HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

OPINION

14 December 2011

YERVOY 5 mg/ml, concentrate for solution for infusion
Vial of 10 ml (CIP code: 580 877-0)
Vial of 40 ml (CIP code: 580 878-7)

Applicant: BRISTOL-MYERS SQUIBB

Ipilimumab
ATC code: L01XC11 (antineoplastic agents – monoclonal antibodies)

List I
Medicinal product reserved for hospital use, restricted to oncologists or doctors with experience in oncology.

Date of Marketing Authorisation (MA) (centralised procedure): 13 July 2011
The MA is accompanied by an RMP which includes in particular the routine follow-up of adverse effects. In addition, BMS has undertaken to set up a randomised comparative study to assess the efficacy and safety of ipilimumab 3 mg/kg in comparison to ipilimumab 10 mg/kg in order to justify the choice of the optimal dose.

Temporary authorisation for use by a named patient program ["ATU nominative" in French]: 144 non-formalised temporary authorisations for use by a named patient program granted between October 9, 2007 and July 28, 2010 and 646 documented temporary authorisations for use by a named patient program between July 29, 2010 and July 17, 2011.
Group temporary usage authorisation (TUA): 208 group TUAs granted between July 18 and September 30, 2011.

Reason for request: Inclusion on the list of medicines approved for hospital use.

Medical, Economic and Public Health Assessment Division

1. CHARACTERISTICS OF THE MEDICINAL PRODUCT

1.1. Active ingredient:
Ipilimumab

1.2. Background
YERVOY is a human monoclonal antibody which activates T cells; the infiltration of tumours by lymphocytes leads to the destruction of tumour cells.

1.3. Indication
"YERVOY is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy".

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

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 suggestive of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY (see Tables 1A and 1B).

Permanent discontinuation of treatment or omission of doses: Management of immune-related adverse reactions may require omission of a dose or permanent discontinuation of YERVOY therapy and institution of systemic high-dose corticosteroid or, in some cases, the addition of other immunosuppressive therapy (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 omission of scheduled doses are described in Tables 1A and 1B. Detailed guidelines for the management of immune-related adverse reactions are described in section 4.4 of the SPC".

Table 1A When to permanently discontinue YERVOY	
Permanently discontinue YERVOY in patients with the following adverse effects. Management of these adverse effects may also require systemic high-dose corticosteroid therapy if demonstrated or suspected to be immune-related (see section 4.4 for detailed management guidelines).	
Severe or life-threatening adverse effects	**NCI-CTCAE v3 Grade[a]**
Gastrointestinal: Severe symptoms (abdominal pain, severe diarrhoea or significant change in the number of stools, blood in stool, gastrointestinal haemorrhage, gastrointestinal perforation)	Grade 3 or 4 diarrhoea or colitis
Hepatic: Severe elevations in aspartate aminotransferase (AST), alanine aminotransferase (ALT), or total bilirubin or symptoms of hepatotoxicity	AST or ALT > 8 x ULN or total bilirubin > 5 x ULN
Skin: Life threatening skin rash (including Stevens-Johnson syndrome or toxic epidermal necrolysis) or severe widespread pruritus interfering with activities of daily living or requiring medical intervention	Grade 4 rash or grade 3 pruritus
Neurological: New onset or worsening of severe motor or sensory neuropathy	Grade 3 or 4 motor or sensory neuropathy
Other organ systems[b]: (e.g. nephritis, pneumonitis, pancreatitis, non-infectious myocarditis)	- ≥ Grade 3 immune-related events[c] - ≥ Grade 2 for immune-related eye disorders NOT responding to topical immunosuppressive therapy

a Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).
b Any other adverse effects that are demonstrated or suspected to be immune-related should be graded according to CTCAE. Decision whether to discontinue YERVOY should be based on severity.
c Patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy may remain on therapy.
ULN = upper limit of normal.

