PAN-CANADIAN ONCOLOGY DRUG REVIEW

pan-Canadian Oncology Drug Review
Final Clinical Guidance Report

Ipilimumab (Yervoy) for Advanced Melanoma

April 18, 2012

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1 GUIDANCE IN BRIEF

1.1 Background

The objective of this review is 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 advanced melanoma (stage III or stage IV disease) who have previously received systemic therapy.

1.2 Key Results and Interpretation

1.2.1 Systematic Review Evidence

One multi-centre, randomized, double-blind, placebo-controlled trial (Study MDX010-20, Hodi et al 2010) met the inclusion criteria for the pCODR systematic review.[1] Study MDX010-20 randomized 676 patients with previously treated unresectable stage III or stage IV melanoma in a 3:1:1 ratio to one of three treatment groups, either ipilimumab plus gp100 (n=403), ipilimumab plus placebo (n=137), or gp100 plus placebo (n=136).

The primary endpoint of study MDX010-20 was overall survival for ipilimumab plus gp100 group compared to the gp100 alone group. A significant difference in overall survival was found in favour of ipilimumab plus gp100 (median 10.0 months) compared to gp100-alone (median 6.4 months), with HR 0.68, 95% CI 0.55-0.85, P < 0.001.

Secondary endpoints of study MDX010-20 included overall survival for ipilimumab-alone compared to gp100-alone, best overall response rate, progression-free survival, and duration of response. With respect to overall survival in this comparison, there was a significant difference in favour of the ipilimumab-alone arm (median 10.1 months) compared to the gp100-alone arm (median 6.4 months), with HR 0.66, 95% CI 0.51-0.87, p=0.03. In addition, there were statistically significant differences in progression-free survival and complete or partial response rates in favour of ipilimumab plus gp100 compared with gp100 alone and for ipilimumab alone compared with gp100 alone.

1.2.2 Additional Evidence

pCODR received input on ipilimumab from two patient advocacy groups, Melanoma Network of Canada and Save your Skin Foundation. Provincial Advisory Group input was obtained from eight of the nine of the provinces (Ministries of Health and/or cancer agencies) participating in pCODR.

In addition, one supplemental question was identified during development of the review protocol as relevant to the pCODR review of ipilimumab and is discussed as supporting information:

- Summary of Ipilimumab in the First-Line Setting (Study CA 184-024[2])

1.2.3 Interpretation and Guidance

Recurrent metastatic inoperable melanoma remains a challenge for both patients and treating physicians. Currently available treatments for metastatic melanoma are limited and there is a need for treatment agents that demonstrate improved efficacy and acceptable toxicity.

One randomized controlled trial, study MDX010-20, met the inclusion criteria for the pCODR systematic review. In this study, ipilimumab plus gp100 vaccine, as well as ipilimumab alone, were demonstrated to statistically significantly improve overall survival, progression free survival and complete or partial response rates when compared to gp100 vaccine alone in previously treated, unresectable stage III or stage IV melanoma patients.

Serious adverse events (≥ Grade 3) occurred in 45.5% of patients in the ipilimumab plus gp100 arm, 45.8% of patients in the ipilimumab-alone arm, and 47% of patients in the gp100-alone arm. Most serious adverse events were found to be similar between all three treatment arms, with the exception of diarrhea and fatigue, which were more common in the ipilimumab arms.

There were several limitations identified with study MDX010-20, including the modification of study endpoints while the trial was ongoing, inclusion of only patients with HLA-A*0201 positive melanoma, and the use of gp100 vaccine when it is not currently a Canadian or international standard of treatment. Some of these limitations were addressed in the trial evaluating ipilimumab at 10 mg/kg in the first-line setting.[2]

It was noted that the dosage of ipilimumab used in this second-line trial was 3 mg/kg whereas a trial in the first-line setting utilized a 10 mg/kg dose. To help answer uncertainties with respect to the most appropriate dosage, the FDA has requested a study directly comparing 3 mg/kg versus 10 mg/kg of ipilimumab in both previously treated and untreated patients with metastatic melanoma.[3]

1.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there **is a net overall clinical benefit** to ipilimumab in the treatment of previously treated, unresectable stage III or stage IV melanoma based on one randomized controlled trial, Study MDX010-20,[1] which demonstrated a statistically significant improvement in overall survival for ipilimumab plus gp-100 vaccine compared with gp-100 vaccine plus placebo.

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

- Metastatic melanoma has a significant burden of disease not only to the patients but to society, as noted by patients, caregivers, and treating physicians. To date, there have been limited treatment options and none that have demonstrated an overall survival benefit.
- Although the toxicity associated with ipilimumab can be significant in some cases, the side effects to be manageable and acceptable to patients with melanoma.
- While the manufacturer only requested funding for ipilimumab in previously treated patients, with the publication of randomized controlled trial data evaluating ipilimumab in the first-line setting, patients and clinicians will be interested in the use and funding of ipilimumab for this indication. The randomized controlled trial comparing ipilimumab 3 mg/kg versus 10 mg/kg will address the important issue of the ideal ipilimumab dose.
- Patients who have derived benefit from the first series of ipilimumab induction regimen may derive benefit from re-induction at the time of progression but further evidence is required.

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 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 Clinical Guidance Panel, 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

Ipilimumab has a Health Canada indication for the treatment of unresectable or metastatic melanoma in patients who have failed or do not tolerate other systemic therapy for advanced disease.[4]

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.[5]

Previously treated unresectable stage III or stage IV melanoma is an aggressive skin malignancy with no currently accepted standard therapy. Several agents are used in Canada to treat these patients including dacarbazine, temozolomide, and carboplatin plus paclitaxel.

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 advanced melanoma (stage III or stage IV disease) who have previously received 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 multi-centre, randomized, double-blind, placebo-controlled trial[1,5-15] was identified that investigated the use of ipilimumab 3 mg/kg plus gp100 compared to placebo plus gp100 peptide vaccine compared to ipilimumab 3 mg/kg plus placebo in patients with previously treated unresectable stage III or stage IV melanoma (Study ID: MDX010-20). It should be noted that both the ipilimumab plus gp100 vs.

gp100-alone comparison and the ipilimumab-alone vs. gp100-alone comparison provide useful information. The former (ipilimumab plus gp100 vs. gp100-alone) provides a placebo comparison with ipilimumab by looking at the clinical efficacy of the combination vs. the vaccine alone. The latter comparison looks at the clinical efficacy of ipilimumab as a single agent vs. gp100 as a single agent. A summary of key trial characteristics can be found in Table 1.

The original primary endpoint was best overall response rate (proportion of patients with a partial or complete response) but was changed to overall survival for ipilimumab plus gp100 compared to gp100-alone, based on data from phase II studies and from an ongoing phase III study.[1] That change led to a reassessment of the required sample size. The authors used blinded survival data from the MDX010-20 study as well as historical data to estimate overall survival to determine the new sample size. If the data were unblinded, then the study authors would merely have been calculating the power of the study after the results were already known. Given that the results of the trial remained blinded when the sample size was reassessed, it is reasonable to conclude that the changes did not invalidate the results of the study. In addition, if the primary outcome had not changed, an analysis of overall survival still would have been conducted as it was a secondary endpoint of the study. That analysis still would have found a significant difference in overall survival and if a significant difference were found, then the trial would have been adequately powered to detect that difference.

The baseline demographic and disease characteristics of the study population were balanced between the three treatment arms. The mean age (minimum age to maximum age) was 55.6 years (24 to 84) years in the ipilimumab plus gp100 arm, 56.8 (19 to 88) years in the ipilimumab-alone arm, 57.4 (23 to 90) years in the gp100-alone arm.[1]

Out of the 676 patients who started on the trial 646 patients (95.6%) had either died (77.7%) or had completed the trial (17.9%).[14] The median follow-up was 21.0 months in the ipilimumab plus gp100 group, 27.8 months in the ipilimumab-alone group, and 17.2 months in the gp100-alone group.[1] Of the 30 patients who did not complete the trial, 15 withdrew consent, six were lost to follow-up, one had a protocol violation, and eight discontinued for other reasons.[14]

One potential limitation was the choice of the gp100 vaccine and placebo as the comparators rather than other more commonly used therapies such as dacarbazine or temozolomide. The choice of gp100 was due to the limited treatment options available for this group of patients as well as promising results from a study of gp100 in combination with high-dose interleukin-2.[1] A meta-analysis of 42 phase II trials of metastatic melanoma by Korn et al[16] reported similar median, and one- and two-year overall survivals as that reported for the gp100-alone arm in study MDX010-20 (see Section 2.1.4 for further information) which supports the manufacturers position that gp100 vaccine is at least no worse than placebo. Another potential limitation is that the study included only patients with HLA-A*0201 positive melanoma; however, this patient group was selected because the gp100 vaccine is targeted against HLA-A*0201-positive melanoma. If the treatment effect is partly due to gp100, then the generalizability of the results to patients with HLA-A*0201 negative melanoma is in question as gp100 was designed to target the HLA-A*0201 phenotype. Other studies of ipilimumab have used more standard therapies and included patients with both HLA-A*0201-positive and negative

disease and have reported similar results as study MDX010-20 (see Supplemental Issues in Section 2.1.5 and Section 7).

Table 1. Summary of Included Study, Study MDX010-20[1]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study MDX010-20 125 centres in 13 countries in North America, South America, Europe, and Africa Patients enrolled from September 2004 to August 2008 Enrolled: n=676 Randomized: n=676 Double-blind, placebo-controlled, RCT Randomized in a 3:1:1 ratio Randomization was stratified by: A) Baseline metastasis stage[A] (M0, M1a, M1b, or M1c) B) Prior interleukin-2 therapy (yes or no)	Diagnosis of unresectable stage III or stage IV melanoma and had previously received a therapeutic regimen containing one or more of the following: dacarbazine, temozolomide, fotemustine, carboplatin, or interleukin-2 Age ≥18 years ECOG PS ≤1 Positive for HLA-A*0201 Normal hematologic, hepatic, and renal function No systemic treatment in the previous 28 days	Three arms: Ipilimumab 3 mg/kg plus gp100 peptide vaccine (n=403) Or Ipilimumab 3 mg/kg (n=137) Or gp100 peptide vaccine (n=136) *Note*: gp100 vaccine (or placebo) was administered immediately after ipilimumab. In all three arms, the assigned regimen was administered once every 3 weeks for a total of 4 treatments. A placebo dummy was used in both the ipilimumab-alone arm and the gp100 peptide vaccine-alone arm.	Primary Overall survival (ipilimumab plus gp100 vs. gp100 alone) Secondary Overall survival (ipilimumab plus gp100 vs. ipilimumab alone) Best overall response rate Progression-free survival Duration of response Adverse events Serious adverse events Immune-related serious adverse events Withdrawals due to adverse events Deaths

Notes: ECOG PS=Eastern Cooperative Oncology Group Performance Status.
[A] By TNM categorization for melanoma of American Joint Committee on Cancer.[17,18]

Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the intent-to-treat population, comprised of all randomized study subjects (n=676). The safety population consisted of all randomized patients who had received any amount of study drug (n=643). A summary of key efficacy and harms outcomes can be found in Table 2 below. Outcomes that were important to patients included overall survival, serious or any adverse events, and quality of life.

A statistically significant improvement in median overall survival was observed for ipilimumab plus gp100 (median 10.0 months) compared to gp100-alone (median 6.4

months), with a hazard ratio (HR) of 0.68, 95% confidence interval (CI) of 0.55-0.85, p<0.001.[1] In addition, a statistically significant difference in median overall survival was found for ipilimumab-alone (median 10.1 months) compared to gp100-alone (median 6.4 months), with HR=0.66, 95% CI 0.51-0.87, p=0.003.

The percentage of patients alive for ipilimumab plus gp100 was similar to ipilimumab-alone at one-year (43.6% and 45.6%, respectively), and at two years (21.6% and 23.5%).[1] One-year and two-year overall survival in the gp100-alone arm (25.3% and 13.7%) was lower than either of the ipilimumab arms.[1]

Statistically significant differences in progression-free survival and best overall response rate (complete and partial responses) were found for ipilimumab-gp100 compared to gp100-alone and for ipilimumab-alone compared to gp100-alone (Table 2).[1]

A total of 242 of 403 (60.0%) patients in the ipilimumab plus gp100 arm, 88 of 137 (64.2%) patients in the ipilimumab-alone arm, and 78 of 136 (57.4%) patients in the gp100-alone arm received all four doses of ipilimumab or placebo.[1] A total of 40 patients received reinduction with ipilimumab.[1] Given the small sample size, interpretation of the outcomes data for this subgroup of patients is limited.

