PUBLIC SUMMARY DOCUMENT
Product: IPILIMUMAB, concentrate solution for I.V. infusion, 50 mg in 10 mL, 200 mg in 40 mL, Yervoy®
Sponsor: Bristol-Myers Squibb Australia Pty Ltd
Date of PBAC Consideration: July 2011

1. Purpose of Application

The submission sought Section 100 (Highly Specialised Drugs Program) Authority required listing for treatment of patients with unresectable stage III or stage IV malignant melanoma who have not responded to or were intolerant to prior systemic therapy for metastatic disease.

Highly Specialised Drugs are medicines for the treatment of chronic conditions, which, because of their clinical use or other special features, are restricted to supply to public and private hospitals having access to appropriate specialist facilities.

2. Background

Ipilimumab had not been previously considered by the PBAC.

3. Registration Status

Ipilimumab was TGA registered on 4 July 2011 for treatment, as monotherapy, of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.

4. Listing Requested and PBAC's View

Section 100 (Highly Specialised Drugs Program)
Authority Required
For the treatment of patients with unresectable stage III or stage IV malignant melanoma who have not responded to or were intolerant to prior systemic therapy for metastatic disease;

- where lack of response is determined by clinically verifiable measures, and is defined as failure to achieve or sustain an objective response (partial or complete response) or stable disease;
- where intolerance to prior therapy is defined as Grade 3 or 4 toxicity that is therapy related.

Note that for patients who commence therapy with ipilimumab:

- Decisions concerning efficacy should await completion of the entire induction regimen (four doses) and should be made in conjunction with established criteria for immunological responses. However, induction may be ceased or delayed if symptomatic progressive disease or intolerable adverse events occur and if, in the opinion of the clinician, continuation of treatment poses a risk to the patient.
- Tumour responses may occur beyond the initial 12-week induction phase and evaluation for potential later responses should be undertaken regularly for the first year.
- Re-induction with 4 additional doses of ipilimumab should only be commenced in patients whose disease has progressed following an initial objective response to therapy:
    - where response to therapy is defined as either:
        (i) sustained stable disease of greater than or equal to 3 months duration, or

(ii) achievement of an initial objective response (partial or complete response).

For PBAC's view, see Recommendation and Reasons.

5. Clinical Place for the Proposed Therapy

Melanomas are malignant tumours derived from melanocytes. Advanced melanoma (unresectable stage III to stage IV or metastatic melanoma) is an aggressive and invasive disease, with a median survival of approximately 6 to 9 months. The strongest environmental risk factor in the development of melanoma is intermittent exposure to solar UV radiation. The geographical location of Australia, coupled with the presence of a predominantly Caucasian population results in Australia having the highest incidence of advanced melanoma per population in the world.

The aim of treatment in advanced melanoma is to optimally manage each stage of disease with a view to extending overall survival. Approved therapies for advanced melanoma are limited and include systemic therapy (dacarbazine, fotemustine or temozolomide), palliative care/radiotherapy, palliative surgery or no treatment.

The submission proposed the place in therapy for ipilimumab is as a first-in-class agent for second line treatment of advanced melanoma.

For PBAC's view, see Recommendation and Reasons.

6. Comparator

The submission appropriately nominated dacarbazine (DTIC) and fotemustine as the main comparators.

7. Clinical Trials

The submission presented a single phase III, randomised double-blind, multicentre trial in HLA-A*0201-positive (HLA-A+-positive) subjects with a diagnosis of unresectable Stage III or Stage IV melanoma who had relapsed, failed, or were not able to tolerate at least 1 or more prior treatment regimens (MDX010-20 referred to as study CT-020), as the main clinical evidence for efficacy.

Publications details of study CT-020 are presented in the table below.

Trial ID / First author	Protocol title / Publication title	Publication citation
CT-020 Hodi FS, et al	Improved survival with ipilimumab in patients with metastatic melanoma.	*NEJM*, 2010; 363(8): 711-23

Patients were randomised in a 3:1:1 ratio to the ipilimumab (3mg/kg) plus gp100, ipilimumab monotherapy, or gp100 group. A total of 676 subjects were randomised: 403 to ipilimumab plus gp100, 137 to ipilimumab monotherapy, and 136 to gp100 monotherapy. A minority of subjects received re-induction treatment; 29 (7.2%) in those who initially received ipilimumab plus gp100, 9 (6.6%) in those who initially received ipilimumab monotherapy, and 2 (1.5%) in those who initially received gp100 monotherapy.

8. Results of Trials

Results for overall survival and survival from study CT-020 are presented in the tables and figure below.

