HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion
19 November 2014

YERVOY 5 mg/ml, concentrate for solution for infusion

B/1 10 ml vial (CIP: 34009 580 877 0 7)
B/1 40 ml vial (CIP: 34009 580 878 7 5)

Applicant: BRISTOL-MYERS SQUIBB

INN	ipilimumab
ATC code (2013)	L01XC11 (monoclonal antibodies)
Reason for the review	**Extension of indication**
List(s) concerned	**Hospital use (French Public Health Code L.5123 2)**
Indication concerned	**"YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults"**

Actual Benefit	**moderate as a first-line treatment for adult patients with advanced (unresectable or metastatic) melanoma, without a B-RAF mutation and in patients with slow progression, good general condition and a life expectancy greater than 3 months.**
Improvement in Actual Benefit	**In the absence of demonstrated efficacy or safety greater than the existing therapeutic strategy for first-line treatment of advanced melanoma in adults, YERVOY does not provide any improvement in actual benefit (IAB V, non-existent)**
Therapeutic use	**In this new indication (in first-line treatment), YERVOY is a first-line treatment in patients who do not bear a B-RAF mutation.**
Target population	**The target population for YERVOY in treatment-naive patients with unresectable or metastatic melanoma may be estimated at 1664 to 2009 patients. This target population is probably overestimated insofar as YERVOY must be reserved for patients with non-aggressive melanoma (i.e., progressing slowly, characterised by few metastatic sites, few metastases and progression over several months), a portion of the target population that cannot be quantified.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	31/10/2013 (centralised procedure) European risk management plan: last updated on 18/09/2012
Prescribing and dispensing conditions/special status	List I Medicinal product reserved for hospital use Prescription restricted to oncology specialists or doctors with cancer training. Medicine requiring special monitoring during treatment.

ATC Classification	2013	
	L	Antineoplastic and immunomodulating agents
	L01	Antineoplastic agents
	L01X	Other antineoplastic agents
	L01XC	Monoclonal antibodies
	L01XC11	ipilimumab

02 BACKGROUND

This is a review of the application for inclusion of the proprietary medicinal product YERVOY 5 mg/ml, concentrate for solution for infusion, on the list of medicinal products approved for hospital use. On 31 October 2013, YERVOY obtained a Marketing Authorisation in the treatment of advanced (unresectable or metastatic) melanoma in treatment-naive patients.

In its opinion of 14/12/2011, the conclusions of the Transparency Committee in the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy were:
"In view of the seriousness of the disease concerned, the absence of an alternative validated by a Marketing Authorisation and the modest efficacy observed, ipilimumab provides a substantial actual benefit."
"In the absence of an alternative validated by a Marketing Authorisation, ipilimumab (YERVOY) provides a minor improvement in actual benefit (IAB IV) in its therapeutic use."

The IAB of this proprietary medicinal product was reassessed by the Committee on 10/07/2013 at the request of the Committee and then on 06/11/2013 at the request of the company and the conclusions are now: "Given the new data available, the improvement in actual benefit of ipilimumab (YERVOY) is still minor (IAB IV) in its therapeutic use."

03 THERAPEUTIC INDICATION

"**YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults**"

04 DOSAGE

"Treatment must be initiated and supervised by specialist physicians experienced in the treatment of cancer.

Dosage
Adults: The recommended induction regimen of YERVOY is 3 mg/kg administered intravenously over a 90-minute period every 3 weeks for a total of 4 doses. Patients should receive the entire induction regimen (4 doses) as tolerated, regardless of the appearance of new lesions or growth of existing lesions. Assessments of tumour response should be conducted only after completion of induction therapy.
Liver function tests and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Tables 1A, 1B, and section 4.4 of the SPC).

Permanent discontinuation of treatment or withholding of doses: Management of immune-related adverse reactions may require withholding of a dose or permanent discontinuation of YERVOY therapy and institution of a systemic high-dose corticosteroid. In some cases, addition of other immunosuppressive therapy may be considered (see section 4.4 of the SPC).
Dose reduction is not recommended. Doses that are omitted due to an adverse reaction must not be replaced. Guidelines for permanent discontinuation or withholding of doses are described in Tables 1A and 1B (see SPC). Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4 of the SPC.

Paediatric population: The safety and efficacy of YERVOY in children below 18 years of age have not been established. No data are available. YERVOY should not be used in children below 18 years of age.

Special populations:
Older people: No overall differences in safety or efficacy were reported between elderly (≥ 65 years) and younger patients (< 65 years). No specific dose adjustment is necessary in this population.

Renal impairment: The safety and efficacy of YERVOY have not been studied in patients with renal impairment. Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction (see section 5.2 of the SPC).

Hepatic impairment: The safety and efficacy of YERVOY have not been studied in patients with hepatic impairment. YERVOY must be administered with caution in patients with transaminase levels ≥ 5 x ULN or bilirubin levels > 3 x ULN at baseline (see section 5.1 of the SPC).

Method of administration
The recommended infusion period is 90 minutes.
YERVOY can be used for intravenous administration without dilution or may be diluted in sodium chloride 9 mg/ml (0.9%) solution for injection or glucose 50 mg/ml (5%) solution for injection to concentrations between 1 and 4 mg/ml and stored in glass vials or PVC or non-PVC bags.
YERVOY must not be administered as an intravenous push or bolus injection.

For instructions on the handling of the medicinal product before administration, see section 6.6 of the SPC."