Interpretation of the quality of life data is difficult due to the limited nature of the reporting of the quality of life data for study MDX010-20. Health-related quality of life was not reported in the primary publication.[1] The US FDA Medical Review[14] and one conference abstract[6] reported that quality of life was assessed in the trial using the EORTC QLQ C-30 Health Related Quality of Life questionnaire. The US FDA Medical Review reported that there were no meaningful changes in functional or global health scores; however, no data were reported.[14] The abstract publication reported limited data and the authors reported negligible differences in health-related quality of life outcomes in all three study arms.[6]

Serious adverse events (defined as Grade 3 severity or greater) occurred in a similar proportion of patients in each of the three study arms (ipilimumab plus gp100, 45.5%; ipilimumab-alone, 45.8%; gp100-alone, 47.0%); see Table 2). Of note, diarrhea as a serious adverse event was more common in the ipilimumab plus gp100 arm (4.5%) and the ipilimumab-alone arm (5.3%) than in the gp100-alone arm (0.8%).[1] In addition fatigue, as serious adverse event, was more common in the ipilimumab plus gp100 arm (5.0%) and the ipilimumab-alone arm (6.9%) than in the gp100-alone arm (3.0%).[1] However, no statistical comparisons were reported.

Immune-related serious adverse events (≥ Grade 3) occurred in a higher proportion of patients in both ipilimumab arms (10.2% ipilimumab plus gp100; 14.5% ipilimumab-alone) compared to the gp100-alone arm (3.0%; Table 2).[1] The most common immune-related serious adverse events were gastrointestinal, dermatologic, and endocrine.

Withdrawals due to adverse events occurred in 9.2% of patients in the ipilimumab plus gp100 arm, in 13.0% of patients in the ipilimumab-alone arm, and in 3.8% of patients in the gp100-alone arm (Table 2).[14] The most common reasons for withdrawal due to adverse events were diarrhea and colitis.

A similar proportion of patients in all three study arms experienced at least one adverse event of any Grade (Table 2). The following adverse events occurred in more patients in the ipilimumab plus gp100 arm and the ipilimumab-alone arm than in the gp100-alone arm: diarrhea, any immune-related adverse events,

immune-related dermatologic adverse events, and immune-related gastrointestinal adverse events.[1]

Table 2. Summary of Key Trial Outcomes from Study MDX010-20[1,14]

Efficacy	Intervention	Median [months] (95% CI)	HR (95% CI)	p-value
Overall Survival	Ipi + gp100 Gp100-alone	10.0 (8.5-11.5) 6.4 (5.5-8.7)	0.68 (0.55-0.85)	p<0.001
	Ipi-alone Gp100-alone	10.1 (8.0-13.8) 6.4 (5.5-8.7)	0.66 (0.51-0.87)	p=0.003
Progression-free Survival	Ipi + gp100 Gp100-alone	2.76 (2.73-2.79) 2.76 (2.73-2.83)	0.81 (0.66-1.00)	P=0.0464
	Ipi-alone Gp100-alone	2.86 (2.76-3.02) 2.76 (2.73-2.83)	0.64 (0.50-0.83)	p=0.0007
Best Overall Response Rate (CR+PR)	Ipi + gp100 Gp100-alone	5.7% (3.7-8.4) 1.5% (0.2-5.2)	-	p=0.04
	Ipi-alone Gp100-alone	10.9% (6.3-17.4) 1.5% (0.2-5.2)	-	p=0.001
Harms	**Ipi plus gp100 N=380**	**Ipi-alone N=131**	**Gp100-alone N=132**	**Total N= 643**
Deaths, n (%)	7	3	4[A]	14 (2.2)
SAE, n (%)	173 (45.5)	60 (45.8)	62 (47.0)	295 (45.9)
IR-SAE, n (%)	39 (10.3)	19 (14.5)	4 (3.0)	62 (9.6)
Any AE, n (%)	374 (98.4)	127 (96.9)	128 (97.0)	629 (97.8)
AE leading to withdrawal, n (%)	35 (9.2)	17 (13.0)	5 (3.8)	57 (8.9)

Notes: AE=adverse event; CI=confidence interval; Ipi= ipilimumab; SAE=serious adverse event
[A]The number of deaths for the gp100-alone arm was calculated by pCODR by subtracting the number of deaths in the ipilimumab plus gp100 arm[14] and the ipilimumab-alone arm[14] from the total number of deaths.[1]

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 use of the gp100 vaccine in study MDX010-20 was based on the assumption that the vaccine would be no worse than placebo. To support that assumption, the submitter presented evidence in the form of a meta-analysis, reported by Korn et al[16] that investigated overall survival and progression-free survival in all phase II trials of metastatic melanoma conducted by the Southwest Oncology Group, Eastern Cooperative Oncology Group, Cancer and Leukemia Group B, North Central Cancer Treatment Group, and the Clinical Trials Group of the National Cancer Institute of Canada that completed accrual between 1975 through 2005. The authors reported a median overall survival of 6.2 months (95% CI 5.9 months to 6.5 months), with 1-year overall survival of 25.5% (95% CI 23.6% to 27.4%).[16] Study MDX010-20 reported a similar median overall survival (6.4 months; 95% CI, 5.5 months to 8.7 months)[1] and 1-year overall survival (25.3%; 95% CI, 18.1% to 32.9%)[1,19] for patients in the gp100-alone arm of the MDX010-20 trial.

There are however, potential limitations with respect to the results of the meta-analysis. As the authors stated that only the aforementioned clinical trial groups were contacted, it is unlikely that they conducted a systematic literature search for all phase II trials of metastatic melanoma. However, the sample size was fairly large, consisting of a total of 42 trials with 70 trial arms and 2,100 patients. In addition, the authors conducted an individual patient data meta-analysis which is generally considered higher quality and more robust than a summary statistic meta-analysis. Of note, the authors only included trials of metastatic melanoma (Stage IV). The population of interest for the pCODR review of ipilimumab is previously treated unresectable Stage III or Stage IV melanoma. The meta-analysis did not appear to include trials of unresectable Stage III disease, and it likely included trials of both previously treated patients and treatment-naïve patients.

2.1.5 Summary of Supplemental Questions

Ipilimumab in the First-Line Treatment of Unresectable Stage III or IV Melanoma

The scope of the current pCODR review of ipilimumab is for patients with previously systemically treated disease. Limitations of the Hodi 2010 (MDX010-20)[1] trial evaluating ipilimumab in this setting may have been addressed, in part, in trials evaluating ipilimumab in the first-line setting and would provide supportive information to the pCODR systematic review. A review (non-systematic) of the first-line trials of ipilimumab in the setting of stage III or IV melanoma was conducted. The objective was to report on the efficacy and harms of ipilimumab, as evaluated in trials conducted in the first-line treatment setting of unresectable stage III or IV melanoma. Issues common to the first and second-line setting were investigated, where identified. One double-blind RCT was identified that investigated ipilimumab plus dacarbazine compared to dacarbazine plus placebo.[2] A total of 502 patients were randomized 1:1 to receive either ipilimumab at 10 mg/kg plus dacarbazine 850 mg/m^2 (n=250) or to dacarbazine 850 mg/m^2 (n=252). Of note, the dose of ipilimumab in study CA184-024[2] (first-line setting) was

different than that in study MDX010-20[1] (second-line trial). Both trials were double-blind, placebo-controlled RCTs. There were differences in the studies: Study CA184-024 investigated ipilimumab plus dacarbazine compared to dacarbazine-alone in the first-line setting whereas study MDX010-20 investigated ipilimumab plus gp100 vaccine compared to gp100-alone compared to ipilimumab-alone in the second-line setting. The second-line trial (MDX010-20) enrolled patients with HLA-A*0201-positive melanoma whereas the first-line trial (CA184-024) included patients irrespective of HLA-A status. In the first-line trial (CA184-024), ipilimumab plus dacarbazine was demonstrated to have statistically significant increased overall survival compared to dacarbazine alone (median 11.2 months vs. 9.1 months; HR = 0.72, 95% CI 0.59-0.87, p<0.001). This result is similar to the overall survival results from the second-line trial (MDX010-20) comparing ipilimumab plus gp100 to gp100-alone. The CA184-024 first-line trial also demonstrated increased progression-free survival (Table 11, Section 7.1) in the ipilimumab plus dacarbazine arm. A similar result was observed in the second-line MDX010-20 trial. The adverse events reported in both trials were similar. The adverse events experienced by patients in the first-line CA184-024 study in the ipilimumab arm were similar to those reported for patients in the ipilimumab arms of the second-line MDX010-20 study and included serious or any grade of immune-related adverse events, serious or any grade of diarrhea, and any grade of colitis, pruritis, and rash.

See section 7.1 for more information.

2.1.6 Other Considerations

Patient Advocacy Group Input

From a patient perspective, extending life expectancy to allow more time with family is an important aspect when consideration is given to treatment. There are currently very few effective treatments available in Canada for advanced melanoma and patients welcome new effective therapies. Although ipilimumab is associated with some side effects, patients indicated that they are willing to tolerate certain side effects if this means extending their life expectancy. Patients are also looking for a therapy that will help to improve their quality of life and enable them to continue to work and provide financially for their families.

PAG Input

Input on the ipilimumab review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, dosing issues with ipilimumab would be of greatest importance, including the difference in treatment outcomes and side effect profiles between the 10mg/kg dosage used in the first-line melanoma clinical trial and the 3mg/kg dosage used in the second-line clinical trial. Furthermore, PAG identified that the additional costs of HLA testing if it is required for ipilimumab, the potential for patients to receive more than 4 doses of ipilimumab, and the additional resources required to administer an intravenous product and monitor for potential serious side effects could have an impact on the overall cost-effectiveness of ipilimumab and would need to be considered in the evaluation, as relevant.

Other

- The final Health Canada product monograph for ipilimumab (Yervoy) provided by the manufacturer (Bristol-Myers Squibb [BMS] Canada) provides the following warnings:[4]

  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.

- The US FDA approval for ipilimumab in advanced melanoma mandated the manufacturer (BMS) to design and conduct a clinical trial comparing the efficacy (primary outcome to be overall survival) and safety of ipilimumab monotherapy at doses of 3 mg/kg versus 10 mg/kg every three weeks for four doses in patients with unresectable stage III or stage IV melanoma.[3] This requirement is to establish which dose is more effective in this patient group.

2.2 Interpretation and Guidance

Burden of Illness and Therapeutic Options for Advanced Melanoma
Recurrent metastatic inoperable melanoma remains a challenge for both patients and treating physicians.

Current treatment is limited to traditional chemotherapy agents such as dacarbazine, temozolomide and paclitaxel plus carboplatin. The response rate and overall survival for these drugs have been very low with response rates generally less than 15%, median survival of approximately six to 12 months and five-year survival rate of approximately six percent. Therefore, there is a need for further treatment with agents that demonstrate both efficacy and acceptable toxicity.

Ipilimumab is a fully humanized anti-CTLA4 antibody which blocks CTLA4, inhibiting its negative signaling and therefore enhancing the immune response. As its mechanism of action initially causes an inflammatory response, traditional response criteria (e.g. best overall response, progression free survival) are hard to interpret as continued response may be seen weeks after treatment has been completed. Therefore, the endpoints of overall survival, percent surviving at one year, two years and five years become the most relevant clinical endpoints in advanced melanoma.

Hodi 2010 Study

In the pivotal placebo controlled trial by Hodi et al ipilimumab was initially studied as a second line treatment in which a total of 676 HLA-A*0201 positive patients with unresectable stage III or IV melanoma who had received prior systemic treatment. Patients were randomized to receive ipilimumab 3 mg/kilogram plus gp100 or ipilimumab 3 mg/kilogram plus placebo or placebo plus gp100.[1]

Study endpoints were adjusted in conjunction with the FDA in response to emerging information and experience with the drug in which the endpoint of the objective response was changed to overall survival. The original sample size calculation for best overall response was revised for a primary end point of overall survival. The statistical calculation was undertaken prior to unblinding of the study results, therefore, it is reasonable to conclude that the changes did not invalidate the results of the study.

As gp100 vaccine had shown efficacy in HLA 002 positive patients this was an eligibility criteria for this study. However, based on the efficacy in non selected HLA populations in other ipilimumab studies CA184-024, CA118-4022, CA184-024, HLA 002 status does not appear to influence the efficacy of ipilimumab.