Results of Hazards of Overall Survival for CT-020 (ITT)

Treatment Comparisons	Hazard ratio (95% CI)	Log rank *P*-value
IPI vs gp100	**0.66 (0.51,0.87)**	**0.0026**
IPI +gp100 vs gp100	**0.68 (0.55, 0.85)**	**0.0004**
IPI +gp100 vs IPI	1.04 (0.83) 1.30	0.7575

CI = confidence interval

Note: Stratified log rank test by M-stage and prior IL-2 therapy

Results of Survival for CT-020 (ITT)

Outcomes	IPI N=137	IPI +gp100 N=403	gp100 N=136
Median OS mths (95% CI)	10.12 (8.02, 13.80)	9.95 (8.48, 11.50)	6.44 (5.49, 8.71)
Median Survival follow-up mths (95% CI)	9.46 (0.36, 55.06)	9.43 (0.03,54.08)	6.16 (0.03,44.65)

CI = confidence interval; N = total participants in group

The PBAC noted the results of study CT-020, which demonstrate the survival benefits of ipilimumab. In the ipilimumab + gp100 group the hazard ratio for overall survival equals 0.68 (95% CI: 0.55, 0.85, p=0.0004), in the ipilimumab monotherapy group the hazard ratio equals 0.66 (95% CI: 0.51, 0.87, p=0.0026) when compared with gp100. This translates to a reduction in hazard of death of 32% in the ipilimumab + gp100 group and 34% in the ipilimumab monotherapy group compared to gp100.

The median survival for the ipilimumab monotherapy arm was 10.12 months (95% CI: 8.02 mths to 13.80 mths), compared to 6.44 months in the gp100 arm (95% CI: 5.49 mths 8.71 mths). The PBAC noted that the median difference in survival was approximately 3.6 months.

The PBAC noted the 2-year survival rate was 23.5% for the ipilimumab monotherapy group relative to the gp100 group (13.7%). The submission described a plateau effect which demonstrated a durable survival beyond 24 months which was a result of ipilimumab treatment. The PBAC considered these results were uncertain and difficult to interpret due to the low number of patients remaining in the study.

For PBAC's comments on these results, see Recommendation and Reasons.

The submission claimed that there was no difference in the overall frequency of treatment related adverse events or severe adverse events between the ipilimumab and gp100 arms in study CT-020.

The PBAC noted that the immune related adverse events (irAEs) diarrhoea, pruritus and rash occurred more frequently in the ipilimumab and ipilimumab+gp100 treatment arms. Also approximately 10% of patients in the ipilimumab monotherapy group discontinued due to treatment related adverse events compared to 3% of patients in the gp100 (control) group.

Approximately 62% of patients in the ipilimumab monotherapy group compared to 32% of patients in the gp100 group experienced an irAE. This represents a statistically significant difference.

In patients that received ipilimumab the irAEs that occurred most frequently include: skin irAE (42.7%), gastrointestinal irAE (29.8% all; 8.4% ≥ grade 3), severe (16%), serious (13.7%) and endocrine (7.6%). These irAEs occurred more frequently in patients that received ipilimumab monotherapy (and ipilimumab + gp100) than in patients that received gp100. These differences were all statistically significant.

The submission stated that most irAEs were generally manageable and resolvable using symptomatic or immunosuppressive therapy in accordance with the recommended treatment algorithms for managing irAEs in the Product Information.

9. Clinical Claim

The submission described ipilimumab as superior in terms of comparative effectiveness and that ipilimumab has a different safety profile over DTIC and/or fotemustine. The PBAC considered this claim may not be reasonable as ipilimumab may be considered inferior in terms of immune related adverse events such as skin reactions, bowel perforation and enterocolitis, hepatitis, myopathy, nephritis and Guillian Barre syndrome. *See Recommendation and Reasons.*

10. Economic Analysis

The submission presented a stepped economic evaluation, based on direct randomised trials and implementing a modelled evaluation. The model was a Markov model with a time horizon of ten years. The model produced a cost per additional month survival (based on trial data only), a cost per life year, and a cost per quality-adjusted life year (QALY).

The (corrected) base case incremental cost per QALY gained was between $105,000 and $200,000.

The PBAC noted that the results of univariate sensitivity analyses indicated that the model was most sensitive to the method of extrapolating survival curves, the time point from which extrapolation takes place, the discount rate applied and the time horizon.

11. Estimated PBS Usage and Financial Implications

The estimated financial cost to the PBS was considered to be between $30-60 million in Year 5.

12. Recommendation and Reasons

The PBAC acknowledged that there was a high clinical need for a drug to treat metastatic melanoma as there are few other viable options for patients with this condition.

The PBAC agreed that the appropriate comparator was dacarbazine (DTIC) and fotemustine and noted that gp-100 was used as a proxy for DTIC and fotemustine.