05 THERAPEUTIC NEED[1,2,3,4]

Melanoma is a skin cancer with high metastatic potential, associated with the malignant transformation of melanocytes, skin pigment cells.
The survival rate at 5 years ranges from 88% in cases of detection at an early stage, to 18% for unresectable, advanced stage III cases, and less than 5% for stage IV melanomas (metastatic stage).

The current treatment is based on screening patients as soon as they are diagnosed for a B-RAF mutation (found in 36 to 47% of cases). Consequently, there are two conceivable situations:
- Patients with B-RAF mutation: the choice of treatment will be a targeted therapy currently represented by vemurafenib (ZELBORAF) or dabrafenib (TAFINLAR) in monotherapy.
- Patients without B-RAF mutation: treatment is based on conventional chemotherapy with dacarbazine or fotemustine. High doses of IL-2 (off-label), temozolomide (off-label), paclitaxel (off-label) possibly in combination with carboplatin (off-label), can also be used with modest response rates of about 20% and complete remission rates of less than 5% (Source NCCN 2013).

Recurrences of melanoma are resistant to most of the conventional therapeutic agents, particularly dacarbazine or cytokines.
Ipilimumab (YERVOY) has been indicated up to now in the treatment of advanced stage melanoma after failure of at least one line of chemotherapy treatment. Its use was reserved according to the HAS opinion[5] for patients with non-aggressive disease who failed prior treatment, i.e., patients whose life expectancy is greater than 3 months, in particular in patients who do not have a B-RAF mutation.

[1] NCCN Clinical Practice Guidelines in Oncology. Melanoma. Version 2.2013
[2] ALD Guide [Chronic conditions guide]. Malignant tumours, malignant disease of lymphatic or haematopoietic tissue - cutaneous melanoma. HAS February 2008
[3] Mélanome cutané métastatique. [Metastatic cutaneous melanoma]. INCA October 2013
[4] Survie attendue des patients atteints de cancers en France : état des lieux. [Expected survival of cancer patients in France: current situation.] INCA 2012.
http://www.google.fr/url?sa=t&rct=j&q=&esrc=s&source=web&cd=3&ved=0CC8QFjAC&url=http%3A%2F%2Fwww.e-cancer.fr%2Fcomponent%2Fdocman%2Fdoc_download%2F9863-la-situation-du-cancer-en-france-en-2012&ei=ACCsU_TfB6WK0AWp1IHwBQ&usg=AFQjCNHkB_IX9MypW4AyaeiIZ0-4oFbw8A&bvm=bv.69837884,d.d2k
[5] YERVOY opinion of 06/11/2013

06 CLINICALLY RELEVANT COMPARATORS

The comparators for YERVOY in first-line treatment of advanced (unresectable or metastatic) melanoma are:

06.1 Medicinal products

NAME (INN) *Company*	*Therapeutic category	Indication	Date of opinion	Actual Benefit	Improvement in Actual Benefit (Wording)	Reimbursement Yes/No
DETICENE (dacarbazine) SANOFI	Alkylating agents	Malignant melanomas	N/A	Substantial	N/A	Yes
MUPHORAN (fotemustine) SERVIER	Alkylating agents	Disseminated malignant melanoma (including cerebral localisations)	09/07/2014	Substantial	IAB V	Yes
ZELBORAF (vemurafenib) ROCHE	B-RAF protein kinase inhibitors	In monotherapy: adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	03/10/2012	Substantial	Moderate IAB (level III) in the treatment strategy for BRAF V600 mutation-positive unresectable or metastatic melanoma	Yes
TAFINLAR (dabrafenib) GlaxoSmithKline	B-RAF protein kinase inhibitors	In monotherapy: adult patients with BRAF V600 mutation-positive unresectable or metastatic melanoma	07/05/2014	Substantial	(IAB V, non-existent) in the current treatment of BRAF V600 mutation-positive unresectable or metastatic melanoma.	Yes

NA: not available

For information purposes, the following proprietary medicinal products are also available: INTRONA (interferon alpha-2b) and ROFERON-A (interferon alpha-2a), indicated as an adjuvant to surgery. TEMODAL (temozolomide) is a chemotherapy recommended by NCCN 20131 and INCa-SFD[6] that may be used in the treatment of metastatic melanoma (off-label use).

[6] INCa, SFD. Recommandations Profesionnelles. Mélanome cutané métastatique - Rapport intégral. [Clinical Practice Guidelines. Metastatic cutaneous melanoma - Full report]. Opinion & Guidelines Collection September 2013

06.2 Other health technologies

In patients with limited stage IV metastatic melanoma, surgical resection of metastases is recommended whenever possible.

Conclusion

The comparators listed in the table are all clinically relevant.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	Reimbursement	
	Yes/No/Assessment in progress or duly documented change	Scope (indications) and special condition(s)
Austria	Yes	MA indication
Bulgaria		
Denmark		
Finland		
Greece		
Ireland		
Norway		
Netherlands		
Germany	In progress	
United Kingdom		
Belgium		
Cyprus		
Spain		
France		
Iceland		
Italy		
Luxembourg		
Slovenia		
Switzerland		
Croatia		
Estonia		
Hungary		
Latvia		
Lithuania		
Malta		
Poland		
Portugal		
Czech Republic		
Romania		
Slovakia		
Sweden		

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

The company provided:

- a pooled analysis including chemotherapy-naive patients, resulting from 4 randomised studies (3 phase II studies: CA184-004, CA184-022, MDX010-08 and one phase III study: MDX010-20) treated with ipilimumab at a dose of 3 mg/kg;
- two retrospective observational cohort studies (CA184-332 and CA184-338) of patients followed up in the United States;
- a phase III study (CA184-024) that evaluated ipilimumab in the Marketing Authorisation indication at the dose of 10 mg/kg, which is not the dose in the Marketing Authorisation;
- an indirect comparison whose objective was to compare the efficacy of ipilimumab 3 mg/kg to that of vemurafenib and to other first-line treatments in treatment-naive patients with advanced melanoma.