Effectiveness of Ipilimumab

The median overall survival for patients receiving ipilimumab plus gp100 was 10 months, ipilimumab alone was 10.1 months and gp100 alone was 6.4 months. This indicated that ipilimumab combined with gp100 had a 32% reduction in the risk of death ($P < 0.001$) and similarly ipilimumab as monotherapy had a 34% reduction in the risk of death ($P = 0.003$). The survival at one year for ipilimumab plus gp100 was 43.6% and two-year overall survival was 21.6%; ipilimumab alone was 45.6% at one-year and two-year overall survival was 23.5%; gp100 alone one year overall survival was 25.3% and two-year survival was 13.7%. Since the original publication there is no further update on the overall survival for the study except for an abstract by Haanen in the Annals in Oncology.[7] In the abstract, survival greater than three years in the ipilimumab plus gp100 vaccine 6%, ipilimumab alone 9.5% and gp100 vaccine 3.7%. It is noted as these patients were followed by telephone contact not all patients were followed for two years or more, therefore the number of long term survivors is likely under estimated.

Due to confounding features with respect to assessing response and progression free survival, data is difficult to interpret and up to 10% of individuals are missing tumour assessments. Finally, approximately 40 patients in the Hodi study were candidates for re-induction treatment. Response rates were achieved in 13% of patients in the ipilimumab plus gp100 group, 37.5% of patients in the ipilimumab alone group and none in the gp100 alone group.

There is unfortunately limited quality of life information available in the Hodi study. In an abstract published by Revicki in Annals of Oncology there appeared to be little decline in the health related quality of life during the 12 weeks of the re-induction treatment.[6] Further details on both short-term and long-term quality of life are awaited.

There are several significant limitations to this study. This is a relatively small single Phase III trial in patients with previously treated melanoma. The study was modified over its course. The gp100 vaccine was included in intervention and control groups and is currently not a Canadian or international standard of care. The manufacturer indicated that the melanoma targeted gp100 vaccine was chosen because as at the time this study was initiated it appeared to be a promising agent and had shown evidence of an immune response in immunized patients. The survival outcomes compared with historical data of

dacarbazine indicates that gp100 vaccine is no worse than placebo treatment or first-line treatment.

Supporting Trials Evaluating Ipilimumab

In support of the efficacy of ipilimumab there is a first line study (Robert et al 2011) in which 502 previously untreated metastatic melanoma patients were randomized to ipilimumab 10 mg/kg plus dacarbazine versus placebo plus dacarbazine.[2] As in the Hodi 2010 study[1] the primary endpoint was also changed from progression-free survival to overall survival in discussion with the FDA. The overall survival in the ipilimumab plus dacarbazine arm was 11.2 months versus 9.1 months in the dacarbazine alone arm (HR=0.72, P < 0.001). Survival was improved in the ipilimumab plus dacarbazine arm versus dacarbazine with a one year survival of 47.3% versus 36.3%, respectively, two-year survival of 28.5% versus 17.9%, respectively, and three-year survival of 20.8% versus 12.2 %, respectively. Many of the limitations in the Hodi 2010 trial were addressed in this first-line trial, such as including all patients regardless of HLA 002 status and using a standard comparator [2].

Ipilimumab Dosing

The Health Canada approved dosing of ipilimumab is 3mg/kg per every three weeks for four doses in the second line setting. However, the optimal dose of ipilimumab has been questioned given that ipilimumab 3 mg/kg was evaluated in previously treated patients (Hodi 2010) and ipilimumab 10 mg/kg has been evaluated in the first-line setting (Robert 2011). The FDA has requested a study directly comparing 3 mg/kg versus 10 mg/kg of ipilimumab and this will be undertaken in previously treated and untreated patients with metastatic melanoma.[3] It will be important in this trial that the previously treated patients that there is stratification for type of prior treatment with respect to systemic chemotherapy, molecular targeted agents or immune modulating agents. In the interim, different studies examining different ipilimumab doses have been considered including MDX010-20, CA184-022 and CA184-008. The median survival time for the 3 mg/kg dose has ranged from 8.7 months to 10.1 months across different studies and for the 10 mg/kg dose median survival has ranged from 10.2 to 11.4 months across different studies. However, cross-trial comparisons are limited in their nature. The phase II trial by Wolchok et al randomized previously treated metastatic melanoma patients to ipilimumab 0.3 mg/kg, 3 mg/kg, 10 mg/kg every three weeks for four doses.[20] However the study was not designed to determine overall survival and the data suggest a non-significant trend towards improved survival with increased dose. The trial requested by the FDA will hopefully address this important issue of optimal ipilimumab dosing.

Safety of Ipilimumab

As ipilimumab causes an up regulation of the immune system, it is associated with significant toxicity with respect to immune-related adverse events such as colitis, hepatitis and endocrinopathy. In an effort to understand the impact of adverse events on the administration of this drug several data points may be important. The proportion of patients completing all four treatments was approximately 60-64% in the ipilimumab groups and 57% in the gp100 alone group. Approximately 10-15% of patients receiving ipilimumab suffered grade three or four immune related adverse advents compared with 3% patients in the gp100 alone group. Approximately, 9-13% of ipilimumab patients withdrew due to adverse events compared with 4% of patients in the gp100 group. In an effort to effectively manage the toxicity of ipilimumab, guidelines and physician education will be very important. Prompt recognition of side effects and administration of steroids appear to attenuate the side effects of this drug. The side effect profile may predict

response to disease, as up regulation of the immune system resulting in toxicity also appears to correlate with improved survival.

2.3 Conclusions

The pCODR Melanoma Clinical Guidance Panel concluded that there **is a net overall clinical benefit** to ipilimumab in the treatment of previously treated, unresectable stage III or stage IV melanoma based on one randomized controlled trial, Study MDX010-20,[1] which demonstrated a statistically significant improvement in overall survival for ipilimumab plus gp-100 vaccine compared with gp-100 vaccine plus placebo.

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

- Metastatic melanoma has a significant burden of disease not only to the patients but to society, as noted by patients, caregivers, and treating physicians. To date, there have been limited treatment options and none that have demonstrated an overall survival benefit.

- Although the toxicity associated with ipilimumab can be significant in some cases, the side effects to be manageable and acceptable to patients with melanoma.

- While the manufacturer only requested funding for ipilimumab in previously treated patients, with the publication of randomized controlled trial data evaluating ipilimumab in the first-line setting, patients and clinicians will be interested in the use and funding of ipilimumab for this indication. The randomized controlled trial comparing ipilimumab 3 mg/kg versus 10 mg/kg will address the important issue of the ideal ipilimumab dose.[3]

- Patients who have derived benefit from the first series of ipilimumab induction regimen may derive benefit from re-induction at the time of progression but further evidence is required.

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.

3.1 Description of the Condition

Melanoma is a cancer of melanocytes, which are the cells that produce the pigment in skin. Melanoma may occur in any site in the body with the most common site being that of the skin. Melanoma represents the skin cancer with the most aggressive features. Canadian Cancer Statistics 2011 indicates that the estimated new cases of melanoma for 2011 will be 5,500 with a slight male predominance.[21] The deaths from that will be approximately 950. This represents approximately 3% of all new cancer diagnosis within Canada.

Melanoma is staged using the current American Joint Committee on Cancer 7th edition.[17,18] The prognostic features for melanoma include the Breslow level, ulceration, mitotic rate of the primary tumour, lymph nodes status and evidence of metastatic disease. The prognostic and predictive factors for treatment of melanoma include age, sex, sites of disease, bulk of disease, LDH.

3.2 Accepted Clinical Practice

In its earliest stage melanoma is cured with appropriate surgical management including excision of the primary tumour with appropriate margins. Depending upon the T-stage, a sentinel lymph node biopsy maybe indicated with consideration of complete lymphadenectomy.[22] The latter is still somewhat a topic of debate amongst clinicians. However, approximately 5% of patients present with metastatic melanoma and those with stage III and above have a significant risk of recurrent disease. With isolated metastases, surgery is an option for metastatic disease. Radiotherapy maybe used for bulky nodal disease or metastatic disease. When surgery is not appropriate for metastatic disease systemic therapy is often discussed with the patient. As melanoma has been labeled as being relatively chemotherapy resistant, single agents, multiple agent regimens and most new drugs have been tested against melanoma.[23] Based on *in vivo* and *in vitro* data the course of melanoma is felt to be significantly affected by the immune system. In spite of multiple phase II and III trials the objective response rate in phase III trials remains dismally poor at approximately[24] 15-20%.[25,26] The median survival with single and multiple drug combinations ranges from approximately six to 12 months and the five-year survival rate is approximately six percent.[16] The standard first line therapy is currently dacarbazine.[22,27] Although it is well tolerated durable complete remissions are limited. Dacarbazine has been combined with other systemic chemotherapy agents as well as immune modulating agents including Interleukin II and Interferon.[28] Although objective response rates have improved in some trials this has not translated to improved progression free survival and overall survival. All combinations have seen a small percentage of patients approximately 5% with complete durable remissions.[24,25,29-43]

The second agent often used for this disease is temozolomide. This has been compared to dacarbazine in phase III trials and shows similar progression free survival overall survival with better tolerated side effects.[44-47] Its oral administration provides ease of

administration. As temozolomide crosses the blood brain barrier it may be used in situations with patients with melanoma and known brain metastases. A second line regimen including paclitaxel plus carboplatin has been explored as a second line regimen.[48,49] This regimen had a progression free survival of 17.9 weeks. However, in first line treatment median progression free survival was approximately 4.1 months with overall survival of 11.3 months. Interleukin-2 obtained FDA approval in the late 1990s. This was based on phase II data which revealed an overall response rate of 16%, 6% complete response, and partial response of 10% and median survival of 12 months.[31] The median duration for patients who obtained a complete response was greater than 59 months and those patients who were disease free at 30 months did not develop disease recurrence. High dose interleukin-2 however is accompanied by a significant toxicity profile requiring intensive care monitoring and frequent use of pressor agents. The ability to complete the planned course of treatment initially pioneered by Rosenberg has been limited.

3.3 Evidence-Based Considerations for a Funding Population

Ipilimumab may have a role in both metastatic disease and adjuvant treatment for patients at high risk of recurrence. It is currently licensed for metastatic and recurrent disease. Ipilimumab would be available for all patients with recurrent disease. The risk of recurrence for Stage I disease is approximately 15%, for Stage II disease approximately 50% and for Stage III disease the risk of recurrence varies from 30% for Stage IIIA to 80% for Stage IIIC.[18] It would be expected that this drug would be considered for patients who did not have isolated metastases that were considered potentially curable with surgical intervention.[50] As ipilimumab is a human immunoglobin anti-CTLA-4 antibody, its method of effectiveness is not by targeting molecular pathways within the melanoma cell but rather by an interaction with the immune system. It inhibits CTLA interaction with B7 & B7.2. This therefore inhibits the down regulatory role of the CTLA molecule. Blocking CTLA ligation enhances T-cell responses.[51] Not surprisingly its major significant adverse events have been immune regulatory mediated events.[2,20,26,52-55] Ipilimumab has been studied with recurrent/metastatic melanoma with the primary site being skin or the primary site unknown. Based on this adverse event and toxicity profile patients with autoimmune diseases would not be eligible for this medication.[1] Patients who were on immunosuppressive treatment for other co-morbidities similarly would not be eligible for ipilimumab.

With the advent of BRAF inhibitors for patients with melanoma, it is unknown how treatment sequencing with ipilimumab may occur. There is limited data on response to ipilimumab given as second line treatment following progression while taking a BRAF inhibitor. Expert opinion leaders suggest that ipilimumab may be most effective in patients who have slowly progressive disease or lower bulk of disease and in those patients who have a BRAF mutation appropriate for a BRAF inhibitor and have rapidly progressive disease that ipilimumab would be most suitable in the second line setting for those individuals.

3.4 Other Patient Populations in Whom the Drug May Be Used

Ipilimumab is being studied in other tumour sites including lung and patients with brain metastases. In addition, options for the first-line treatment of patients with advanced melanoma are limited. With the publication of randomized controlled trial data evaluating ipilimumab in the first-line setting, ipilimumab is likely to be used for this indication,

although Health Canada approval has not yet been received. The randomized controlled trial comparing ipilimumab 3 mg/kg versus 10 mg/kg will address the important issue of the ideal ipilimumab dose.[3] Therefore, there remains an unmet clinical need for first and second line treatment in patients with metastatic/recurrent melanoma.[56,57] Depending upon drug development the drug could be used in combination with standard chemotherapy or as a stand alone agent.

4 SUMMARY OF PATIENT ADVOCACY GROUP INPUT

The following patient advocacy groups provided input on ipilimumab for advanced melanoma and their input is summarized below:

- Melanoma Network of Canada.
- Save Your Skin Foundation

The Melanoma Network of Canada conducted an anonymous online survey to gather information about the patient and caregiver experience related to the medical condition and drug under review. The survey was administered via Constant Contact, an online survey and tool designed for small business, organizations, and non-profits, and consisted of multiple choice questions, ranking questions and free-form commentary. Response to the survey was solicited via cancer centers in Canada and on the Melanoma Network of Canada website. There were a total of 42 respondents to Part I of the survey, 8 respondents to Part II of the survey and 7 respondents to Part III of the survey.