Table 1B When to suspend treatment with YERVOY	
Suspend treatment with YERVOY[a] in patients with the following immune-related adverse effects. See section 4.4 for detailed management guidelines.	
Mild to moderate adverse reactions	**Action**
Gastrointestinal: Moderate diarrhoea or colitis that either is not controlled with medical management or that persists (5-7 days) or recurs.	1. Suspend treatment until the adverse effect resolves to Grade 1 or Grade 0 (or returns to baseline). 2. If resolution occurs before the next scheduled dose, resume treatment at the next scheduled dose. 3. If resolution has not occurred before next scheduled dose, continue to suspend treatment until resolution then resume according to the predefined schedule. 4. Discontinue YERVOY if the adverse effect does not resolve to Grade 1 or Grade 0 (or return to baseline).
Hepatic: Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels	
Skin: Moderate to severe (Grade 3)b skin rash or widespread/intense pruritus regardless of aetiology	
Endocrine: Severe adverse effects in the endocrine glands, such as hypophysitis and thyroiditis that are not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy.	
Neurological: Moderate (Grade 2)b unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)	
Other moderate adverse effect[c]	

a No reduction in the dose of YERVOY is recommended. Doses omitted due to an adverse effect must not be replaced.
b Adverse effects are graded are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).
c Any other organ system adverse effect considered to be immune-related should be graded according to CTCAE. The decision on whether to suspend treatment should be based on severity.
ULN = upper limit of normal.

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

Special populations:
Elderly patients: 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 impairment (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."

2. SIMILAR MEDICINAL PRODUCTS

2.1. ATC Classification (2011)
L : Antineoplastic and immunomodulating agents
L01 : Antineoplastic agents
L01X : Other antineoplastic agents
L01XC : Monoclonal antibodies
L01XC11: Ipilimumab

2.2. Medicines in the same therapeutic category
Other antineoplastic agents indicated in metastatic melanoma:
- Other monoclonal antibodies: none.

- Tyrosine kinase inhibitor (vemurafenib): group TUA since May 2011, accepted by the FDA in October 2011 and received a favourable opinion of the CHMP on December 15, 2011.

2.3. Medicines with a similar therapeutic aim
These are the other therapeutic options used in the treatment of cutaneous melanoma:
1. Chemotherapies:
   - carmustine (BICNU),
   - dacarbazine (DETICENE and generics),
   - fotemustine (MUPHORAN),
   - lomustine (BELUSTINE).

2. Immunotherapies: interferon alpha-2a (ROFERON), PROLEUKIN (aldesleukin)

3. ANALYSIS OF AVAILABLE DATA

The assessment of the efficacy and tolerance of ipilimumab (YERVOY) in the treatment of advanced melanoma (unresectable or metastatic) in adults who have received prior therapy is based on:

- a (pivotal) phase III clinical study (MDX010-20[1]) the aim of which was to assess the efficacy and tolerance of ipilimumab in comparison to gp100 (peptide vaccine without MA) in terms of overall survival in HLA-A2*0201 positive patients with unresectable stage III and IV melanoma after failure of first-line treatment,

- two phase II clinical studies in patients with unresectable stage III and IV melanoma followed up for 48 weeks:
  - study CA184022 the aim of which was to determine the efficacy of 3 doses of ipilimumab in terms of the percentage of patients showing a complete or partial response.
  - study CA184004 the aim of which was to determine potential predictive markers of response to and/or toxicity of ipilimumab at doses of 3 and 10 mg/kg.

The company also supplied a phase III study (CA184024[2]) the aim of which was to assess the efficacy and tolerance of ipilimumab + dacarbazine versus dacarbazine in terms of overall survival in treatment-naïve patients with unresectable melanoma; since this indication does not correspond to the validated MA for ipilimumab, it will not be discussed in this document.

Similarly, study MDX010-08, performed in treatment-naïve patients (off-label) and studies CA184008, CA184007, CA184042 and MDX010-15 and MDX010-28, performed with a dose of 10 mg/kg (off-label), will not be discussed in this document.

3.1. Efficacy

3.1.1. Pivotal phase III study: MDX010-20[1]

Method: randomised, double-blind comparative phase III study of ipilimumab + placebo versus gp100 + placebo versus ipilimumab + gp100 performed in 676 HLA-A2*0201-positive patients with unresectable stage III or stage IV melanoma previously treated with at least one line of treatment containing the following chemotherapies: IL-2, dacarbazine, temozolomide, fotemustine and/or carboplatin, for 24 months.
gp100 is an experimental peptide vaccine which has no MA and is not available on the French market.