8.1.1 Pooled analysis of the 4 studies

This is a descriptive pooled analysis of individual data from subgroups of chemotherapy-naive patients or patients previously treated with a first line of immunotherapy and extracted from 4 clinical studies (**Table 1**) whose objective was to assess the overall survival rate at one year of patients treated with ipilimumab 3 mg/kg in monotherapy.

Table 1: pooled summary of clinical studies

MDX010-08	Phase II study in treatment-naive patients treated with ipilimumab 3 mg/kg ± dacarbazine (12 sites - United States)
MDX010-20	Phase III study in pretreated patients, and receiving ipilimumab at 3 mg/kg ± gp100 (125 sites - Europe, North and South America, Africa) – pivotal study of the initial listing dossier.
CA184-004	Phase II study in pretreated or naive patients, treated with ipilimumab at 3 versus 10 mg/kg (14 sites - Europe, North and South America)
CA184-022	Phase II study in pretreated or naive patients, receiving ipilimumab at 0.3 versus 3 versus 10 mg/kg (66 sites - Europe, North and South America, Australia and South Africa)

Inclusion and non-inclusion criteria

The inclusion criteria were, in particular:

- chemotherapy-naive patients or patients previously treated with a first-line immunotherapy;
- patients classified ECOG 0-1 and Karnofsky > 60% (MDX010-08);
- patients with unresectable stage III or stage IV melanoma;
- patients treated with ipilimumab 3 mg/kg x 4 injections, with the possibility of re-induction (MDX010-20) or maintenance (CA184-004/022).

The non-inclusion criteria notably included a diagnosis of:

- ocular melanoma (CA184-004, MDX010-20);
- mucosal melanoma (CA184-022);
- active brain metastases (MDX010-20, CA184-004);
- any known brain metastasis (CA184-022).

Primary efficacy endpoint

- Overall survival rate at 1 year.

Statistical analysis
In this type of study design, there is no sample size calculation.
Overall survival was estimated according to the Kaplan-Meier method.

Results
A total of 78 patients were included. The mean age of the patients was 57.4 years (60.3% men). The B-RAF status of the patients was not specified.
The percentage of patients who received a first line of immunotherapy (type not specified) was 52.6% (41 patients).
The percentage of patients with an ECOG performance index of 0 was 57.7% (45 patients), 38.5% (30 patients) for those with an ECOG index of 1 and 3.8% (3 patients) for those with an ECOG index > 2.
The median patient follow-up time was 11.6 months:

Primary efficacy endpoint
The overall survival rate estimated at 1 year was 54.1%, 95% CI = [42.5-65.6].

Secondary endpoints
The overall survival rate estimated at 2 years was 31.6%, 95% CI = [20.7-42.9].
The overall survival rate estimated at 3 years was 23.7%, 95% CI = [14.3-34.4].
The median estimated survival was 13.5 months, 95% CI = [11.2-19.6].

This analysis has several statistical and methodological weaknesses that must be emphasised:
- The potential biases related to a *post-hoc* pooled analysis by subgroups with failure to comply with the hypothetical-deductive approach (no prospective validation of a starting hypothesis) include confounders, selection bias and uncontrolled alpha risk inflation.
- Non-comparative analysis (before-after)

In all, given these comments, these results can only be considered exploratory and do not permit a precise and reliable quantification of the effect of treatment in this indication.

Moreover, the percentage of patients with melanoma carrying a B-RAF mutation at inclusion was not defined, so this treatment cannot be positioned in naive patients, given current treatment guidelines. Half of the patients included in this analysis were treated previously with a first-line immunotherapy (type of immunotherapy not defined), which means that these patients are chemotherapy-naive but not treatment-naive, which adds a degree of confusion in positioning treatment with ipilimumab 3 mg/kg in the first line of the therapeutic strategy.

8.1.2 Real-life use data: studies CA184-332 and CA184-338

This is an interim analysis (final analysis planned for September 2016) for two observational and retrospective cohort studies under real conditions of use in treatment-naive patients with advanced (unresectable or metastatic) melanoma and treated with ipilimumab 3 mg/kg in the United States.
These studies had the following objectives:
- determine patient demographic and clinical characteristics;
- define the safety profile during treatment;
- analyse the conditions of use for ipilimumab in real life (dose, number and date of injections, treatment indication, reasons for treatment discontinuation, etc.);
- estimate patient overall survival (mean, median and rate at 1, 2, 3 and 4 years).

Inclusion and non-inclusion criteria
The inclusion criteria were:
- stage III unresectable or stage IV melanoma regardless of the type of primary tumour (cutaneous, mucosal, ocular, other or unknown);
- age ≥ 18 at the time of diagnosis;
- treatment with ipilimumab 3 mg/kg in monotherapy.

The non-inclusion criteria were:
- prior treatment for unresectable stage III or stage IV melanoma;
- participation in another clinical trial or an early access programme;
- current treatment for a cancer other than melanoma.

A patient was included in the analysis if their minimum follow-up duration was one year from treatment initiation.

The overall survival was estimated for each patient from the first dose of ipilimumab administered until the date of death or the date of the patient's last known follow-up visit.