The Save Your Skin Foundation conducted one-on-one interviews to gather information about the patient and caregiver experience related to the medical condition and drug under review.

From a patient perspective, extending life expectancy to allow more time with family is an important aspect when consideration is given to treatment. There are currently very few effective treatments available in Canada for advanced melanoma and patients welcome new effective therapies. Although ipilimumab is associated with some side effects, patients indicated that they are willing to tolerate certain side effects if this means extending their life expectancy. Patients are also looking for a therapy that will help to improve their quality of life and enable them to continue to work and provide financially for their families.

Please see below for a summary of specific input received from the patient advocacy groups.

4.1 Condition and Current Therapy Information

4.1.1 Experiences Patients have with Advanced Melanoma

Patients with advanced melanoma may experience a number of debilitating symptoms as a result of their cancer, which can have a negative impact on their quality of life. Some of these symptoms include shortness of breath, severe pain, fatigue, loss of coordination, loss of sight, lymphedema and weight loss. In addition, patients with metastatic disease may experience further symptoms dependent upon the site of the metastases, including headaches, numbness in the extremities, bone fractures, hair loss, depression, anxiety, memory loss, decreased mobility and constipation.

Patient input indicated that advanced melanoma can have an effect on the patient's physical appearance. In addition, surgeries to remove tumours can lead to scarring which can further impact the physical appearance of the patient and cause body image issues. Furthermore, surgeries to remove tumours or lymph nodes can lead to decreased mobility and a loss of functioning or capacity of certain organs.

Patients may experience various psychological effects with their diagnosis, including fear, anxiety and depression. Moreover, it is not uncommon for patients to experience moderate to severe emotional distress when dealing with melanoma.

Many patients with melanoma are unable to continue employment, either due to anxiety and depression surrounding the diagnosis or loss of mobility due to muscle and tissue removal during surgery. This can lead to emotional and financial hardships for patients and their families.

From a patient perspective, treatment alternatives that prevent the progression of the disease or securing funding for new treatments that can stop the progression of the cancer are important considerations.

4.1.2 Patients' Experiences with Current Therapy for Advanced Melanoma

Current therapies for advanced melanoma include interferon, dacarbazine, temozolomide, stereotactic radiation (for brain stem tumours) and interleukin-2. Patient input highlighted that the current medications available for the treatment of melanoma are fairly limited and relatively ineffective.

With the currently available treatment options, patients often experience numerous side effects, many of which were felt by patients to be severe and debilitating. Patients indicated that side effects related to treatment leads to a decreased quality of life overall. For example, patients receiving interferon treatment reported experiencing fatigue, nausea, flu-like symptoms, decreased mood, fever, chills, compromised liver function, hair loss and weight loss. As a result of side effects, some patients have had to discontinue treatment prematurely.

Furthermore, patient input highlighted that access to currently available treatment agents can be difficult for some patients. Some patients have been required to travel considerable distances to receive treatment and incurred several expenses, such as flight, hotel, meals and rental car. Securing funding for treatments was raised as an issue for a number of patients as well, particularly with respect to treatments that were received out-of-hospital. Some patients found it necessary to participate in clinical trials due to a lack of drug coverage.

Patients indicated that there is potentially a high tolerance for side effects from new treatments, particularly if those side effects can be effectively managed and the treatment they were receiving could extend their life. A survey conducted by one of the patient groups indicated that quality of life is considered a "fairly important aspect" when deciding to take a new treatment. Respondents to a survey conducted by the other patient advocacy group indicated that approximately half of patients would try anything to try to cure their cancer whereas the other half would be willing depending on the severity of the side effects.

4.1.3 Impact of Advanced Melanoma and Current Therapy on Caregivers

Patient advocacy group input indicated that the impact of this cancer on caregivers can be quite significant. Caregivers are required to take on a number of additional roles, including helping patients in managing adverse effects of treatment, making up for lost income, assuming more household duties, and providing emotional support.

Caregivers are often required to cancel long-term plans. Community and social involvement can be adversely affected by the physical requirements, time commitments and emotional stress of caring for the patient. Some families have had to hire a caregiver for the patient at considerable expense if they cannot free themselves from work obligations.

Being a caregiver can be a challenging role and some report being overstressed.

4.2 Information about the Drug Being Reviewed

4.2.1 Patient Expectations for and Experiences to Date with Ipilimumab

Input from patients without direct experience with ipilimumab highlighted the fact that there are currently very few effective treatments available in Canada for advanced melanoma and effective treatment options for this disease would be welcomed by patients as well as their families.

Patients with advanced melanoma are seeking drug therapies which would help to extend their life expectancy and allow them more time to spend with their family. Treatments which result in a positive impact on quality of life for patients and their families, such as milder side effects or more manageable treatment protocols, would be considered an additional benefit of any therapy for advanced melanoma. In addition, patients seek a treatment that will enable them to continue to work and continue to provide financially for their families.

Overall, patients deem that the benefits of a new therapy which offers the above benefits outweigh the potential risks that may be encountered.

Patients with direct experience with ipilimumab indicated they had positive effects from the treatment. One patient reported experiencing complete tumour regression, another patient reported a three year disease-free period, and a third patient has surpassed the life expectancy given to them by their oncologist. Patients have also reported that ipilimumab has helped to eliminate, shrink and stabilize their tumours.

In addition, some patients report that they were able to return to work and provide financially for their families while receiving ipilimumab treatment. A number of patients also indicated that they are able to live a relatively normal and full life after receiving ipilimumab treatment.

Patient input also pointed to the fact that many patients found ipilimumab easier to use than other therapies currently available for advanced melanoma.

Although input from the patient advocacy groups indicated that patients did experience side effects with ipilimumab, most of the side effects, such as diarrhea, skin break-outs, fatigue, nausea and itching, were found to be mild and manageable for the most part. A survey performed by one of the patient advocacy groups indicated that the side effects from ipilimumab were found to be much milder overall compared to other treatments for advanced melanoma.

4.3 Additional Information

One of the patient advocacy groups indicated that locating patient members in the community can be a challenge. In addition, they indicated that it would be helpful if physicians who treat advanced cancer had more knowledge and understanding of the pCODR process. It was also suggested that a set of standardized patient questions which could be passed by a Research Ethics Board on a one-time basis on behalf of all patient groups could help to avoid delays in submitting patient advocacy input.

5 SUMMARY OF PROVINCIAL ADVISORY GROUP (PAG) INPUT

The following issues were identified by the Provincial Advisory Group as factors that could affect the feasibility of implementing a funding recommendation for ipilimumab for 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).

Input on the ipilimumab (Yervoy) review was obtained from eight of the nine provinces (Ministries of Health and/or cancer agencies) participating in pCODR. From a PAG perspective, dosing issues with ipilimumab would be of greatest importance, including the difference in treatment outcomes and side effect profiles between the 10mg/kg dosage used in the first-line melanoma clinical trial and the 3mg/kg dosage used in the second-line clinical trial. Furthermore, PAG identified that the additional costs of HLA testing if it is required for ipilimumab, the potential for patients to receive more than 4 doses of ipilimumab, and the additional resources required to administer an intravenous product and monitor for potential serious side effects could have an impact on the overall cost-effectiveness of ipilimumab and would need to be considered in the evaluation.

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

5.1 Factors Related to Comparators

PAG noted that there are few options available for the second-line treatment of advanced melanoma. Ipilimumab appears to represent a new standard of care in this setting where previously patients would have received treatment with interferon, temozolomide or dacarbazine or enrolled in a clinical trial.

PAG noted that the pivotal trial for ipilimumab utilized a vaccine as the comparative agent which is not currently used for the treatment of advanced melanoma in Canada.

5.2 Factors Related to Patient Population

As advanced melanoma affects a relatively small patient population, PAG recognized that there may only be a small number of patients accessing ipilimumab.

PAG noted that the patient population in the clinical trial for ipilimumab were HLA-A 0201-positive patients. Evidence on the efficacy of ipilimumab in patients who are HLA-A 0201-negative would be helpful to understand if it a relevant marker.

PAG identified that ipilimumab could be used in other clinical settings, especially in the first-line treatment of advanced melanoma given that there is currently a published clinical trial in the first-line setting demonstrating an overall survival advantage. In addition, PAG noted that the recommended dosage schedule for first-line treatment is higher than that in second-line and thus, it will likely be more costly to use in the first-line setting which would be considered a barrier for jurisdictions to implement funding resources. Therefore, evidence comparing the efficacy and safety of ipilimumab in the first versus second-line setting may be needed if funding were to be provided for this population.

5.3 Factors Related to Accessibility

PAG noted that ipilimumab requires intravenous administration and subsequent monitoring for serious side effects and as such, would have to be given in an advanced facility. PAG identified that this may present as a barrier to accessibility. This may impact patients in less central or rural areas who cannot travel to specialized treatment centres. In addition, PAG identified that there may be limits to the number of patients that could be treated at each specialized center due to increased resources required for administration and monitoring. Although it is anticipated that only a small number of patients will be accessing ipilimumab treatment, the current treatment options for second-line therapy do not require such specialized resources.

Alternatively, as ipilimumab is administered in specialized treatment centers, access to clinical expertise and specialized monitoring would be available, which would be considered an enabler to therapy.

PAG identified that the patient population in the ipilimumab clinical trial were HLA-A 0201-positive. Additional information on HLA testing, if it is required for ipilimumab therapy, would be helpful, including whether the test has been approved by Health Canada, the costs of the test and the accuracy of the test. Information on how HLA testing could be implemented into jurisdictions would also be helpful to determine potential staffing needs and additional budget impact. Furthermore, it would be helpful for PAG to be aware of any clinical data on the use of ipilimumab in patients who are not HLA-A 0201-positive and whether it is possible that patients who have not received the HLA test at all may still receive treatment with ipilimumab.

As some jurisdictions do not currently fund any therapies for the second-line treatment of advanced melanoma, introduction of ipilimumab would be expected to increase overall costs to provincial drug programs.

Some patients may travel out of province to receive treatment in a clinical trial; PAG recognized that having an option for these patients to receive a treatment in their own province would likely be more beneficial to the patient.

5.4 Factors Related to Dosing

PAG recognized that the appropriate dosage of ipilimumab may become an issue for jurisdictions as a 10mg/kg dosage was used in the first-line trial and a 3mg/kg dosage was used in the second-line trial. Therefore, it would be beneficial to have any available information on the comparative efficacy and safety of the two different dosing regimens in the second-line treatment setting. Furthermore, PAG noted that dose reductions, dose increases or dose interruptions may occur with ipilimumab, depending on patient response, and information on the efficacy and safety of this practice would be of interest to jurisdictions.

PAG identified that there may be uncertainty surrounding the appropriate duration of treatment with ipilimumab. Although the manufacturer recommends that ipilimumab be given for a total course of four doses, additional doses were given to patients in the clinical trial. PAG noted that jurisdictions may be pressured to fund more than 4 doses of

ipilimumab. In addition, PAG would be interested to understand the cost of additional doses in the overall budget impact analysis.

As ipilimumab requires intravenous administration and patients must also be monitored for side effects from the treatment, it is likely that tertiary care expertise will be required.

5.5 Factors Related to Implementation Costs

PAG noted that there would be additional strains placed on many resources, such as additional pharmacy resources for preparing the ipilimumab, additional nursing time for administration and monitoring of patients and additional chemo chair time. PAG estimates that each treatment session would require approximately three hours (90 minutes for the infusion and 1 hour for monitoring time) of chemo chair time. Additional costs in the way of laboratory tests and in-line filters would also be required. PAG would be interested in seeing these additional resources factored into the economic analysis.

As ipilimumab is associated with some severe side effects, patients will require close monitoring after each dose of ipilimumab. In addition, treatment of any serious, life threatening side effects may require hospitalization, which PAG would also be interested in seeing incorporated into the economic analysis.

Since ipilimumab is an intravenous medication, there is a potential for drug wastage. The commercial product in the US is available in two different size formats, 50mg and 200mg, and instructions recommend discarding part vials. PAG noted that more information on the stability of opened vials would be beneficial. In addition, it would be helpful to factor the potential for wastage into the economic analysis.

5.6 Other Factors

PAG identified that ipilimumab is the first agent that has demonstrated an improvement in overall survival in advanced melanoma in many years.

6 SYSTEMATIC REVIEW

6.1 Objectives

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 advanced melanoma (stage III or stage IV disease) who have previously received systemic therapy (see Table 3 in Section 6.2.1 for outcomes of interest and comparators).

Note: One supplemental question relevant to the pCODR review and to the Provincial Advisory Group was identified while developing the review protocol and is outlined in section 7.