1Hodi FS et al. Improved survival with ipilimumab in patients with metastatic melanoma N Engl J Med. 2010 Aug 19;363(8):711-23.
2 Robert C et al. Ipilimumab plus dacarbazine for previously untreated metastatic melanoma. N Engl J Med. 2011 Jun 30;364(26):2517-26.

Inclusion criteria: HLA-A2*0201 patients over 18 years-old with unresectable stage III or IV melanoma and:

- a relapse after an objective response (partial or complete), a failure or intolerance of one or more substances (dacarbazine, temozolomide, fotemustine, carboplatin),
- a period of at least 28 days since the previous chemotherapy, immunotherapy or surgery and of 14 days since the previous radiotherapy,
- a life expectancy ≥ 4 months,
- an ECOG (Eastern Cooperative Oncology Group) performance status between 0 and 1.
- laboratory tests: leucocytes ≥ 2500/µl, neutrophils ≥ 1500/µl, platelets ≥ 100 x 103/µl, haematocrit ≥ 30%, haemoglobin ≥ 10 g/dl, creatinine ≤ 2 ULN, ASAT < 2 x ULN, total bilirubin < 2 x ULN.

*Inclusion was restricted to HLA-A2*0201-positive patients since the gp100 peptide vaccine would be active only in patients with this genetic marker, which is present in 40 to 50% of the general population[3].*

Treatments:
Patients were randomised to three groups in a 3:1:1 distribution.

- ipilimumab (3 mg/kg) + gp100 (2 mg of peptide A and 2 mg of peptide B), n = 403,
- ipilimumab (3 mg/kg) + placebo, n = 137,
- gp100 (2 mg of peptide A and 2 mg of peptide B) + placebo, n = 136.

These treatments were administered every 3 weeks for 4 cycles.

Primary endpoint: overall survival.
The main analysis concerned the comparison between the groups ipilimumab + gp100 versus gp100 + placebo.

Results: intention to treat (cf. Table 1)
A total of 151/676 patients (22%) were alive at the end of the study (24 months). The median period of follow-up was 20.99 months in the ipilimumab + gp100 group, 27.83 months in the ipilimumab group and 17.18 months in the gp100 group. Only a few patients were followed up to 55 months.
Patients' mean age at inclusion was 56.2 years [19; 90].

All the patients included had a stage M1a to M1c metastatic melanoma except one patient in the ipilimumab group (0.7%) and 4 patients in the gp100 group (2.9%).

The patients in the gp100 group had globally received more prior treatments than the patients in the ipilimumab group:

- IL-2: 23.4% in the ipilimumab group versus 24.3% in the gp100 group,
- 1 line of treatment: 37.2% versus 29.4%,
- 2 lines: 24.8% versus 24.3%,
- 3 lines: 16.1% versus 19.9%,
- 4 lines: 6.6% versus 8.8%,
- ≥ 5 lines: 15.3% versus 17.6%.

3 This study was performed in 125 European sites and in 676 patients, including 17 French sites (67 patients), but also in North and South America and in Africa.

Table 1: Overall survival

	Ipilimumab+gp100 n=403	**Ipilimumab+ placebo n=137**	Gp100+placebo n=136
Number of deaths (%)	306 (76%)	100 (73%)	119 (88%)
Median survival (months) 95% CI	9.95 [8.48; 11.50]	10.12 [8.02; 13.80]	6.44 [5.49; 8.71]
HR versus gp100 95% CI p	0.68 [0.55; 0.85] 0.0004	**0.66** **[0.51; 0.87]** **0.0026**	
HR versus Ipilimumab 95% CI p	1.04 [0.83;1.30] NS		

In terms of overall survival, a median gain of 3.68 months was observed in the ipilimumab group in comparison to the gp100 group: median survival 10.12 months versus 6.44 months, HR 0.66 [0.51; 0.87], p = 0.0026. No significant difference was observed between the ipilimumab and ipilimumab + gp100 groups: HR 1.04 [0.83; 1.30], NS.