Statistical analysis
Overall survival was estimated by the Kaplan-Meier method in order to determine the median survival and the survival rates at 1, 2 and 3 years. The 95% confidence interval was calculated by the Brookmeyer & Crowley method. In this analysis, if the vital status of a patient was unknown at the end of follow-up, they were censored (considered deceased) on the date of the last visit of the patient.

Results
Study CA184-332
The data collected are those of patients followed up in oncology centres affiliated with the US Oncology Comprehensive Strategic Alliance network, using the iKnowMed electronic medical system.
In all, 90 patients (among the 108 patients meeting the inclusion criteria and identified in the database) were included from 1/04/2011 to 30/09/2012. The mean age of the patients was 64 years (66.7% men).
The percentage of patients with melanoma carrying a B-RAF mutation at baseline was 15.6% (n=14), 53.3% for those with melanoma without B-RAF mutation (n=48), and 31.1% for patients not tested for B-RAF mutation at baseline (n=28).
The percentage of patients with an ECOG performance index of 0 was 64.5% (58 patients), 27.8% (25 patients) for those with an ECOG index of 1 and 3.3% (3 patients) for those with an ECOG index > 2.
Main locations of metastases: lung (52.2%), lymph nodes (45.6%), liver (41.1%) and brain (31.1%).

At the time of the interim analysis, 53% of patients (n=48) were deceased.
The overall survival rate observed at 1 year was 49.4%, 95% CI = [38.3-59.6].
The overall survival rate observed at 1.5 years was 37.1%, 95% CI = [24.2-50.0].
The median survival observed was 11.5 months, 95% CI = [7.2- NA].

Study CA184-332
The data collected are those of patients followed up in centres affiliated with the Cytokine Working Group.
In all, 160 patients were included from 1/04/2011 to 15/05/2012. The mean age of the patients was 62.1 years (65.6% men).
The percentage of patients with melanoma carrying a B-RAF mutation at baseline was 16.9% (n=27), 65.6% for those with melanoma without B-RAF mutation (n=105), and 17.5% for patients not tested for B-RAF mutation at baseline (n=28).
The percentage of patients with an ECOG performance index of 0 was 39.4% (63 patients), 47.5% (76 patients) for those with an ECOG index of 1 and 5.0% (8 patients) for those with an ECOG index > 2.

The percentage of patients with brain metastases was 10% (16 patients).
Furthermore, 28 patients were previously treated with adjuvant immunotherapy (when the disease was classified at a lower stage), including 26 treated with interferon alpha. In addition, 79 patients (49.4%) had received adjuvant therapy during the last induction dose: temozolomide (15.6%), vemurafenib (6.9%) and paclitaxel (6.3%).

At the time of the interim analysis, 52.5% of patients (n=84) were deceased.
The overall survival rate observed at 1 year was 60.8%, 95% CI = [52.8-67.9].
The overall survival rate observed at 1.5 years was 46.7%, 95% CI = [38.0-55.0].
The median survival observed was 15.5 months, 95% CI = [13.2-19.1].

The study population consisted of patients able to receive ipilimumab (ECOG 0-1) because the majority had a life expectancy ≥ 4 months.
It must be emphasised that these are interim results from observational retrospective cohort studies with a risk of recall bias. Moreover, they are non-comparative studies (added value of treatment difficult to estimate). These results can be debated, but their level of evidence remains low.

For information purposes, in study CA184-338, according to a *post-hoc* subgroup analysis, the percentage of overall 1-year survival of patients with melanoma carrying a B-RAF mutation at baseline (n=27) was 70% (95% CI [48.8-83.7]); this percentage was 60.5% (95% CI [50.4 to 69.1]) for patients with melanoma without a B-RAF mutation (N=105), and finally 53.6% (95% CI [33.8 to 69,]) for patients not tested for B-RAF mutation at baseline (N=28). These results are only exploratory.

8.1.3 Indirect comparison

The objective of this indirect comparison or network meta-analysis, conducted and funded by BMS, was to compare the efficacy of ipilimumab 3 mg/kg to the available treatment regimens, including vemurafenib, in terms of overall survival and progression-free survival in adult patients with advanced (unresectable or metastatic) melanoma and receiving first-line treatment. Prior adjuvant immunotherapy was allowed.
A literature search was performed in Medline from 1948 to 2013, Embase from 1988 to 2011 and the ASCO and ESMO conferences from 2010. The studies selected were randomised and compared the efficacy of dacarbazine in monotherapy to the combinations of dacarbazine + IFN + oblimersen, dacarbazine + another substance excluding IFN, and to paclitaxel, fotemustine, temozolomide, ipilimumab, and vemurafenib. Trials comparing the efficacy of temozolomide in monotherapy to the combination of temozolomide + IFN and temozolomide + another substance excluding IFN were also included.

On this basis, 16 randomised clinical trials were identified and included. An ipilimumab 3 mg/kg comparator arm had to be estimated in the absence of comparative studies evaluating ipilimumab 3 mg/kg versus dacarbazine; data from the dacarbazine arm of study CA184-024 were used to develop a predictive multivariate regression model of overall survival and progression-free survival on dacarbazine and then applied to the characteristics of patients in the ipilimumab 3 mg/kg studies. Different models were tested to identify the most relevant factors for prognosis; however, the lack of trials with a direct comparison of ipilimumab 3 mg/kg versus dacarbazine makes it more difficult to validate the assumption of exchangeability among the trials. Then, Kaplan-Meier survival curves by treatment were digitised and combined in the form of a Bayesian network meta-analysis in order to compare different treatment regimens.

