 and CA184-338 included 90 and 120 patients respectively. There were some clinically relevant differences in the baseline characteristics between the three studies; these differences included ECOG performance status, presence of brain metastases, disease stage, and duration of melanoma.

Table 10. Study design and participant baseline characteristics of the Pooled analysis and the observational studies.

	Pooled chemotherapy-naïve (from clinical trials)[6]	CA184-338[8]	CA184-332[7]
Location	Multiple sites in multiple countries	27 sites in US headed by medical oncologist physician investigators	Multiple US oncology sites
Design	Pooled analysis of treatment-naïve or chemotherapy naïve patients randomised to 3mg/kg Ipi monotherapy treatment arms of three phase 2 trials (MDX010-08, CA184-004, and CA184-022) and one phase 3 study MDX010-20	Multisite observational retrospective chart review study of "real world" advanced melanoma patients receiving 3mg/kg Ipi for first-line treatment	Multisite observational retrospective chart review study of "real world" advanced melanoma patients who were treated with 3 mg/kg IPI monotherapy in the first line setting
Intervention	Ipi 3mg/kg	Ipi 3mg/kg	Ipi 3mg/kg
Treatment schedule	Four doses with the option for retreatment (MDX010-20) or maintenance therapy (CA184-004/022)	75.8% of patients completed 4 doses	NR

	Pooled chemotherapy-naïve (from clinical trials)[6]	CA184-338[8]	CA184-332[7]
	55% of patients received all 4 doses		
Primary outcomes	Overall survival	Baseline characteristics, safety and overall survival	Baseline characteristics, and overall survival
Secondary outcomes	Safety		
Duration of follow-up, months	Median (min, max): 11.6 (0.03-69.7)	Interim analysis Median (range): 12 (0.5-21.7)	Interim analysis Median (range): 9.6 (2.8-14.4)
Sample size, n	78	120	90
Age, years	Mean: 57.4	Median: 63	Mean: 64
Male, n (%)	47 (60.3)	79 (65.8)	60 (66.7)
ECOG performance status, n (%)	0 = 45 (57.7) 1 = 30 (38.5) ≥ 2 = 3 (3.8)	0 = 49 (40.8) 1 = 62 (51.7)	0 = 58 (64.5) 1 = 25 (27.8) ≥ 2 = 3 (3.3) Unknown/missing = 4 (4.4)
Metastasis stage, n (%)	M0 = 0 M1a = 18 (23.1) M1b = 16 (20.5) M1c = 44 (55.6)	III = 14 (11.7) IV = 106 (88.3) Stage M1c =66 (55.0)	M1a = 21 (23.3) M1b = 27 (30.0) M1c = 40 (44.5) Unknown/missing = 2 (2.2)
Brain metastasis, n (%)	NR	9 (7.5)	28 (31.1)
Duration of melanoma, median months	39.0	NR	9.0
Lactate dehydrogenase, n (%)	Elevated 21 = (26.9) Normal = 56 (71.8) Not reported = 1 (1.3)	> institutional ULN= 36.7%	> ULN = 28 (31.1) Normal = 43 (47.8) Unknown/missing = 19 (21.1)
BRAF V600 mutation, n (%)	NR	Mutated = 21 (17.5 Wild-type = 76 (63.3) Not tested = 23 (19.2)	Negative = 48 (53.3) positive = 14 (15.6) Unknown/Missing = 28 (31.1)
Prior immunotherapy, n(%)	41 (52.6)	NR	NR

Ipi=ipilimumab; NR = not reported; ULN = upper limits of normal

Outcomes

The primary outcome in the pooled analysis was overall survival while it was baseline characteristics, safety and overall survival in the two observational studies. A summary of the key outcomes from the studies can be found in Table 11.