Given the methods selected for this study, which assessed the efficacy of ipilimumab in comparison to and in combination with gp100, a substance which has no MA, the results must be interpreted with caution, particularly since the performance of gp100 seems to be of the same order than that of placebo (median survival without treatment: 7 months). In fact, although a difference in overall survival was observed, the therapeutic contribution of ipilimumab is difficult to quantify given the choice of comparator.

This study also assessed patients' quality of life on the basis of the EORTC QLQ-C30 scale[4]. Compared with status at inclusion, a marked deterioration in the patients' quality of life was observed in the ipilimumab (-8.8 [-13.5; -4.1]) and gp100 (-10.4 [-15.3; -5.5]) groups without any significant difference being revealed between the two groups: difference 1.6 [-5.0; 8.2], NS.

3.1.2. Phase II studies

CA184022

Method: randomised, double-blind comparative, phase II dose-finding study of ipilimumab 0.3 mg/kg versus ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg performed in 217 patients with unresectable stage III or stage IV melanoma, previously treated with other treatments and followed up for 48 weeks.

Inclusion criteria: Patients over 16 years-old with unresectable stage III or IV melanoma and:
- a relapse after an objective response (partial or complete), a failure or intolerance of at least one other substance.
- A life expectancy ≥ 16 weeks,
- an ECOG (Eastern Cooperative Oncology Group) performance status between 0 and 1.

Treatments:
- ipilimumab 0.3 mg/kg, n=73,
- ipilimumab 3 mg/kg, n=72,
- ipilimumab 10 mg/kg, n=72.

These treatments were administered every 3 weeks for 4 cycles.

4 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: this questionnaire covers the same areas than the HRQoL scale which is validated for clinical studies in oncology.

Primary endpoint: best objective response rate i.e. the percentage of patients showing a complete or partial response defined according to the modified WHO criteria[5].

Results:
An objective response was observed in 3/72 (4.2%) of patients in the ipilimumab 3 mg/kg group and 8/72 (11.1%) of patients in the ipilimumab 10 mg/kg group: difference 6.9%, 95% CI [-1.7; 15; 5], NS.
No objective response was observed in patients treated with ipilimumab 0.3 mg/kg.

CA184004
Method: randomised, double-blind phase II study, exploring predictive factors, of ipilimumab 3 mg/kg versus ipilimumab 10 mg/kg, performed in 82 patients with resectable stage III or stage IV melanoma followed up for 48 weeks.

Inclusion criteria: Patients over 16 years-old with unresectable stage III or IV melanoma and:
- a relapse after an objective response (partial or complete), a failure or intolerance of at least one other substance.
- a life expectancy ≥ 16 weeks,
- an ECOG (Eastern Cooperative Oncology Group) performance status between 0 and 1.

Treatments: ipilimumab 3 mg/kg, n=40, ipilimumab 10 mg/kg, n=42.
These treatments were administered every 3 weeks for 4 cycles.

Main objective: to define markers predictive of response to and/or toxicity of ipilimumab.

Secondary objectives, in particular: to determine the best objective response rate i.e. the percentage of patients showing a complete or partial response defined according to the modified WHO criteria[6].

Results:
Biomarkers predictive of response were identified: increase in the level of lymphocytes at week 12, infiltration of the tumour by lymphocytes at week 4, expression of FoxP3[7] at inclusion, presence of the immunoregulatory enzyme indolamine 2,3-dioxygenase.

An objective response was observed in 3/40 (7.5%) of patients in the ipilimumab 3 mg/kg group and 5/42 (11.9%) of patients in the ipilimumab 10 mg/kg group.

5 Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clin Cancer Res* 2009;15:7412-20.
6 Guidelines for the Evaluation of Immune Therapy Activity in Solid Tumors: Immune-Related Response Criteria. *Clin Cancer Res* 2009;15:7412-20.
7 Regulatory T cell marker

3.2. Adverse effects

In study MDX010-20, adverse effects were observed in 549/643 patients (85.4%): 339/380 (89.2%) in the ipilimumab + gp100 group, 106/131 (80.9%) in the ipilimumab group and 104/132 (78.8%) in the gp100 group.