Results (Table 2):

Table 2: Overall survival rate

Estimated survival rate	At 6 months 95% CI	At 12 months 95% CI	At 18 months 95% CI	At 24 months 95% CI
Dacarbazine	62% [59-65]	38% [35-42]	24% [21-27]	15% [13-18]
Temozolomide	65% [60-70]	41% [36-47]	25% [20-31]	15% [10-21]
Ipilimumab*	70% [53-82]	52% [31-68]	40% [21-47]	32% [14-51]
Vemurafenib (B-RAF + patients)	74% [68-79]	52% [45-59]	36% [28-43]	23% [16-31]

* This analysis assumes equivalent efficacy for ipilimumab whether or not patients carry the B-RAF mutation.

The results of this indirect comparison suggest that in terms of long-term overall survival (≥ 24 months), ipilimumab appears superior to the other monotherapy treatment regimens assessed (dacarbazine, temozolomide and vemurafenib). A hazard ratio in favour of ipilimumab relative to dacarbazine was observed at 24 months: HR = 0.46, 95% CI = [0.23-0.90], and relative to temozolomide: HR = 0.40, 95% CI = [0.18-0.85], and finally relative to vemurafenib: HR = 0.47; 95% CI = [0.23-0.98]. (The analysis including vemurafenib assumes equivalent efficacy for ipilimumab whether or not patients carry the B-RAF mutation).

In this indirect comparison, progression-free survival with vemurafenib appears superior to other treatment regimens in the B-RAF+ population during the first 10 months of follow-up. No difference was evidenced among the treatment regimens regardless of patient B-RAF status.

The estimate of a comparator arm for ipilimumab 3 mg/kg, made in the absence of comparative studies evaluating ipilimumab 3 mg/kg versus dacarbazine, limits the validity of this network meta-analysis compared with a network meta-analysis with only randomised clinical trials; in fact, the assumption of inter-trial exchangeability/transferability cannot be guaranteed. Thus, the results of this indirect comparison suggesting that overall survival improved with ipilimumab versus comparators, do not allow formal conclusions to be drawn and they must be confirmed by comparative clinical trials.

8.1.4 Study CA 184-024

This is a phase III, randomised, double-blind study whose objective was to compare the efficacy and safety of the combination of ipilimumab 10 mg / kg + dacarbazine versus dacarbazine in monotherapy in terms of overall survival in treatment-naive patients with advanced (unresectable or metastatic) melanoma.

In this study ipilimumab was administered at a dose of 10 mg/kg, which is not the dose in the Marketing Authorisation (3 mg/kg); this study is not presented as no conclusion can be drawn.

08.2 Adverse effects

8.2.1 Data from clinical studies

Pooled analysis
The safety results were analysed in 75 patients who could be assessed.
The percentage of adverse events considered treatment-related was 81.3% (61/75).

The most common adverse events related to treatment were:
- skin and subcutaneous tissue disorders (54.7%), mainly including skin rash (29.3%) and pruritus (24.0%),
- gastrointestinal disorders (40.0%) mainly including nausea (22.7%) and diarrhoea (22.7%),
- general disorders and administration site conditions (50.7%),

The percentage of treatment discontinuations due to adverse events considered treatment-related was 6.7%.
Serious treatment-related adverse events (grade ≥ 3) were reported in 13.3% of patients.
The percentage of deaths attributed to treatment was 2.7% (2 patients including 1 associated with an immune-mediated event: intestinal perforation).
The percentage of adverse events considered to be immune-mediated was 64.0% (48/75). These were mainly cutaneous (52.0%) and gastrointestinal (22.7%). Finally, the percentage of serious adverse events (grade ≥ 3) considered to be immune-mediated was 9.3%.

Observational cohort studies
Safety data were not collected during the interim analysis of study CA184-332.

In study CA 184-338, safety results were analysed in 160 patients. The percentage of adverse events was 59.4% (95/160). The percentage of adverse events considered treatment-related was 53.8% (86/160).

The most common adverse events related to treatment were:
- skin and subcutaneous disorders (28.0%), mainly including pruritus (14.0%) and dermatitis (11.0%),
- gastrointestinal disorders (26.0%) mainly including diarrhoea (13.0%).

The percentage of treatment discontinuations due to adverse events was 10.6%. The percentage of treatment discontinuations due to adverse events considered treatment-related was 9.4%.
Serious treatment-related adverse events (grade ≥ 3) were reported in 14.4% of patients.
In all, 84 deaths were reported and none were attributed to treatment.
The percentage of adverse events considered to be immune-mediated was 50.6% (81/160). These were mainly cutaneous (28%) and gastrointestinal (23.0%). Finally, the percentage of serious adverse events (grade ≥ 3) considered to be immune-mediated was 11.9%.

Study CA184-024
In this study ipilimumab was administered at a dose of 10 mg/kg in combination with dacarbazine versus dacarbazine as monotherapy, which is not the dose in the Marketing Authorisation (3 mg/kg); the safety data from this study will not be presented.

8.2.2 PSUR data

Since the one-year reassessment dossier for YERVOY, two new six-month periodic safety update reports (PSUR) have been published. The analysis of these latest PSURs covering the period from 25 September 2012 to 24 September 2013 allowed estimating the exposure of patients to treatment at 7,351 patient-years.
No new pharmacovigilance signal was evidenced in these latest two PSURs.

Note that ipilimumab is associated with the occurrence of severe immune-mediated reactions, and a risk management plan was implemented at the time of the European Marketing Authorisation for YERVOY. The major risks identified are the following:

- Immune-mediated gastrointestinal reaction (diarrhoea, colitis, intestinal perforation)
- Immune-mediated hepatic reaction (hepatitis)
- Immune-mediated cutaneous reaction (rash, pruritus)
- Immune-mediated neurological reaction (meningitis, neuropathy)
- Immune-mediated endocrine reaction (hypopituitarism, hypothyroidism, adrenal insufficiency)
- Other immune-mediated reactions (pancreatitis, etc.)
- Severe infusion-related reaction.