Table 11. Summary of Outcomes from the Pooled analysis and the observational studies

Efficacy	Pooled chemotherapy-naïve (n = 78)[6]	CA184-338 (n = 120)[8]	CA184-332 (n = 90)[7]
Overall Survival, Median, months (95% CI)	13.47 (11.20, 19.58)	14.3 (12.1, --)	11.5 (7.2, --) patients without brain metastases: 14.2 (8.9, --) patients brain metastases: 5.4 (2.4, 16.6)
Survival Rates at Year-1, % (95% CI)	54.1 (42.5, 65.6)	All patients = 59.5 (50.1, 67.8) BRAF-mutated = 71.4 (47.2, 86.0), wild-type = 58.9 (47.0, 69.1), untested patients 50.5 (28.4, 69.0)	49.4 (38.3, 59.6)
Survival Rates at Year-2, % (95% CI)	31.6 (20.7, 42.9)	-	-
Survival Rates at Year-3, % (95% CI)	23.7 (14.3, 34.4)	-	-
Harms	Pooled chemotherapy-naïve (n = 75)[6]	CA184-338 (n = 120)[8]	CA184-332[7]
SAE, n (%)	10 (13.3)*†	19 (15.8)	NR
Any AE, n (%)	61 (81.3)†	72 (60.0)	NR
Immune-related SAE, n (%)	6 (8.0)*	16 (13.3)*	NR
Any Immune-related AE, n (%)	63 (84.0)	63 (52.5)	NR
AE leading to ipilimumab discontinuation, n (%)	5 (6.7)	12 (10.0)	NR
Treatment-related AEs with outcome of death	2 (2.7)	0	NR

"--"=not applicable; AE=adverse event; NR=not reported; SAE=serious adverse events

* Serious Adverse Events (≥ Grade 3)

† Treatment related adverse event

Efficacy Outcomes

Overall Survival

In all 3 studies Kaplan-Meier estimates were used to analyze overall survival. Median overall survival was 13.47 months in the pooled analysis, while it was 11.5 and 14.3 in studies CA184-332 and CA184-338 respectively. One year survival rate was 54.1%, 49.4% and 59.5% in the pooled analysis, study CA184-332, and study CA184-338, respectively (Table 11)

In study CA184-338 there were no differences in survival function among BRAF-mutated, wild-type, and untested groups of patients.

Harms Outcomes

Only the pooled analysis and study CA184-338 reported harms outcomes. Major harms outcomes are summarized in Immune-related adverse events of any grade occurred in 84% and 52.5% of patients included in the pooled analysis and study CA184-338, respectively, with Grade 3 or higher immune-related adverse events occurring in 8.0% and 13.3% of patients in the pooled analysis and study CA184-338, respectively.

Immune-related adverse events that occurred in the pooled analysis included gastrointestinal and skin, while those occurred in study CA184-338 included gastrointestinal, skin (cutaneous), and liver. Grade 3 or higher immune-related adverse events that occurred in the pooled analysis were gastrointestinal and skin, while those occurred in study CA184338 were gastrointestinal, skin, liver, and Endocrine.

Limitations

Studies included in the pooled analysis had different design and different objectives (one was dose ranging, one was biomarker study, one was phase II and one phase III), these differences in study design would make heterogeneity arise. Overall survival was the primary outcome in only one of the studies (MDX010-20) of which only 13 patients were included in the pooled analysis. In the methods section it was mentioned that only patients who had received ipilimumab alone were included in the analysis; at the checkpoint meeting with the manufacturer it was indicated that 40 patients from study MDX010-80 were included in the pooled analysis, however Hersh et al.[69] indicated that out of the 40 patients randomized to receive 3 mg/kg ipilimumab only 37 patients received ipilimumab monotherapy treatment. These differences in numbers between what is used and what should have been used make the reviewer suspect the quality of the pooled analysis overall and how it was undertaken especially as it is not possible to validate what was done. Patients were included in the analysis if they met certain inclusion criteria, and out of 1,051 patients included in these studies only 78 (7.4%) were included in the pooled analysis. This method of selecting patients for inclusion would introduce bias due to breaking randomization and being selective, also this method is similar to pooling results from case reports which is unreliable. The follow-up period in the pooled analysis ranged from 0.03 to 69.7 months indicating huge variation in the length of follow-up between the studies included in the pooled analysis. Given the limitations mentioned above, there is high risk of bias associated with the pooled analysis. Finally of the 78 chemotherapy naïve patients included in the pooled analysis, 41 received prior immunotherapy treatment, hence ipilimumab would be considered as first line treatment for only 37 patients. There are many limitations related to the analysis of the 37 patients who received ipilimumab as first line treatment, due to the small sample. Given all of the limitations in the pooled analysis mentioned above, conclusions from the pooled analysis should be drawn with extreme caution.