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 3. Selection Criteria

Clinical Trial Design	Patient Population	Intervention	Appropriate Comparators*	Outcomes
Published or unpublished RCT	Patients with unresectable stage III or stage IV melanoma who previously received systemic therapy.	Ipilimumab alone or in combination	Dacarbazine Temozolomide Interferon-alfa 2b gp100 vaccine Aldesleukin Best supportive care Placebo	- **Overall survival** - Progression-free survival - Response rate - **Serious adverse events** (immune mediated) - **Adverse events** - WDAEs - **QOL** - % patients requiring maintenance doses -% patients requiring re-induction
i.v.=intravenously; RCT=randomized controlled trial.				

** 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-November Week 3, 2011) with in-process records & daily updates via Ovid; EMBASE (1980-Week 46, 2011) via Ovid; The Cochrane Central Register of Controlled Trials (2011, Issue 4) via Wiley; 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 and melanoma.

Methodological filters were applied to limit retrieval to randomized controlled trials and controlled clinical trials as the initial number of citations was greater than 500. Where possible, retrieval was limited to the human population. Retrieval was not limited by publication year. Retrieval was not limited by language.

The initial search was completed on December 7, 2011 and was updated during the review. The search is considered up to date as of March 5, 2012.

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 Ontario Institute for Cancer Research. Ontario Cancer Trials) and relevant conference abstracts. Searches of conference abstracts of the American Society of Clinical Oncology (ASCO) and European Society for Medical Oncology (ESMO) 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.

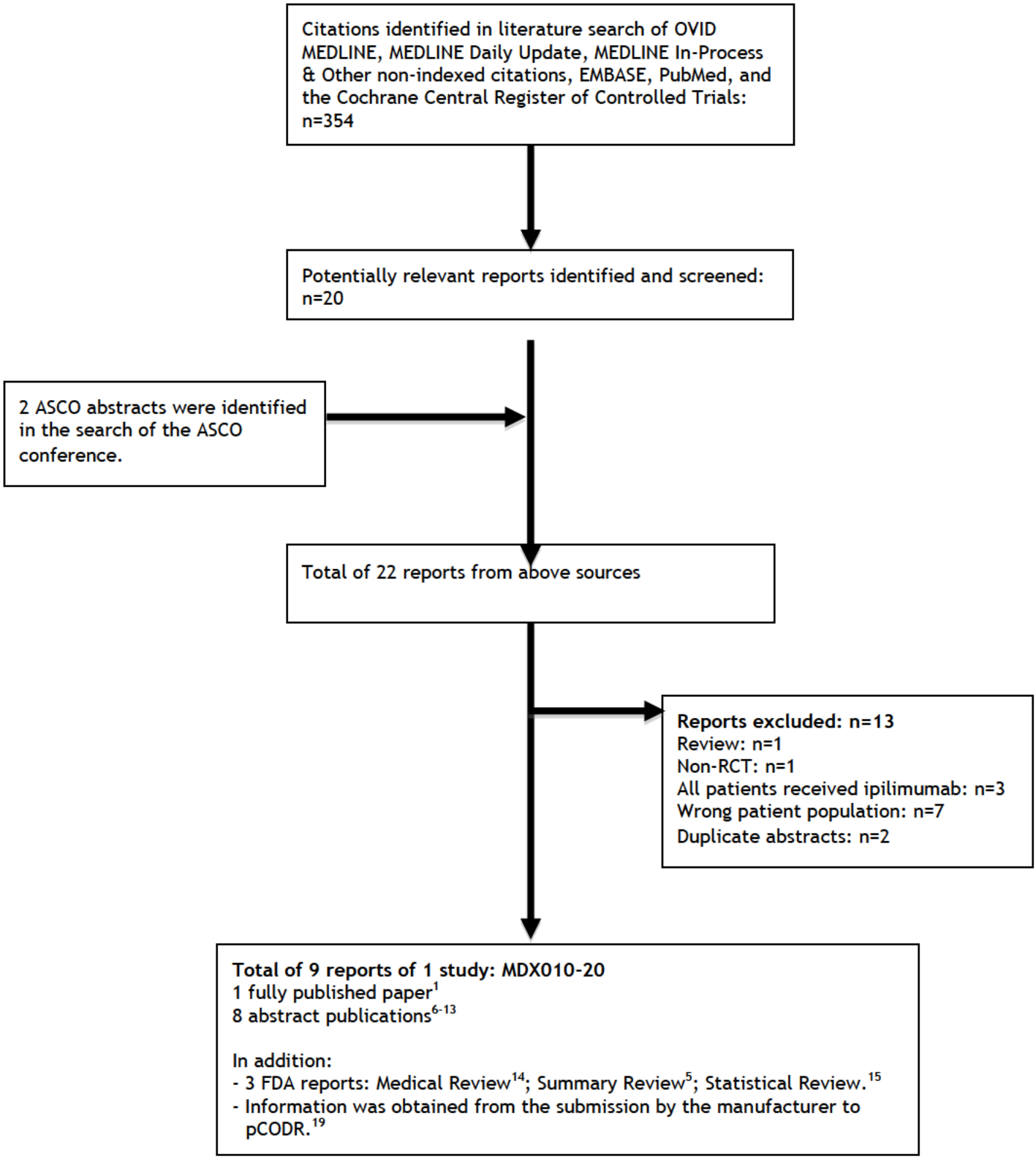
- The pCODR Secretariat wrote summaries of the input provided by patient advocacy groups and by the Provincial Advisory Group (PAG).

6.3 Results

6.3.1 Literature Search Results

Of the 20 potentially relevant reports identified, nine reports of one study were included in the pCODR systematic review[1,6-13] and 11 studies were excluded (Figure 1). Studies were excluded because they were reviews[58], single-arm trials[59], randomized trials in which all patients received ipilimumab[60-62] or trials that enrolled patients with previously untreated advanced melanoma.[20,63-67] Additional information was available from three FDA reports on ipilimumab in melanoma.[5,14,15]

Figure 1. Flow Diagram for Inclusion and Exclusion of Studies.



6.3.2 Summary of Included Studies

One double blind, placebo-controlled RCT (study MDX010-20) was identified that met the eligibility criteria.[1] The study compared ipilimumab plus the gp100 peptide vaccine versus (vs.) ipilimumab plus placebo vs. placebo plus gp100 in patients with unresectable Stage III or IV melanoma who previously received systemic therapy.

6.3.2.1 Detailed Trial Characteristics

a) Trials

One double-blind, placebo-controlled RCT (Study MDX010-20) was included in this review (Table 1).[1,5,14,15] The study was conducted in 125 centres in 13 countries in North America, South America, Europe, and Africa. The study was sponsored by the manufacturer. The study site personnel and the patients were blinded; the sponsor was not blinded in order to monitor patient safety and the study site pharmacist was also unblinded. A total of 676 patients were randomized from a centralized office in a 3:1:1 ratio to ipilimumab plus gp100, ipilimumab-alone, or gp100-alone. Randomization was stratified by baseline metastasis stage (M0, M1a, M1b, or M1c) and by prior interleukin-2 therapy (yes or no). The procedures for randomization, allocation concealment, and blinding were considered appropriate.

The original primary outcome was the best overall response rate (defined as the proportion of patients with a partial or complete response). While the study was ongoing, but prior to the study data being unblinded, the primary endpoint was changed to overall survival for the ipilimumab plus gp100 arm compared to the gp100-alone arm.[1] This change was based on phase II data and an ongoing phase III trial of ipilimumab plus dacarbazine compared to dacarbazine plus placebo in patients with untreated unresectable stage III or IV melanoma. The required sample size was reassessed and using blinded survival data from the study as well as historical data to estimate overall survival, the authors estimated that 385 events among a total of 500 patients randomly assigned to the ipilimumab plus gp100 and the gp100-alone groups, the study would have a power of 90% to detect a difference in overall survival, at a two-sided alpha level of 0.05. Assuming that the events were distributed in a 3:1:1 ratio in the ipilimumab plus gp100, ipilimumab-alone, and gp100-alone groups, respectively, a total of 481 events would be required. Secondary endpoints were changed at this amendment and included best overall response rate, progression-free survival, and duration of response. Of note, overall survival was a secondary endpoint up until the protocol amendment of the primary endpoint.

b) Populations

The baseline demographic and disease characteristics were balanced between the three treatment arms. The mean age (minimum to maximum) was 55.6 (24-84) years in the ipilimumab plus gp100 arm, 56.8 (19-88) years in the ipilimumab-alone arm, and 57.4 (23-90) years in the gp100-alone arm.[1,14] Of the 676 patients in the trial, 59.3% were male, with a slightly lower proportion of males in the gp100-alone arm (53.7% of 136) than in the ipilimumab plus gp100 arm (61.3% of 403) and the ipilimumab-alone arm (59.1% of 137).[1]

Central nervous system (CNS) metastases were present in 12.1% of 676 patients at baseline, with a slightly higher proportion of patients with a CNS metastasis in the

gp100-alone arm (15.4% of 136) than in either of the ipilimumab-based arms (ipilimumab plus gp100, 11.4% of 403; ipilimumab-alone, 10.9% of 137).[1]

c) Interventions

Ipilimumab (or placebo in the gp100-alone arm) was administered at 3 mg/kg intravenously over 90 minutes on day one of week 1. In the two arms that received the gp100 vaccine, administration was subcutaneous, immediately after the 90 minute infusion of ipilimumab or placebo. If no toxic effects that could not be tolerated, no rapidly progressive disease, and no significant decline in performance status, patients received an additional treatment during weeks 4, 7, and 10.

A total of 242 of 403 (60.0%) patients in the ipilimumab plus gp100 arm, 88 of 137 (64.2%) patients in the ipilimumab-alone arm, and 78 of 136 (57.4%) patients in the gp100-alone arm received all four doses of ipilimumab or placebo.[1]

Patients with stable disease for three months' duration after week 12 or a confirmed partial or complete response were offered additional courses of therapy (reinduction) with their assigned treatment regimen if they had disease progression.

d) Patient Disposition

A total of 676 patients started on the study. Although the primary publication of the trial did not report on patients discontinuing the study, the Food and Drug Administration (FDA) Medical Review of ipilimumab[14] reported that 15 patients withdrew consent, six were lost to follow-up, one had a protocol violation, and eight discontinued for other reasons. At the data cut-off of June 19, 2010, 95.6% of all 676 patients had either died (77.7%) or had completed the trial (17.9%).[14] The median follow-up was 21.0 months in the ipilimumab plus gp100 group, 27.8 months in the ipilimumab-alone group, and 17.2 months in the gp100-alone group.[1] Table 4 summarizes the patient disposition in MDX010-20.

Table 4. Patient Disposition in Study MDX010-20[1,14]

	Ipilimumab plus gp100	Ipilimumab-alone	Gp100-alone	Total
Randomized	403	137	136	676
Not treated	22 (5.5)	6 (4.4)	5 (3.7)	33 (4.9)
Treated	381 (94.5)	131 (95.6)	131 (96.3)	643 (95.1)
Discontinued Study				
Death	306 (75.9)	100 (73.0)	119 (87.5)	525 (77.7)
Subject withdrew consent	10 (2.5)	2 (1.5)	3 (2.2)	15 (2.2)
Lost to follow-up	3 (0.7)	2 (1.5)	1 (0.7)	6 (0.9)
Protocol violation	0	0	1 (0.7)	1 (0.1)
Other	3 (0.7)	3 (2.2)	2 (1.5)	8 (1.2)
Trial Completed	81 (20.1)	30 (21.9)	10 (7.4)	121 (17.9)

e) Limitations/Sources of Bias

The main comparators were the gp100 vaccine and placebo, rather than more commonly used therapies such as dacarbazine or temozolomide. The investigators assumed the vaccine to be no worse than placebo. One theoretical concern is that if the vaccine were more harmful than placebo or had a synergistic effect with ipilimumab, any benefit in overall survival for ipilimumab plus gp100 arm may be driven by the effects of gp100. However, examining data from the three arms of Study MDX010-20 partly addresses this concern. The similarity between overall survival in the ipilimumab plus gp100 arm and the ipilimumab alone arm suggest there are no synergistic effects of gp100 with ipilimumab. Therefore, the effect of gp100 is no longer a factor when comparing the results of the ipilimumab plus gp100 arm with the gp100 alone arm because gp100 is included in both treatment arms and its effects cancel out.

The study included only patients with HLA-A*0201 positive melanoma. This is due to the vaccine gp100 being designed to target this phenotype. If the treatment effect is partly due to gp100 in the ipilimumab plus gp100 group, then the generalizability of the results to patients with HLA-A*0201 negative melanoma is in question.