Severe adverse effects (grade ≥ 3) were more frequent in the ipilimumab group (26%) than in the other treated groups: 19.5% in the ipilimumab + gp100 group and 12.1% in the gp100 group.

The most frequently observed adverse effects (> 10%) were:
- diarrhoea: 30.3% in the ipilimumab + gp100 group, 27.5% in the ipilimumab group and 13.6% in the gp100 group,
- nausea: 19.2% vs 23.7% vs 17.4%,
- vomiting: 9.5% vs 12.2% vs 6.8%,
- fatigue: 23.9% vs 24.4% vs 19.7%,
- pruritus: 17.6% vs 24.4% vs 11.4%,
- rash: 17.9% vs 19.1% vs 3.8%.

In this study discontinuations of treatment due to adverse effects were observed in three times more patients in the ipilimumab group than in the gp100 group: 9.9% in the ipilimumab group, 6.8% in the ipilimumab + gp100 group and 3% in the gp100 group.

In the phase II studies, adverse effects were observed with the following frequencies:
- study CA184022: 46/73 (63.9%) in the 0.3 mg/kg group, 55/72 (77.5%) in the 3 mg/kg group and 59/72 (83.1%) in the 10 mg/kg group,
- study CA184004: 33/40 (82.5%) versus 32/42 (76.2%).

The most common adverse effects were gastrointestinal, cutaneous and endocrine disorders.

According to the SPC, YERVOY was administered to more than 3000 patients in a clinical programme evaluating its use at various doses and in various tumour types. YERVOY is most commonly associated with adverse effects resulting from an increased or excessive immune activity.
The most commonly reported adverse effects (≥ 10%) with ipilimumab 3 mg/kg (YERVOY) were: reduced appetite, diarrhoea, vomiting, nausea, rash, pruritus, asthenia, reaction at the injection site, fever.

These adverse effects were often severe (grades 3 and 4):
- severe diarrhoea and colitis, reported in 5% of cases,
- severe hepatotoxicity of immunological origin, including cases of fatal liver failure, reported in < 1% of patients,
- cutaneous adverse effects, possibly of immunological origin, including cases of fatal toxic epidermal necrolysis, reported in <1% of patients,
- severe adverse neurological effects of immunological origin, including a fatal Guillain-Barré syndrome, reported in < 1% of patients,
- severe hypopituitarism (grades 3 or 4), reported in 3% of patients.

3.3. Conclusion

The efficacy and tolerance of ipilumumab (YERVOY) in patients with advanced stage III and IV melanoma (unresectable or metastatic) in adult patients who had already received a treatment, were evaluated mainly in one randomised double-blind study comparing 3 groups, ipilimumab + placebo, gp100 *(experimental peptide vaccine with no MA which is not available on the French market*) + placebo and ipilimumab + gp100, in 676 HLA-A2*0201-positive patients.

The median overall survival was increased with ipilimumab in comparison to gp100 (10.12 months versus 6.44 months, HR 0.66 [0.51; 0.87], p = 0.0026), with an absolute improvement of 3.68 months. No difference was observed between ipilimumab and ipilimumab + gp100.
Given the methods selected for this study, which assessed the efficacy of ipilimumab in comparison to and in combination with gp100, a substance which has no MA, the results must be interpreted with caution, particularly since the performance of gp100 seems to be of the same order than that of placebo (median survival without treatment: 7 months). In fact, although a difference in overall survival was observed, the therapeutic contribution of ipilimumab is difficult to quantify given the choice of comparator (cf. analysis of data).

In this study, a marked deterioration in patients' quality of life (EORTC QLQ-C30 scale[8]) was observed in the ipilimumab (-8.8 [-13.5; -4.1]) and gp100 (-10.4 [-15.3; -5.5] groups, but no significant difference was shown between the two groups: difference 1.6 [-5.0; 8.2], NS.