Furthermore, a type II variation was submitted to the EMA (SPC update 30 May 2013) to add a warning regarding concomitant administration of ipilimumab and vemurafenib to section 4.4. This update followed the occurrence of an asymptomatic elevation of hepatic markers in a phase I clinical trial, CA184-161: "Treatment of subjects who have metastatic melanoma that expresses an activated mutant form of the B-RAF oncogene (V600E) with a combination of the specific B-RAF inhibitor, vemurafenib, and a CTLA-4 inhibitor, ipilimumab".

Finally, a signal of posterior reversible encephalopathy / leukoencephalopathy (PRAC 10-13 June 2014, Pharmacovigilance Risk Assessment Committee of the European Medicines Agency) was reported following the occurrence of 13 cases of hospitalisation. To determine whether there is a causal link between the use of YERVOY and the occurrence of these events, PRAC confirms the need for the company to provide, in the next PSUR (collection completed on 24 September 2014), a cumulative review of clinical data, post-marketing reports and literature cases of posterior reversible encephalopathy, including consistent MedDRA and SMQ terms (standardised MedDRA queries).

8.2.3 SPC data

In the prior examination by the Transparency Committee, several changes were made to the SPC (**Table 3**):

Table 3: Main changes made in the SPC

SPC section (Summary of product characteristics)	*Date of revision of Marketing Authorisation*	*Change in wording*
4.1 Therapeutic indications	EC Decision of 31 October 2013	Extension of indication to treatment-naive patients
4.2 Posology and method of administration	EC Decision of 31 October 2013	As part of the adaptation of treatment in cases of immune-mediated adverse effects, doses should be suspended and not discontinued from now on. As a result, the entire section has been changed.
4.4 Special warnings and precautions for use	CHMP opinion of 30 May 2013*	Addition of a paragraph on the results of a phase I study on co-administration of ipilimumab/vemurafenib, describing hepatotoxicity.
	EC Decision of 31 October 2013	The section has been modified in particular to implement the change in section 4.2 Posology and method of administration, relating to the suspension rather than discontinuation of injections in case of immune-mediated adverse effects
4.8 Undesirable effects	CHMP opinion of 30 May 2013*	Addition of a paragraph relating to Adverse Effect Reporting
	EC Decision of 31 October 2013	Update to the section with safety data obtained during the extension of indication to treatment-naive patients.
	EC Decision of 18 December 2013	Addition of "Anaphylactic reaction" + frequency in the tabulated list of adverse reactions.

*Variation not listed in Article 23(1a) (a): CHMP is valid for authorising the change in the Marketing Authorisation.

08.3 Summary & discussion

Main efficacy results

In a pooled analysis including chemotherapy-naive patients, resulting from 4 randomised studies (3 phase II studies: CA184-004, CA184-022, MDX010-08 and one phase III study: MDX010-20) and treated with ipilimumab at the dose of 3 mg/kg (n=78 patients), the overall survival rate estimated at one year (primary efficacy endpoint) was 54.1%, 95% CI = [42.5-65.6].
The secondary endpoints include: the estimate of the median overall survival was 13.5 months, 95% CI = [11.2-19.6].
This analysis has several statistical and methodological weaknesses that must be emphasised:
- The potential biases related to a post-hoc pooled analysis by subgroups of patients from different studies with failure to comply with the hypothetical-deductive approach (no prospective validation of a starting hypothesis) include confounders, selection bias and uncontrolled alpha risk inflation.
- The absence of comparative analysis with the existing therapeutic strategy.

Consequently, these results can only be considered exploratory and do not permit a precise and reliable quantification of the effect of treatment in this indication.

In the interim analysis of two observational and retrospective cohort studies under real conditions of use in treatment-naive patients with advanced (unresectable or metastatic) melanoma and treated with ipilimumab 3 mg/kg in the United States, the results were as follows:
In study CA184-332 (n=90 patients), the overall survival rate observed at one year was 49.4% (95% CI = [38.3-59.6]) and the median survival observed was 11.5 months (95% CI = [7.2- NA]).
In study CA184-338 (n=160 patients), the overall survival rate observed at one year was 60.8% (95% CI = [52.8-67.9]) and the median survival observed was 15.5 months (95% CI = [13.2-19.1]).
The percentage of patients carrying a B-RAF mutation at baseline was specified, but the results have not been presented according to whether or not this mutation is present. In fact the percentage of overall survival at 1 year according to patient mutation status was calculated only during a post-hoc subgroup analysis of study CA184-338; these results were presented for information purposes (see "efficacy" section).
It must be emphasised that these observational retrospective cohort studies have a risk of recall bias. Moreover, they are non-comparative studies (relative value of treatment impossible to estimate). The level of evidence of these results remains low.