Studies CA184-332 and CA184-338 were generally adequate; however there is high risk of bias associated with their study design. Potential loss to follow-up, missing data, potential for selection bias, and underreported or incomplete data collection based upon available data in patient medical charts are limitations in retrospective observational studies. Also it was unclear whether the same patients were included in the two studies, because both of them enrolled patients treated in the US between April 2011 and September 2014. The dosing schedule of ipilimumab was not reported. None of them reported if prior immunotherapy was used. In the methods sections of both observational studies, it was mentioned that patients for whom at least 12 months have elapsed since initiation of 3 mg/kg ipilimumab were included in the interim analysis, however the range of follow-up was 2.8 to 14.4 month in study CA184-332 and 0.5 to 21.7 month in study CA184-338 which means patients with less than 12 months since the initiation of treatment were included in the analysis, which contradicts what was mentioned in the methods section. This would lead us to suspect the accuracy of the presented results.

7.2.3 Summary

A pooled analysis of treatment-naïve or chemotherapy-naïve advanced melanoma patients who were included in four RCTs (MDX010-20, MDX010-08, CA184-004, and CA184-022) and two ongoing retrospective observational studies (CA184-332, and CA184-338) investigated the use of 3mg/kg ipilimumab monotherapy in patients with unresectable or metastatic melanoma. The pooled analysis included 78 patients while studies CA184-332 and CA184-338 included 90 and 120 patients respectively. There were some clinically relevant differences in the baseline characteristics (such as ECOG performance status, presence of brain metastases, disease stage and duration of melanoma) between the three studies. Median overall survival was 13.47 months in the pooled analysis, while it was 11.5 and 14.3 in studies CA184-332 and CA184-338 respectively. The one year survival rate was 54.1%, 49.4%, and 59.5% in the pooled analysis, study CA184-332, and study CA184-338, respectively. The two and three year survival rates in the pooled analysis were 31.6% and 23.7%, respectively. The adverse events were reported only in the pooled analysis and study CA184-338. Immune-related adverse events of any grade occurred in 84% and 52.5% of patients included in the pooled analysis and study CA184-338, respectively, with Grade 3 or higher immune-related adverse events occurred 8.0% and 13.3% of patients in the pooled analysis and study CA184-338, respectively. Results reported in the pooled analysis might be unreliable due to the many limitations in that analysis. In addition, results from the two observational studies should be interpreted with caution due to the high risk of bias associated with their design.

8 ABOUT THIS DOCUMENT

This Final Clinical Guidance Report was prepared by the pCODR Melanoma Clinical Guidance Panel and supported by the pCODR Methods Team. This document is intended to advise the pCODR Expert Review Committee (pERC) regarding the clinical evidence available on ipilimumab (Yervoy) as first line therapy for advanced melanoma. Issues regarding resource implications are beyond the scope of this report and are addressed by the relevant pCODR Economic Guidance Report. Details of the pCODR review process can be found on the pCODR website (www.pcodr.ca).

pCODR considers it essential that pERC recommendations be based on information that can be publicly disclosed. Information included in the Clinical Guidance Report was handled in accordance with the pCODR Disclosure of Information Guidelines. There was no non-disclosable information in the Clinical Guidance Report provided to pERC for their deliberations.

This Final Clinical Guidance Report is publicly posted at the same time that a pERC Final Recommendation is issued. The Final Clinical Guidance Report supersedes the Initial Clinical Guidance Report. Note that no revision was made in between posting of the Initial and Final Clinical Guidance Reports.

The pCODR Melanoma Clinical Guidance Panel is comprised of three clinical oncologists. The panel members were selected by the pCODR secretariat, as outlined in the pCODR Nomination/Application Information Package, which is available on the pCODR website (www.pcodr.ca). Final selection of the Clinical Guidance Panels was made by the pERC Chair in consultation with the pCODR Executive Director. The Panel and the pCODR Methods Team are editorially independent of the provincial and territorial Ministries of Health and the provincial cancer agencies.

APPENDIX A: LITERATURE SEARCH STRATEGY

See section 6.2.2 for more details on literature search methods.