In this study discontinuations of treatment due to adverse effects were observed in three times more patients in the ipilimumab group than in the gp100 group: 9.9% in the ipilimumab group, 6.8% in the ipilimumab + gp100 group and 3% in the gp100 group.

The adverse events most frequently observed with ipilimumab were: reduced appetite, diarrhoea, vomiting, nausea, rash, pruritus, asthenia, reaction at the injection site, fever. Ipilimumab was most commonly associated with adverse effects resulting from an increased or excessive immune activity. These adverse effects were severe (stage III and IV) in 1 to 5% of cases (severe diarrhoea and colitis, hepatotoxicity, toxic epidermal necrolysis, Guillain-Barré syndrome, severe hypopituitarism).

8 European Organization for Research and Treatment of Cancer Quality of Life Questionnaire: this questionnaire covers the same areas as the HRQoL scale which is validated for clinical studies in oncology.

4. TRANSPARENCY COMMITTEE CONCLUSIONS

4.1. Actual benefit

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

This proprietary medicinal product is intended as curative therapy.

It is a second-line therapy.

Given the modest efficacy observed in comparison to gp100, a substance which has no marketing authorisation, and the frequency and severity of the adverse effects observed with ipilimumab and the discontinuations of treatment linked to these adverse effects, its efficacy/adverse effects ratio is moderate.

> *Public health benefit:*
> The public health burden of cutaneous melanoma and other skin cancers is moderate (about 160,000 DALYs). The burden represented by advanced melanomas (unresectable or metastatic) can be regarded as small.
> The improvement in the management of patients with cancer is a public health need set out in the Cancer Plan 2009-2013.
> 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 tolerance problems encountered.
> Therefore the medicinal product 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.

The alternatives currently available are dacarbazine, fotemustine, temozolomide, paclitaxel, cisplatin and carboplatin, used off-label, and vemurafenib on a group TUA since May 2011.

In view of the seriousness of the concerned disease, the absence of an alternative validated by a MA and the modest efficacy observed, ipilimumab provides a substantial actual benefit.

4.2. Improvement in actual benefit (IAB)

In the absence of an alternative validated by a MA[9], ipilimumab (YERVOY) provides a minor improvement in actual benefit (IAB IV) in therapeutic use.

4.3. Therapeutic use[10,11]

Metastatic melanomas are associated with an unfavourable prognosis (median survival of 7 months).

Various standard chemotherapies are used in practice: dacarbazine, fotemustine, temozolomide, high doses of IL-2, paclitaxel (off-label) whether or not in combination with cisplatin or carboplatin (off-label), with modest response rates of the order of 20% and complete remission rates of less than 5%.

---

9 Verumafenib on group TUA since May 2011, was approved by the FDA in October 2011 and received a favourable opinion of the CHMP on 15 December 2011.

10 NCCN Clinical Practice Guidelines in Oncology. Melanoma. Version 1-2012.

11 Guide to chronic diseases. Malignant tumour, malignant disorder of the lymphatic or haematopoietic tissue Cutaneous melanoma. HAS February 2008

In patients with stage IV melanoma:

- with limited metastasis (resectable): surgical resection of the metastases is recommended; in case of incomplete resection, the use of treatments for the disseminated metastases (described below) can be proposed.
- with disseminated metastasis (unresectable): the treatment depends on whether or not there are brain metastasis.
    - In patients with no brain metastasis: dacarbazine, fotemustine, temozolomide and high-dose interleukin can be used. Combinations of chemotherapy alone (dacarbazine or temozolomide with cisplatin) or combined with a cytokine (IL-2 or interferon alfa) or paclitaxel-based chemotherapies (whether or not in combination with cisplatin or carboplatin) can also be proposed.
    - In patients with brain metastasis: chemotherapy can be combined with corticosteroids and radiotherapy.

Recurrences of melanoma are resistant to most of the classic therapeutic agents, particularly dacarbazine or cytokines.
According to the experts, current management moves towards selecting patients according to whether or not they have the B-RAF mutation (this mutation is found in 40 to 60% of cases [12, 13]); the choice of treatment then involves a targeted therapy represented by vemurafenib which has been available in France since May 2011 under a group TUA.