A possible source of bias is that the original outcome was best overall response rate but was changed in January 2009, approximately six months prior to the data cut-off date, to overall survival for ipilimumab plus gp100 compared to gp100-alone. At the point of the change, the data were not yet unblinded. Prior to the change overall survival was a secondary endpoint. The required sample size was reassessed using blinded survival data from the study as well as historical data to estimate overall survival. One concern here is that if the results of the study were known (i.e., unblinded) then the authors would have been calculating the power of the study after the results were already known. However, the pCODR manufacturer submission[19] and the FDA review[14,15] both note that the results remained blinded. In addition, the estimate of median overall survival for the ipilimumab plus gp100 arm was similar to that reported in the first-line trial of ipilimumab and dacarbazine (Study CA184-024[2] —see Section 7.1) and the estimate of median overall survival for the gp100-alone arm was similar to that reported in a meta-analysis of 42 trials in metastatic melanoma reported by Korn et al[16] (see Section 2.1.4). Although the change in outcome and required sample size is a methodological concern, it is reasonable to conclude that the changes did not invalidate the results of the study.

Another potential limitation is the possibly of unblinding of study data for those patients that experienced Grade 3 or greater diarrhea.

6.3.2.2 Detailed Outcome Data and Summary of Outcomes

The primary efficacy analysis was based on the intent-to-treat population, comprising all randomized study subjects. The safety population consisted of all randomized patients who had received any amount of study drug (N=643). The data cut-off was June 19, 2010. The study protocol stated that patients who discontinued treatment would remain in the study and follow all study procedures.

Efficacy Outcomes

Overall Survival

The primary endpoint of study MDX010-20 was overall survival between the ipilimumab plus gp100 group and the gp100-alone group. Overall survival was defined as the time from randomization to death from any cause and was analyzed using the intent-to-treat population. Kaplan-Meier estimates were used to analyze overall survival with comparisons between arms made using a log-rank test adjusted by TNM M-stage (M0, M1a, M1b, M1c) and prior treatment with interleukin-2 (yes, no). 95% confidence intervals were calculated using Cox model.

A significant difference in overall survival was found for ipilimumab plus gp100 (median 10.0 months) compared to gp100-alone (median 6.4 months), with HR 0.68, 95% CI 0.55-0.85, p<0.001 (Table 2).[1] Subgroup analyses of overall survival were conducted and showed that the effect of ipilimumab (ipilimumab plus gp100 arm and the ipilimumab-alone arm) on overall survival compared to the gp100-alone arm was independent of sex, age, tumour metastasis (M) stage at study entry, baseline lactate dehydrogenase levels, and prior use of interleukin-2 (Figure 3).[1]

The authors also reported a significant difference in overall survival for the ipilimumab-alone arm (median 10.1 months) compared to the gp100-alone arm (median 6.4 months), with HR 0.66, 95% CI 0.51-0.87, p=0.003 (Table 2)[1], although this was not the primary comparison the study was designed to evaluate.

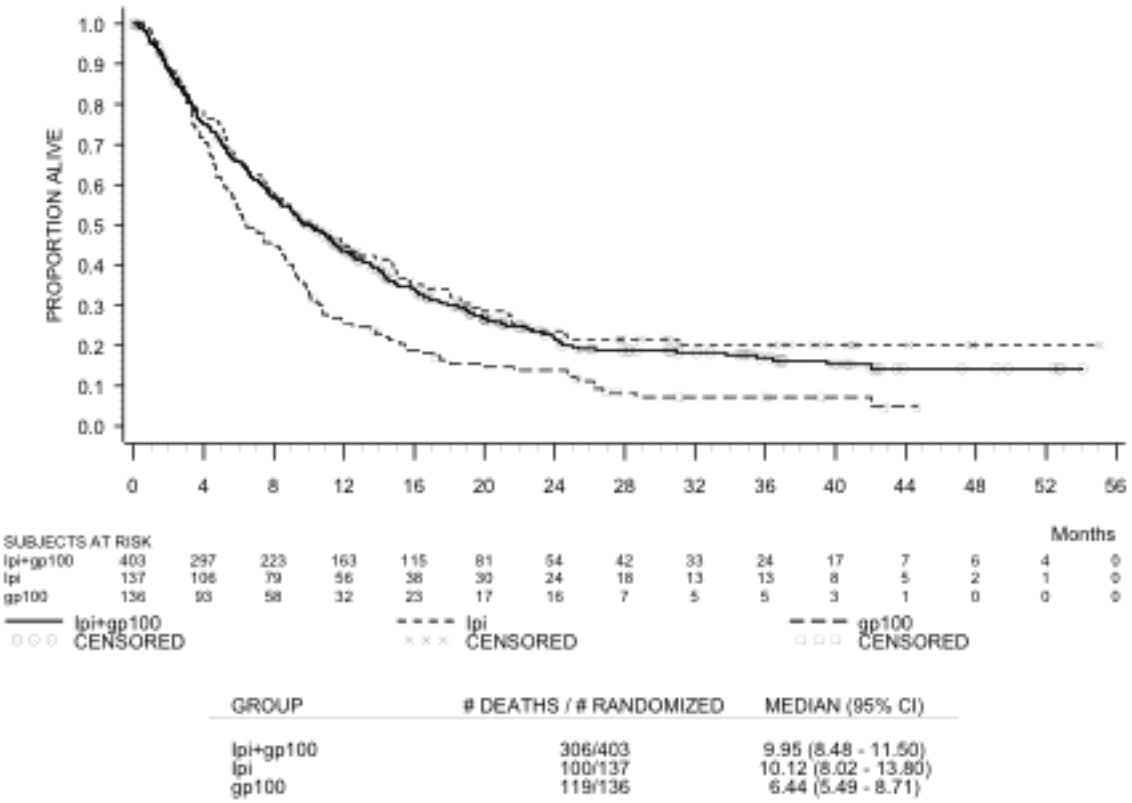
Overall survival at one-year and two-years can be found in Table 5. The percentage of patients alive was similar for ipilimumab plus gp100 and for ipilimumab-alone at one-year (43.5% vs. 45.6%, respectively) and at 2-years (21.6% vs. 23.5%).[1] The percentages of patients alive at one and two years in the gp100-alone arm was less than both of the ipilimumab arms (1-year, 25.3%; 2-year 13.7%).[1] The Kaplan-Meier survival curves for all three treatment arms can be found in Figure 2. The maximum follow-up was 55 months (one patient; Table 5). Median follow-up was 21.0 months in the ipilimumab plus gp100 group, 27.8 months in the ipilimumab-alone group, and 17.2 months in the gp100-alone group.[1] The curves were similar through the first four months of treatment, after which both ipilimumab curves separated from the gp100-alone control arm. This separation was sustained over time.

Table 5. Overall Survival at one year and two years in MDX010-20.[1,19]

Intervention	N	1-year OS [%] (95% CI)	2-year OS [%] (95% CI)	Follow-up range [months]
ipi + gp100	403	43.6 (38.6-48.5)	21.6 (17.2-26.1)	0.03-54.1
ipi-alone	137	45.6 (37.1-53.9)	23.5 (15.9-31.5)	0.36-55.1
gp100-alone	136	25.3 (18.1-32.9	13.7 (8.0-20.0)	NR

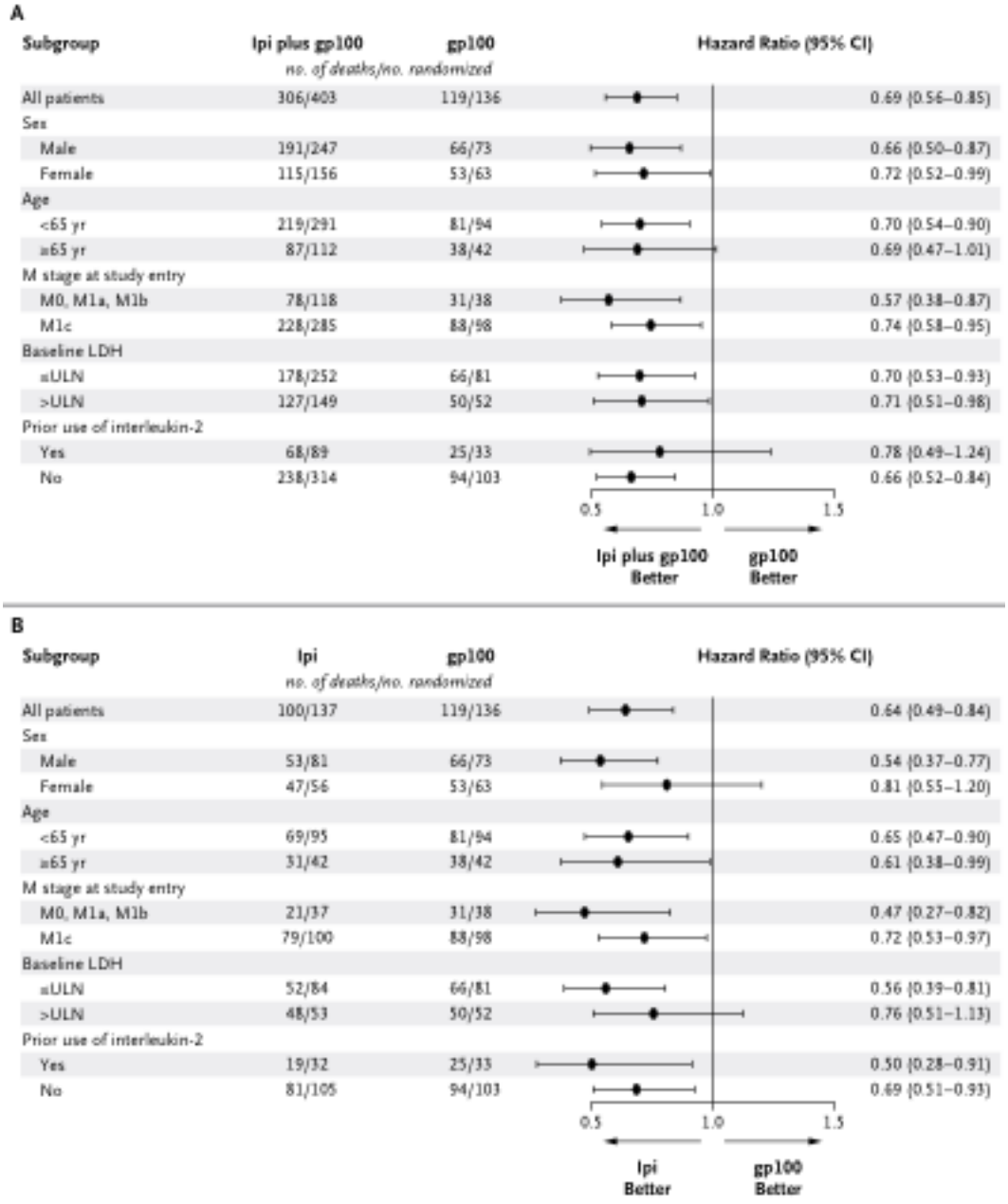
Notes: CI=confidence interval; N=number of patients randomized; NR=not reported; OS=overall survival.
Data for OS 95% CI's and follow-up range were obtained from pCODR manufacturer's submission.[19]

Figure 2. Kaplan-Meier survival curves for all treatment arms in MDX010-20.[1]



Notes: CI=confidence interval; ipi=ipilimumab.
Source: Manufacturer submission to pCODR.[19] Also available in Hodi et al[1], and FDA review.[5,14,15]

Figure 3. Subgroup analyses of overall survival in MDX010-20.[1]



Notes: CI=confidence interval; ipi=ipilimumab; LDH=lactate dehydrogenase; M-stage=metastasis stage; no.=number; ULN=upper limit of the normal range.
From: Hodi et al. N Engl J Med. 2010;363(8):711-23.[1]

Progression-free Survival

Progression-free survival was reported as a secondary endpoint. The primary publication did not report a statistical comparison of the treatment arms for progression-free survival[1]; however, the FDA Medical Review[14] reported the investigator-assessed analysis. A significant difference in progression-free survival was reported in favour of ipilimumab plus gp100 compared to gp100-alone (median 2.76 months for both arms, HR 0.81, 95% CI 0.66-1.00, p=0.0464) and in favour of ipilimumab-alone compared to gp100-alone (median 2.86 months versus 2.76 months, respectively; HR 0.64, 95% CI 0.50-0.83; p-0.0007) (Table 2).

Best Overall Response Rate

Best overall response rate was reported as a secondary endpoint and included both complete and partial responses. A statistically significantly higher proportion of patients in the ipilimumab plus gp100 group achieved a complete or partial response compared to the gp100-alone group (5.7% vs. 1.5%, respectively; p=0.04; Table 2).[1] In addition, a statistically significantly higher proportion of patients in the ipilimumab-alone group achieved a complete or partial response compared to the gp100-alone group (10.9% vs. 1.5%, respectively; p=0.001; Table 2).