1. Literature search via OVID platform

Database(s): Database(s): **EBM Reviews - Cochrane Central Register of Controlled Trials** July 2014, **Embase** 1974 to 2014 August 15, **Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present

Original search run on August 18, 2014:

#	Searches	Results
1	(ipilimumab* or yervoy* or winglore* or MDX010 or "MDX 010" or MDX101 or MDX 101 or BMS 734016 or BMS734016 or MDX-CTLA-4 or MDX-CTLA4).ti,ab,ot,sh,hw,rn,nm.	3978
2	(477202-00-9 or 799813-32-4 or 6T8C155666).rn,nm.	2470
3	or/1-2	3978
4	3 use pmez	827
5	3 use cctr	49
6	*ipilimumab/	793
7	(ipilimumab* or yervoy* or winglore* or MDX010 or "MDX 010" or MDX101 or MDX 101 or BMS 734016 or BMS734016 or MDX-CTLA-4 or MDX-CTLA4).ti,ab.	2024
8	or/6-7	2124
9	8 use oemezd	1376
10	(Randomized Controlled Trial or Controlled Clinical Trial).pt.	898073
11	Randomized Controlled Trial/	736244
12	Randomized Controlled Trials as Topic/	157592
13	"Randomized Controlled Trial (topic)"/	56534
14	Controlled Clinical Trial/	475981
15	Controlled Clinical Trials as Topic/	8234
16	"Controlled Clinical Trial (topic)"/	3125
17	Randomization/	165245
18	Random Allocation/	165245
19	Double-Blind Method/	351321

20	Double Blind Procedure/	117385
21	Double-Blind Studies/	312541
22	Single-Blind Method/	51027
23	Single Blind Procedure/	18689
24	Single-Blind Studies/	51027
25	Placebos/	311907
26	Placebo/	256917
27	Control Groups/	65405
28	Control Group/	65405
29	(random* or sham or placebo*).ti,ab,hw.	2729894
30	((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	573289
31	((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw.	1289
32	(control* adj3 (study or studies or trial*)).ti,ab.	871543
33	(Nonrandom* or non random* or non-random* or quasi-random* or quasirandom*).ti,ab,hw.	65695
34	allocated.ti,ab,hw.	112822
35	((open label or open-label) adj5 (study or studies or trial*)).ti,ab,hw.	62575
36	or/10-35	3465824
37	4 or 9	2203
38	36 and 37	567
39	5 or 38	616
40	exp animals/	37417455
41	exp animal experimentation/ or exp animal experiment/	1803203
42	exp models animal/	1206651
43	nonhuman/	4355833
44	exp vertebrate/ or exp vertebrates/	36473251
45	or/40-44	38666856

46	exp humans/	29160533
47	exp human experimentation/ or exp human experiment/	340410
48	or/46-47	29162611
49	45 not 48	9505832
50	39 not 49	612
51	limit 50 to english language	573
52	remove duplicates from 51	456

2. Literature search via PubMed

Original search run on August 18, 2014:

Search	Query	Items found
#3	Search #1 AND #2	45
#2	Search publisher [sb]	456981
#1	Search (ipilimumab OR yervoy OR winglore OR MDX010 OR "MDX 010" OR MDX101 OR "MDX 101" OR "BMS 734016" OR BMS734016 OR “MDX-CTLA-4” OR “MDX-CTLA4”)	819

3. Cochrane Central Register of Controlled Trials (Central)

Searched via Ovid (see above).

4. Grey Literature search via:

Clinical trial registries:

U.S. NIH ClinicalTrials.gov
http://www.clinicaltrials.gov/

Canadian Partnership Against Cancer Corporation. Canadian Cancer Trials
http://www.canadiancancertrials.ca/

Search terms: Inteventions - ipilimumab OR yervoy OR winglore OR MDX010 OR "MDX 010" OR MDX101 OR "MDX 101" OR "BMS 734016" OR BMS734016 OR "MDX-CTLA-4" OR "MDX-CTLA4". Conditions - Melanoma.

Select international agencies including:

Food and Drug Administration (FDA):
http://www.fda.gov/

European Medicines Agency (EMA):
http://www.ema.europa.eu/

Search terms: Yervoy or ipilimumab

Conference abstracts:

American Society of Clinical Oncology (ASCO)
http://www.asco.org/

Search terms: ipilimumab or Yervoy or MDX 010 or "MDX 010" or BMS734016 or "BMS 734016" or MDX 101 or "MDX 101" or Winglore or MDX-CTLA-4 or "MDX-CTLA4" / last 5 years

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