In the indirect comparison provided by the company that included 16 randomised clinical trials, the results suggest that in terms of overall survival:
- Long term (≥ 24 months) ipilimumab seems superior to the other monotherapy treatment regimens assessed (dacarbazine, temozolomide, vemurafenib). A hazard ratio in favour of ipilimumab relative to dacarbazine was observed at 24 months: HR = 0.46, 95% CI = [0.23-0.90], and relative to temozolomide: HR = 0.40, 95% CI = [0.18-0.85], and finally relative to vemurafenib: HR = 0.47; 95% CI = [0.23-0.98]. The analysis including vemurafenib assumes equivalent efficacy for ipilimumab whether or not patients carry the B-RAF mutation.
Moreover, the results of this indirect comparison suggest that in terms of progression-free survival:
- vemurafenib appears superior to other regimens in the B-RAF+ population during the first ten months of follow up. No difference was evidenced among the treatment regimens regardless of the patient B-RAF status.
However, the estimate of a comparator arm for ipilimumab 3 mg/kg (in terms of overall survival) in the absence of comparative studies evaluating ipilimumab 3 mg/kg versus dacarbazine, limits the validity of this network meta-analysis; the assumption of inter-trial exchangeability cannot be guaranteed. Thus, the results of this indirect comparison suggest that overall survival improved with ipilimumab versus comparators but do not allow formal conclusions to be drawn.

Finally, the company provided a phase III, randomised, double-blind study whose objective was to compare the efficacy and safety of the combination of ipilimumab 10 mg / kg + dacarbazine versus dacarbazine in monotherapy in terms of overall survival in treatment-naive patients with advanced (unresectable or metastatic) melanoma. Since the dosage evaluated was not the dosage in the Marketing Authorisation (3 mg/kg), this study was not presented and no conclusions can be drawn.

In conclusion, all the data provided by the company are of a low level of evidence and need to be confirmed by clinical trials of better methodological quality.

Main safety results

The adverse effects most commonly observed with ipilimumab in this new indication were skin rash, pruritus, nausea and diarrhoea.
Serious adverse events (≥ grade 3) related to treatment were reported in 13 to 14% of patients; the most frequently observed are immune-mediated (see PSUR and RMP)
The safety data provided in this new indication are comparable to the currently known safety profile for this proprietary medicinal product.
The difference in safety with this medicinal product relative to treatments used at this stage of the disease is unknown.

08.4 Planned studies

Ongoing studies at the request of the EMA :

- Study CA184-169: randomised, comparative study whose objective is to assess efficacy in terms of survival and safety of dosages of 3 mg/kg versus 10 mg/kg in the treatment of advanced melanoma. Results expected for 2015.
- IMAGE study (A Multi-National, Prospective, Observational Study in Patients with Unresectable or Metastatic Melanoma: CA184-143): Prospective observational study in patients with unresectable or metastatic melanoma. Results expected for 2017.

Follow-up programme from the MELBASE database: follow-up study of a national cohort of patients with unresectable stage III cancer or stage IV cancer with virtual biological sample collection. Results expected for 2016.

09 THERAPEUTIC USE

The current first-line treatment for advanced (unresectable or metastatic) melanoma is based on screening patients as soon as they are diagnosed for a B-RAF mutation.

- In the absence of a B-RAF mutation, as first-line treatment according to the NCCN guidelines, ipilimumab (YERVOY) is considered to be a preferred "NCCN category 1" option. In the specific case of non-B-RAF mutated tumours and associated only with brain metastases, treatment relies on the use of ipilimumab (YERVOY) or fotemustine. The role of additional radiation therapy must be discussed.

- With a mutation, the choice of treatment will be a targeted therapy, currently with vemurafenib (ZELBORAF) or dabrafenib (TAFINLAR) in monotherapy.

Note that all the available data so far show that the duration of response with ipilimumab is fairly long, but that the number of responders is low and that no predictive factor for response has been identified to date. Given the small proportion of patients responding to ipilimumab (< 15%) and its delayed onset of action (more than 3 months), the use of ipilimumab should be reserved for patients with slow progression (over several months), that is to say patients with few metastatic sites, few metastases, good general condition and a life expectancy greater than 3 months.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee's opinion is as follows:

010.1 Actual benefit

◗ Melanoma is a skin cancer with a strong metastatic potential which can, when advanced, be complicated by metastases and be life-threatening in the short or medium term.

◗ This medicinal product is a curative treatment, specifically for melanoma.

◗ Due to the low level of evidence of the data presented to justify the efficacy of YERVOY as a first-line treatment for advanced melanoma and the notable adverse effects encountered and attributable to ipilimumab, the efficacy/adverse effects ratio is considered modest in the first line.

◗ There are pharmacological treatment alternatives represented by vemurafenib (ZELBORAF) and dabrafenib (TAFINLAR) in patients with a B-RAF mutation, and dacarbazine (DETICENE) fotemustine (MUPHORAN) and temozolomide (TEMODAL) in patients without a B-RAF mutation.

◗ It is a first-line treatment in patients without a B-RAF mutation.

◗ Public health benefit:
In terms of public health, the burden of cutaneous melanomas and other skin cancers is moderate (approximately 160,000 DALYs). In advanced (unresectable or metastatic) melanoma, it may be considered to be low.
The improvement in the management of patients with cancer is a public health need set out in the Cancer Plan 2014-2019.
In view of the available data, the impact of YERVOY on morbidity and mortality is moderate. A negative impact on quality of life cannot be ruled out, particularly in view of the notable adverse effects encountered. YERVOY provides only a partial response to the identified public health need.
Consequently, the proprietary medicinal product YERVOY is not expected to benefit public health in this indication.

Given the low level of evidence of the studies presented, the Committee considers that the actual benefit of YERVOY 5 mg/mL is <u>moderate</u> in the extension of indication in first-line treatment for adult patients with advanced (unresectable or metastatic) melanoma, without a B-RAF mutation and in patients with slow progression, good general condition and a life expectancy greater than 3 months.