Patients Requiring Re-Induction

Re-induction was offered to patients with stable disease for three months duration after week 12 or a confirmed partial or complete response if they had disease progression. A total of 40 patients, 29 in the ipilimumab plus gp100 group, nine in the ipilimumab-alone group, and two in the gp100-alone group received re-induction therapy. Of those 40 patients, eight were not included in the efficacy analysis of re-induction as three had major protocol violations and five were not eligible as their best overall response during induction was progressive disease and they were inadvertently given re-induction when they were not eligible.[1]

Best overall response rate (CR+PR) was 3 of 23 patients (13.0%) in the ipilimumab plus gp100 group, 3 of 8 patients (37.5%) in the ipilimumab-alone group, and none of two in the gp100-alone group.[1]

Of the 40 patients who received re-induction, 34 received four doses of ipilimumab.[19] Of those 40 patients, seven (three in the ipilimumab-alone arm and 4 in the ipilimumab plus gp100 arm) received a second re-induction, of whom five patients received four doses of ipilimumab. Of those seven patients, one received a third re-induction with four doses of ipilimumab. No further data on re-induction were reported.

Quality of Life

Health-related quality of life was assessed using the EORTC QLQ C-30 Health-Related Quality of Life questionnaire. The primary publication[1] did not report on any quality of life outcomes. The FDA Medical Review[14] as well as an abstract[6] published in the proceedings of the 35th Annual ESMO Congress in 2010 reported very limited data on quality of life in study MDX010-20. Health-related quality of life was assessed using the EORTC QLQ C-30 at weeks 1, 12, and 24. The FDA Medical Review[14] reported that the baseline completion rate was approximately

95%, dropping to between 61-65% at week 12 and less than 15% at week 24. The FDA Medical Review reported that there were no meaningful changes in any of the functional or global scores; however, no data were reported. Revicki et al[6] reported in abstract form only, on the difference in health-related quality of life outcomes from baseline to week 12. Changes were interpreted by mean change in score as "no change" (<5 points), "a little" (5-10 points), "moderate" (11-20 points), and "very much" (>20 points). The authors reported that questionnaires were completed by 236 of 381 patients (61.9%) in the ipilimumab plus gp100 arm, 85 of 131 patients (64.9%) in the ipilimumab-alone arm, and 80 of 131 patients (61.1%) in the gp100-alone arm. The authors reported negligible differences in health-related quality of life outcomes in all three arms of the study (Table 6).[6]

Table 6. Mean change in Health-Related Quality of Life Outcomes from Baseline to Week 12 in Study MDX010-20 reported in abstract form only.[6]

Outcome	Ipilimumab plus gp100 (N=236)	Ipilimumab-alone (N=85)	Gp100-alone (N=80)
Physical function	-6.2	-5.1	-10.1
Role function	-9.3	-10.5	-13.7
Emotional function	-1.5	-3.6	-1.5
Cognitive function	-3.1	-4.3	-3.4
Social function	-5.6	-7.5	-4.2
Global health	-7.4	-8.8	-10.4
Symptom scales			
Fatigue	10.6	12.5	14.5
Nausea/vomiting	4.6	3.1	4.4
Pain	5.6	7.9	11.9
Dyspnea	3.5	5.3	9.1
Sleep disturbance	6.5	10.1	11.0
Appetite loss	8.5	11.6	10.3
Constipation	5.2[A]	1.9[A]	11.8
Diarrhea	6.4	9.1	2.1

Notes: For the functioning and global health scores, positive numbers indicate improvements. For the symptom scales, negative numbers indicate improvments.
[A]p<0.05 versus gp100-alone group.

Harms Outcomes

A total of 643 patients comprised the safety population, which consisted of randomized patients who had received any dose of study drug.

Serious Adverse Events

Serious adverse events (≥ Grade 3) occurred in 45.5% of 380 patients in the ipilimumab plus gp100 arm, 45.8% of 131 patients in the ipilimumab-alone arm, and 47% of 132 patients in the gp100-alone arm. Table 7 summarizes the serious adverse events reported in the study. Of note, diarrhea occurred in a higher proportion of patients in both ipilimumab arms (ipilimumab plus gp100, 4.5% and ipilimumab-alone 5.3%) compared to the gp100-alone arm (0.8%). Fatigue was also slightly more common in the ipilimumab arms (5.0% ipilimumab plus gp100 and 6.9% ipilimumab-alone) compared to the gp100-alone arm (3.0%). The remaining serious adverse events were similar between the treatment arms (Table 7).

Table 7. Serious Adverse Events (≥Grade 3) reported in MDX010-20.[1]

Adverse Event	Ipilimumab plus gp100 N=380 (%)	Ipilimumab-alone N=131 (%)	gp100-alone N=132 (%)
Any	173 (45.5)	60 (45.8)	62 (47.0)
Any drug-related	66 (17.4)	30 (22.9)	15 (11.4)
Gastroinestinal			
Diarrhea	17 (4.5)	7 (5.3)	1 (0.8)
Nausea	6 (1.6)	3 (2.3)	3 (2.3)
Constipation	3 (0.8)	3 (2.3)	1 (0.8)
Vomiting	7 (1.8)	3 (2.3)	3 (2.3)
Abdominal pain	6 (1.6)	2 (1.5)	7 (5.3)
Other			
Fatigue	19 (5.0)	9 (6.9)	4 (3.0)
Deceased appetite	6 (1.6)	2 (1.5)	4 (3.0)
Pyrexia	2 (0.5)	0	2 (1.5)
Headache	4 (1.1)	3 (2.3)	3 (2.3)
Cough	1 (0.3)	0	0
Dyspnea	14 (3.7)	5 (3.8)	6 (4.5)
Anemia	11 (2.9)	4 (3.1)	11 (8.3)

Serious Adverse Events – Immune-Related

Table 8 provides data on the immune-related adverse events reported in study MDX010-20. Of note, Grade ≥3 immune-related adverse events occurred in a higher proportion of patients in both the ipilimumab plus gp100 arm (10.3% of 380 patients) and the ipilimumab-alone arm (14.5% of 131 patients) as compared to the gp100-alone arm (3.0% of 132 patients). Grade ≥3 immune-related gastrointestinal, dermatologic, and endocrine adverse events occurred in a higher proportion of

patients in both ipilimumab arms than in the gp100 arm (Table 8). No statistical comparisons were reported.

Table 8. Immune-Related Serious Adverse Events (≥Grade 3) reported in MDX010-20.[1]

Adverse Event	Ipilimumab plus gp100 N=380 (%)	Ipilimumab-alone N=131 (%)	gp100-alone N=132 (%)
Any immune-related	39 (10.3)	19 (14.5)	4 (3.0)
Dermatologic	9 (2.4)	2 (1.5)	0
Pruritis	1 (0.3)	0	0
Rash	5 (1.3)	1 (0.8)	0
Gastrointestinal	22 (5.8)	10 (7.6)	1 (0.8)
Diarrhea	14 (3.7)	6 (4.6)	1 (0.8)
Colitis	12 (3.2)	7 (5.3)	0
Endocrine	4 (1.1)	5 (3.8)	0
Hypothyroidism	1 (0.3)	0	0
Hypopituitarism	2 (0.5)	2 (1.5)	0
Hypophysitis	2 (0.5)	2 (1.5)	0
Adrenal insufficiency	2 (0.5)	0	0
Hepatic	4 (1.1)	0	3 (2.3)
Increase in alanine aminotransferase	2 (0.5)	0	0
Increase in aspartate aminotransferase	1 (0.3)	0	0
Hepatitis	1 (0.3)	0	0
Other	5 (1.3)	3 (2.3)	1 (0.8)

Withdrawals Due to Adverse Events

Of a total of 643 patients in the safety population, 35 of 380 patients (9.2%) in the ipilimumab plus gp100 arm and 17 of 131 patients (13.0%) in the ipilimumab-alone arm withdrew due to adverse events compared to 5 of 132 patients (3.8%) in the gp100-alone arm.[14] The most common reasons for withdrawal due to adverse events in the ipilimumab arms were colitis (ipilimumab plus gp100 arm, 10 of 380 patients [2.6%]; ipilimumab-alone, 3 of 131 patients [2.3%]) and diarrhea (ipilimumab plus gp100, 10 of 380 patients [2.6%]; ipilimumab-alone, 2 of 131 patients [1.5%]).[14] Diarrhea and colitis were the reason for withdrawal due to adverse events for 57.1% of 35 withdrawals in the ipilimumab plus gp100 arm and for 29.4% of 17 withdrawals in the ipilimumab-alone arm.[14]

Any Grade Adverse Events

A similar proportion of patients in all three treatment arms experienced at least one adverse event of any Grade (Table 9). Diarrhea occurred in more patients in the ipilimumab arms (ipilimumab plus gp100, 38.4% of 380 patients; ipilimumab-alone, 32.8% of 131 patients) than in the gp100-alone arm (19.7% of 132 patients). In addition, any immune-related adverse events, immune-related dermatologic adverse events and immune-related gastrointestinal adverse events all occurred in more patients in both ipilimumab arms than in the gp100-alone arm (Table 9).

Table 9. Adverse Events of any Grade reported in more than 10% of patients in Study MDX010-20.[1]

Adverse Event	Ipilimumab plus gp100 N=380 (%)	Ipilimumab-alone N=131 (%)	gp100-alone N=132 (%)
Any event	374 (98.4%)	127 (96.9%)	128 (97.0%)
Any drug-related event	338 (88.9)	105 (80.2)	104 (78.8)
Gastrointestinal			
Diarrhea	146 (38.4)	43 (32.8)	26 (19.7)
Nausea	129 (33.9%)	46 (35.1)	52 (39.4)
Constipation	81 (21.3)	27 (20.6)	34 (25.8)
Vomiting	75 (19.7)	31 (23.7)	29 (22.0)
Abdominal pain	67 (17.6)	20 (15.3)	22 (16.7)
Fatigue	137 (36.1)	55 (42.0)	41 (31.1)
Decrease appetite	88 (23.2%)	35 (26.7)	29 (22.0)
Pyrexia	78 (20.5)	16 (12.2)	23 (17.4)
Headache	65 (17.1)	19 (14.5)	19 (14.4)
Cough	55 (14.5)	21 (16.0)	18 (13.6)
Dyspnea	46 (12.1)	19 (14.5)	25 (18.9)
Anemia	41 (10.8)	15 (11.5)	23 (17.4)
Any immune-related event	221 (58.2)	80 (61.1)	42 (31.8)
Dermatologic	152 (40.0)	57 (43.5)	22 (16.7)
Pruritis	67 (17.6)	32 (24.4)	14 (10.6)
Rash	67 (17.6)	25 (19.1)	6 (4.5)
Gastrointestinal	122 (32.1)	38 (29.0)	19 (14.4)
Diarrhea	115 (30.3)	36 (27.5)	18 (13.6)

6.4 Ongoing Trials

No ongoing studies of ipilimumab in patients with previously treated unresectable stage III or IV melanoma were identified that met the eligibility criteria for this review (i.e., compared treatment with ipilimumab to treatment without ipilimumab). In addition a search was conducted for new or ongoing trials of ipilimumab in combination with vemurafenib for the treatment of unresectable stage III or IV melanoma. No trials were identified.

Of note, as part of the United States FDA approval for ipilimumab in previously treated unresectable advanced melanoma, the FDA mandated the manufacturer (BMS) to design and conduct a trial comparing the efficacy (primary outcome to be overall survival) and safety of ipilimumab monotherapy at doses of 3 mg/kg versus 10 mg/kg every three weeks for four doses in patients with unresectable stage III or stage IV melanoma.[3]

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 have previously received systemic therapy:

- **Ipilimumab for the first-line treatment of stage III or IV melanoma.** The scope of the current pCODR review of ipilimumab is for patients with previously systemically treated disease. Limitations of study MDX010-20[1] trial evaluating ipilimumab in this setting may have been addressed, in part, in trials evaluating ipilimumab in the first-line setting and would provide supportive information to the pCODR systematic review.

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

7.1 Ipilimumab in the First-Line Treatment of Unresectable Stage III or IV Melanoma

7.1.1 Objective

The objective is to report on the efficacy and harms of ipilimumab, as evaluated in trials conducted in the first-line treatment setting of unresectable stage III or IV melanoma. Any issues common to the first and second-line setting will be investigated, if identified.