In view of the results of study MDX010-20, the tolerance profile of YERVOY and the change in therapeutic use (check for B-RAF mutations), treatment with YERVOY can be proposed to patients in whom at least one line of treatment with chemotherapy has failed and whose tumour shows no B-RAF mutation.
In the absence of available efficacy data in patients in whom vemurafenib has failed, the Transparency Committee cannot give an opinion on the benefit of ipilimumab in this population.

4.4. Target population

The target population of YERVOY is defined by adult patients treated for advanced stage III or IV melanoma (unresectable or metastatic) who have already been treated with a first-line chemotherapy.

- Prevalence of stage III and IV melanomas

The snapshot partial prevalence calculated at the end of 2004 is 31,278 cases of melanoma, including 28,968 cases without metastasis and 2310 cases with metastasis (stage IV) based on the FRANCIM data[14].
The prevalence of cases of inoperable stage III melanoma is not accurately known. The MELODY study provides some information: the sample at inclusion consisted of 195 patients with stage IV and 23 patients with unresectable stage III at inclusion, corresponding to a ratio of 11.8% between these two categories of patients.
The change over time in the prevalence of cases of unresectable stage III or stage IV melanoma in France can be regarded as increasing slightly. It can be said conservatively that this change follows the change in gross incidence over time of 2.2% a year[15] i.e. an estimated 2633 cases of stage IV melanoma at the end of 2010.

---

12 Keith T. et al. Inhibition of Mutated, Activated BRAF in Metastatic Melanoma. N Engl J Med 2010; 363:809-19

13 INCa programme for the prospective detection of biomarkers emerging in lung cancer, colorectal cancer and melanoma: a new approach for rapid access to targeted therapies. INCA June 2010.

14 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. Abstract ISPOR 2009. Value in Health 2009, Vol. 12, Issue 7, Page A261, PCN28

15 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.

On the basis of the hypotheses set out above (ratio of 11.8% between stage IV and unresectable stage III in the MELODY study), the number of prevalent cases of unresectable stage III melanoma would be 311.

Given the therapeutic strategy optimising the management of these patients, a check for B-RAF mutations, found in 50% (median rate) of patients with advanced melanomas[12], will be carried out. Consequently, there are two conceivable situations:

1. *Patients with no B-RAF mutation*: n = 1472
In these patients the number of patients who have already received one treatment can be estimated from the following information:
The percentage of patients on systemic treatment (91%) from the MELODY study and the percentage of patients who did not respond to a first treatment (89%) in the same study can be used to determine the size of the target population for YERVOY as: 1472 x 0.91 x 0.89 = 1192 patients.

2. *Patients with B-RAF mutation*: n = 1472
In these patients, the choice of a targeted therapy is advisable (vemurafenib); the first available published data (FDA) can be used to estimate at about 50% the patients who do not respond to vemurafenib, i.e. 1472 x 0.50 = 736 patients. In the absence of available efficacy data for ipilimumab in patients in whom vemurafenib has failed, the estimate of this population remains purely theoretical.

- For information, 650 temporary authorizations for use by a named patient program were granted for ipilimumab between July 2010 and July 2011.

On the basis of these data, the target population for YERVOY can be estimated between 650 and a maximum of 1900 patients. This estimate will be reviewed in the light of all the data available when vemurafenib is assessed by the Transparency Committee.

4.5. Transparency Committee recommendations

The transparency Committee recommends inclusion on the list of medicines approved for hospital use and various public services in the indication and doses of the marketing authorisation.

Given the modest efficacy demonstrated in the pivotal study in comparison to gp100, a substance which has no marketing authorisation, the frequency and severity of adverse effects observed with ipilimumab, the ongoing post-MA studies to justify the choice of dose (3 versus 10 mg/kg) and the ongoing change in therapeutic use, including in particular the arrival of vemurafenib (on group TUA since 2011, accepted by the FDA in August 2011 and having obtained a favourable opinion of the CHMP on 15 December 2011), the Transparency Committee wishes to reassess this proprietary medicinal product in one year.