The Committee recommends inclusion on the list of medicines refundable by National Health Insurance and on the list of medicines approved for hospital use in first-line treatment for adult patients with advanced (unresectable or metastatic) melanoma, without a B-RAF mutation and in patients with non-aggressive or slowly progressing disease who have failed prior treatment, have a good general condition and a life expectancy greater than 3 months and at the dosages in the Marketing Authorisation.

010.2 Improvement in actual benefit (IAB)

In the absence of demonstrated efficacy or safety greater than the existing therapeutic strategy for first-line treatment of advanced melanoma in adults, YERVOY does not provide any improvement in actual benefit (IAB V, non-existent)

010.3 Target population

The target population of YERVOY (ipilimumab) as first-line monotherapy corresponds to adult patients with unresectable (IIIc) or distant metastatic (IV) melanoma without a B-RAF mutation.

According to the FRANCIM data, the snapshot partial prevalence calculated at the end of 2004 was 31,278 cases of melanoma, 28,968 cases without metastasis and 2310 cases with metastasis (stage IV).[7] The change in prevalence of advanced melanoma over time may be considered to be slightly increasing. Given the hypothesis of a change in prevalence equal to that of the change in the crude incidence of 2.2% per year, the prevalence of stage IV melanomas is estimated at 2810 patients at the end of 2013.[8]

The ratio between unresectable stage IIIc and stage IV is not known. It is estimated at 11.8% based on the MELODY study (the sample at baseline for MELODY included 195 stage IV patients and 23 stage III unresectable patients)[9] or 330 (2810 x 11.8%) unresectable stage (IIIc) patients. This would therefore make the population of unresectable stage (IIIc) or metastatic stage (IV) melanomas 3,140 patients (2,810 + 330) at most.

The frequency of the B-RAF mutation varies for the most recent data:
- from 36% (INCa, 2012)[10] on the one hand,
- to 46% (Menzies et al.),[11] 47% (Jakob et al.,)[12] 48%(Long et al.),[13] 50% (Jang et al.),[14] 50% (Menzies et al.)[15] and 53% (Edlundh-Rose et al.)[16] or a percentage of mutations consistent with the 47% B-RAF mutation rate found in patients tested in the national melanoma CeNGEPS-GMFMel[17,18] [French Skin Melanoma Multidisciplinary Group Clinical Investigation

[7] FRANCIM COLLABORATIVE STUDY, Lyon Civil Hospices, InVS, CepiDc. Change in the incidence and mortality of cancer in France, 1980 to 2005. Data sheet: Cutaneous melanoma. 30 January 2008
[8] Binder-Foucard F, Olteanu S, Levrat F et al. Incidence and prevalence of cutaneous melanoma in France: a population based study from eight cancer registries. ISPOR 2009 abstract. Value in Health 2009;12:A261, PCN28
[9] Transparency Committee YERVOY (ipilimumab) opinion of 14 December 2011
[10] INCa. Synthèse de l'activité des plateformes hospitalières de génétique moléculaire des cancers en 2012[Summary of cancer molecular genetics platform activity in hospitals in 2012]. January 2014.
[11] Menzies AM, Haydu LE, Visintin L, et al. Distinguishing clinicopathologic features of patients with V600E and V600K BRAF-mutant metastatic melanoma. Clin Cancer Res. 2012;18:3242–49
[12] Jakob JA, Bassett RL Jr, Ng CS, et al. NRAS mutation status is an independent prognostic factor in metastatic melanoma. Cancer. 2012;118:4014-23
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[16] Edlundh-Rose E, Egyházi S, Omholt K, et al. NRAS and BRAF mutations in melanoma tumours in relation to clinical characteristics: a study based on mutation screening by pyrosequencing. Melanoma Res. 2006;16:471–8
[17] National cohort of patients with melanoma from the French Skin Melanoma Multidisciplinary Group Clinical Investigation Network, (CeNGEPS-GMFMel). Available online: [URL]: http://www.cengeps.fr/sites/default/files/reseaux-investigation/Plaquette%20GMFMel%202013-04-25.pdf

Network] cohort (database consulted on 5 November 2014, 10,299 patients with melanoma all stages combined, 1,850 patients with stage III unresectable / IV including 592/1267 patients tested carrying a BRAF mutation) on the other hand.

By applying a percentage from 64 to 53% of patients without B-RAF mutation, between 1664 (3140 x 53%) and 2009 (3140 x 64%) patients are estimated in the target population for ipilimumab in treatment-naive patients with no B-RAF mutation. This is a maximum; due to its delayed onset of action (more than 3 months), ipilimumab is not recommended in cases of aggressive melanoma (rapid progression).

In all, the target population for YERVOY in treatment-naive patients with unresectable or metastatic melanoma may be estimated at 1664 to 2009 patients. This target population is probably overestimated insofar as YERVOY must be reserved for patients with non-aggressive melanoma (i.e., progressing slowly, characterised by few metastatic sites, few metastases and progression over several months), a portion of the target population that cannot be quantified.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ Packaging

Appropriate for the prescribing conditions according to the indication, dosage and treatment duration.

[18] Foureau A et al. Intérêt du partenariat public-privé pour le suivi épidémiologique des formes rares de cancers : exemple de la cohorte nationale de patients atteints de mélanome du réseau d'investigation clinique du groupe multidisciplinaire français du mélanome cutané [Benefit of the public-private partnership for the epidemiological monitoring of rare cancers: example of the national cohort of melanoma patients from the French Skin Melanoma Multidisciplinary Group Clinical Investigation Network (CeNGEPS-GMFMel). Revue d'Épidémiologie et de Santé Publique. 2014;62:S5.