7.1.2 Findings

Trial Design and Patient Characteristics

A systematic search was not conducted to identify RCTs of ipilimumab in the first-line treatment of unresectable stage III or IV melanoma. The Methods Team is aware of one RCT comparing ipilimumab plus dacarbazine to dacarbazine plus placebo in patients with previously untreated unresectable stage III or IV melanoma, Study CA184-024.[2] The trial results are reported in a fully published article by Robert et al.[2] Details of the trial design can be found in Table 1. The trial enrolled patients who were at least 18 years of age and who had previously untreated unresectable stage III or IV melanoma. Patients must have had measurable lesions and an ECOG PS ≤1. The study was double-blind and the randomization was stratified by metastasis stage, study site, and ECOG PS. A total of 502 patients were randomized 1:1 to receive either ipilimumab at 10 mg/kg plus dacarbazine 850 mg/m^2 (n=250) or to dacarbazine 850 mg/m^2 plus placebo (n=252).

The original primary outcome was progression-free survival; however, due to emerging data from other trials, on October 9, 2008 the FDA approved an amendment to change the primary outcome to overall survival, prior to the unblinding of the study results. No change in sample size was required as the trial was already designed so that after 416 deaths, the study would have a power of 90% to detect a 37% increase in median overall survival to 11 months with ipilimumab plus dacarbazine, with a sample size of 500 patients (250 per arm) and a median overall survival of 8 months in the dacarbazine-alone arm. Secondary outcomes are identified in Table 10.

Table 10. Summary of Included Study (CA184-024)[2]

Trial Design	Inclusion Criteria	Interventions and Comparators	Outcomes
Study CA184-024 Multinational Patients enrolled from August 8, 2006 to January 22, 2008 Enrolled: n=502 Randomized: n=502 Double-blind, placebo-controlled, RCT Randomization was stratified by: A) Baseline metastasis stage[A] (M0, M1a, M1b, or M1c) B) Study site C) ECOG PS	Diagnosis of previously untreated unresectable stage III or stage IV melanoma Age ≥18 years ECOG PS ≤1	Two arms: Ipilimumab 10 mg/kg plus dacarbazine 850 mg/m^2 or Dacarbazine 850 mg/m^2 plus placebo Schedule for both arms: at weeks 1, 4, 7, and 10, followed by dacarbazine alone every 3 weeks through week 22.	Primary Overall survival Secondary Best overall response rate (CR+PR) Progression-free survival Rate of disease control (CR+PR+SD) Time to response Duration of response Safety

Notes: CR=complete response; ECOG PS=Eastern Cooperative Oncology Group Performance Status; PR=partial response; SD=stable disease.
[A]By TNM categorization for melanoma of American Joint Committee on Cancer.[17,18]

The baseline demographic and disease characteristics were balanced between the two arms. The mean age was 57.5 years in the ipilimumab plus dacarbazine arm and 56.4 years in the dacarbazine-alone arm. Of the 502 patients in the trial, 301 (60.0%) were male.

Details of treatment administration can be found in Table 10. A total of 92 patients (36.8%) in the ipilimumab plus dacarbazine group and 165 patients (65.5%) in the dacarbazine-alone group received all four doses of ipilimumab. At least one maintenance dose was administered in 43 patients (17.2%) in the ipilimumab plus dacarbazine group and in 53 patients (21.0%) in the dacarbazine-alone group.

A total of 115 of 250 patients (46%) in the ipilimumab plus dacarbazine group and 195 of 252 patients (77%) in the dacarbazine-alone group discontinued treatment due to disease progression. In addition, 89 of 247 patients (36%) who received at least one dose of the study drug in the ipilimumab plus dacarbazine arm discontinued treatment due to a drug-related adverse event. In the dacarbazine-alone arm, 10 of 251 patients who received at least one dose of the study drug discontinued treatment due to a drug-related adverse event.

Outcomes

The primary efficacy analysis was based on the intent-to-treat population. The safety population consisted of all randomized patients who received at least one dose of the study drug (N=498). A summary of the key outcomes from the study can be found in Table 11.

Table 11. Summary of Key Trial Outcomes from Study CA184-024.[2]

Efficacy	Intervention	Median (months)	HR (95% CI)	p-value
Overall Survival	Ipililimumab + dacarbazine	11.2	0.72 (0.59-0.87)	p<0.001
	Dacarbazine	9.1		
Progression-free survival	Ipililumab + dacarbazine	2.6[A]	0.76 (0.63-0.93)	p=0.006
	dacarbazine	2.6[A]		
Best Overall Response Rate	Ipilimumab + dacarbazine (N=250)	15.2% (n=38)	-	Not reported
	Dacarbazine (N=252)	10.3% (n=26)	-	
Harms	**Ipilimumab + dacarbazine N=247**	**Dacarbazine N=251**		
SAE, n (%)	139 (56.3)	69 (27.5)	-	p<0.001
Any AE, n (%)	244 (98.8)	236 (94.0)	-	NR
Immune-related SAE, n (%)	103 (41.7)	15 (6.0)	-	NR
Any Immune-related AE, n (%)	192 (77.7)	96 (38.2)	-	NR

Notes: "-"=not applicable; AE=adverse event; NR=not reported; SAE=serious adverse events;
[A]Median progression-free survival was estimated from Kaplan-Meier Curves for Survival.

Efficacy Outcomes

Overall Survival

The primary endpoint of study CA184-024 was overall survival. Analysis was done using the intent-to-treat population. Kaplan-Meier estimates were used to analyze overall survival with comparisons made between arms using a Cox proportional-hazards model.

A statistically significant difference in overall survival was found in favour of ipilimumab plus dacarbazine (median 11.2 months) compared to dacarbazine alone (median 9.1 months), with HR 0.72, 95% CI 0.59-0.87), p<0.001 (Table 11).

Progression-free Survival

Progression-free survival was reported as a secondary endpoint. The authors did not report the median progression-free survival; instead these values were estimated from the Kaplan-Meier curves. The authors reported a statistically significant difference in progression-free survival in favour of ipilimumab plus dacarbazine (estimated median 2.6 months) compared to dacarbazine alone (estimated median 2.6 months), with HR 0.76 (0.63-0.93), p=0.006 (Table 11).

Best Overall Response Rate

The authors reported that the best overall response rate was 15.2% of 250 patients in the ipilimumab plus dacarbazine arm and 10.3% of 252 patients in the dacarbazine-alone arm. No statistical comparisons were reported.

Harms Outcomes

A total of 498 patients comprised the safety population, which consisted of all randomized patients who had received at least one dose of study drug. Major harms outcomes are summarized in Table 11. Of note, more patients in the ipilimumab plus dacarbazine arm experienced any Grade of alanine aminotransferase levels (33.2% vs. 5.6%), elevation of aspartate aminotransferase levels (29.1% vs. 5.6%), diarrhea (36.4% vs. 24.7%), pruritis (29.6% vs. 8.8%), and rash (24.7% vs. 6.8%) than in the dacarbazine-alone arm. Grade 3 or higher adverse events occurred in a statistically higher proportion of patients in the ipilimumab plus dacarbazine arm (56.3% vs. 27.5%, $p<0.001$).

Immune-related adverse events of any grade occurred more frequently in the ipilimumab plus dacarbazine arm than in the dacarbazine alone arm (77.7% vs. 38.2%, Table 11). In addition, Grade 3 or higher immune-related adverse events occurred more frequently in the ipilimumab arm than in the dacarbazine arm (41.7% vs. 6.0%, Table 11). Immune-related adverse events that occurred more frequently in the ipilimumab arm included any Grade of pruritis, rash, diarrhea, colitis, increase in alanine aminotransferase, and increase in aspartate aminotransferase. Grade 3 or higher immune-related adverse events that occurred more frequently in the ipilimumab arm included diarrhea, increase in alanine aminotransferase, and increase in aspartate aminotransferase.

7.1.3 Summary

Study CA184-024[2] and Study MDX010-20[1] investigated the use of ipilimumab in patients with unresectable Stage III or Stage IV melanoma. Both trials were double-blind, placebo-controlled RCTs. There were differences in the studies: Study CA184-024 investigated ipilimumab plus dacarbazine compared to dacarbazine-alone in the first-line setting whereas study MDX010-20 investigated ipilimumab plus gp100 vaccine compared to gp100-alone compared to ipilimumab-alone in the second-line setting. The second-line trial (MDX010-20) enrolled patients with HLA-A*0201-positive melanoma whereas the first-line trial (CA184-024) included patients irrespective of HLA-A status. In the first-line trial (CA184-024), ipilimumab plus dacarbazine was demonstrated to have statistically significant increased overall survival compared to dacarbazine alone (median 11.2 months vs. 9.1 months; HR 0.72, 95% CI 0.59-0.87, $p<0.001$). This result is similar to the overall survival results from the second-line trial (MDX010-20) comparing ipilimumab plus gp100 to gp100-alone. The CA184-024 first-line trial also demonstrated increased progression-free survival (Table 11) in the ipilimumab plus dacarbazine arm. A similar result was observed in the second-line MDX010-20 trial. The adverse events reported in both trials were similar. The adverse events experienced by patients in the first-line CA184-024 study in the ipilimumab arm were similar to those reported for patients in the ipilimumab arms of the second-line MDX010-20 study and included serious or any Grade of immune-related adverse events, serious or any Grade of diarrhea, and any Grade of colitis, pruritis, and rash.

8 ABOUT THIS DOCUMENT

This 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) 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 will supersede this Initial Clinical Guidance Report. Note that no revisions were 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

1. Literature Search via OVID Platform.

Ovid MEDLINE (R), Ovid MEDLINE (R) In-Process & Other Non-Indexed Citations, and Ovid MEDLINE (R) Daily Update.

1. ipilimumab:.ti,ab.
2. yervoy:.ti.ab.
3. mdx-101.ti,ab.
4. mdx-101.ti,ab.
5. or/1-4
6. melanoma:.ti,ab.
7. exp Melanoma/
8. 6 or 7
9. 5 and 8
10. exp animals/
11. exp animal experimentation/
12. exp animal experiment/
13. exp models animal/
14. nonhuman/
15. exp vertebrate/
16. or/10-15
17. exp humans/
18. exp human experimentation/
19. or/17-18
20. 16 not 19
21. 9 not 20

Note: human filter was used (lines 10-20).

Ovid EMBASE

1. ipilimumab:.ti,ab.
2. yervoy:.ti,ab.
3. mdx-010.ti,ab.
4. mdx-101.ti,ab.
5. ipilimumab/
6. or/1-5
7. exp melanoma/
8. melanoma:.ti,ab.
9. 7 or 8
10. 6 and 9
11. exp animals/
12. exp animal experimentation/
13. exp models animal/
14. exp animal experiment/
15. nonhuman/
16. exp vertebrate/
17. or/11-16
18. exp humans/
19. exp human experiment/

20. or/18-19
21. 17 not 20
22. 10 not 21
23. (randomized controlled trial or controlled clinical trial).pt.
24. randomized controlled trial/
25. randomized controlled trial as topic/
26. controlled clinical trial/
27. controlled clinical trial as topic/
28. randomization/
29. random allocation/
30. double-blind method/
31. double-blind procedure/
32. double-blind studies/
33. single-blind method/
34. single-blind procedure/
35. single-blind studies/
36. placebos/
37. placebo/
38. control group/
39. control groups/
40. (random: or sham or placebo:).ti,ab,hw.
41. ((singl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
42. ((tripl: or doubl:) adj (blind: or dumm: or mask:)).ti,ab,hw.
43. (control: adj3 (study or studies or trial:)).ti,ab.
44. (non-random: or non random: or non-random: or quasi-random: or quasirandom:).ti,ab,hw.
45. allocated.ti,ab,hw.
46. ((open label or open-label) adj 5 (study or studies or trial:)).ti,ab,hw.
47. or/23-46
48. 22 and 47

Note: human filter was used (lines 11-21); RCT filter was used (lines 23-47).

2. Literature Search via PubMed

PubMed

1. ipilimumab* or yervoy* or mdx-010* or mdx-101*
2. publisher[sb]
3. 1 and 2

3. Literature Search via Cochrane Central Register of Controlled Trials (CENTRAL)

Issue 4, 2011
There were 21 results out of 661393 records for: ipilimumab* or yervoy* or mdx-010* or mdx-010* AND melanoma* in Cochrane Central Register of Controlled Trials.

4. Grey Literature Searches

Clinical Trial Registries:

U.S. NIH ClinicalTrials.gov
www.clinicaltrials.gov

Ontario Institute for Cancer. Ontario Cancer trials
www.ontariocancertrials.ca

Search terms: ipilimumab, yervoy, mdx-010, mdx-101

Select International Agencies:

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

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

Search terms: ipilimumab, yervoy, mdx-010, mdx-101

Conference Abstracts:

American Society of Clinical Oncology (ASCO)
via the Journal of Clinical Oncology search portal: http://jco.ascopubs.org/search

Search terms: ipilimumab, yervoy, mdx-010, mdx-101

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