The PBAC noted the results of the key clinical trial CT-020 which demonstrate the survival benefits of ipilimumab. In the ipilimumab + gp100 group the hazard ratio for overall survival equals 0.68 (95% CI: 0.55, 0.85, p=0.0004), in the ipilimumab monotherapy group the hazard

ratio equals 0.66 (95% CI: 0.51, 0.87, p=0.0026) when compared with gp100. The PBAC also noted that the median difference in survival was approximately 3.6 months. The 2-year survival rate was 23.5% for the ipilimumab monotherapy group relative to the gp100 group (13.7%).

The PBAC noted the recent publication of use of ipilimumab as first-line therapy in combination with DTIC versus DTIC monotherapy (N Engl J Med, 2011 June 5, Robert, C et al). The dose was 10 mg/ kg with a median survival of 11.2 months versus 9.1 months with dacarbazine monotherapy, an incremental benefit of 2.1 months. The PBAC therefore considered that the 3.6 months survival gain in second-line treatment was an overestimate as gp100 is equivalent to BSC but is less effective than chemotherapy, which does offer some survival advantage over BSC. In addition, there were also baseline imbalances in the second-line setting in terms of duration of melanoma which was different between the ipilimumab, ipilimumab+gp100 and gp100 groups. The PBAC considered that the incremental benefit in second-line may be closer to that of first-line treatment with ipilimumab.

The PBAC considered that the results of use of ipilimumab in the first-line setting reduced some of the uncertainty with use in the second-line setting and indicate that ipilimumab works in non HLA-A patients, is likely to be used in combination with DTIC as well as the first-line setting, and is effective without gp-100. The PBAC noted that there may be a plateau effect but this applied to a small number of patients.

However, the PBAC considered there is uncertainty regarding the clinical place of ipilimumab particularly in light of the evolving treatment algorithm for melanoma, in which the molecular subtypes of melanoma will dictate treatment options, e.g. B-RAF and c-KIT. The molecular features will need to be taken into account along with other factors such as the presence of brain metastases, speed of response and symptoms. The PBAC considered that ipilimumab was likely to be used in B-RAF wild type melanoma but it was noted that the efficacy after the B-RAF inhibitors is unknown.

The PBAC considered that the clinical claim that ipilimumab is superior in terms of comparative effectiveness and ipilimumab has a different safety profile over DTIC and/or fotemustine may not be reasonable as ipilimumab may be considered inferior in terms of immune-related adverse events such as skin reactions, bowel perforation and enterocolitis, hepatitis, myopathy, nephritis and Guillian Barre syndrome.

The PBAC considered that the time horizon of 10 years used in the economic modelling was not plausible for treatment of metastatic cancer. Even if a survival advantage for ipilimumab was accepted, it is uncertain whether it is a durable survival effect. The PBAC considered that the use of the trial period as the time horizon was more appropriate. The PBAC also considered that the extrapolation method was not appropriate. The submission adopted a within-trial hazard approach to extrapolation which is appropriate, but extrapolated from the point at which 5% of patients are at-risk. A more appropriate, robust and conservative method would be to extrapolate from the median duration of follow-up.

The PBAC noted that the economic model produced a cost per additional month survival (based on trial data only), a cost per life year, and a cost per quality-adjusted life year (QALY). The base case results from the full modelled economic, with extrapolated costs and outcomes over the ten-year time horizon. The PBAC noted that the QALY values used for

BSC are actually lower than if nothing at all was done (i.e. if no treatment was nominated as the comparator). There is no attributable mortality or morbidity benefit for either fotemustine or dacarbazine in the model, but patients in this arm still experience adverse events. This was considered implausible.

The PBAC noted that a univariate sensitivity analysis was run by the submission, investigating the impact of uncertainty in parameters on the base case results of the economic evaluation. The main drivers of the model are the method of extrapolating survival curves, the time point from which extrapolation takes place, the discount rate applied and the time horizon. The PBAC noted that the impact of extrapolating from the median follow-up point for each of the arms using the corrected model supplied by the sponsor is to increase both the cost per life year, and the cost per QALY to values higher than the base case ICER, which was considered to be very high and uncertain.

The PBAC also considered that the submission's utilisation estimates and revised estimates were highly uncertain due to the use of a clinician survey of 8 clinicians and the treatment pattern study (n=51 patients). The PBAC considered that the number of patients undergoing first-line chemotherapy is likely to increase if ipilimumab is listed on the PBS, as more patients may opt for treatment with fotemustine or DTIC, which may be given for one dose to access ipilimumab, which was not considered to be sound clinical practice.

The PBAC considered that the costs associated with the treatment adverse drug effects were considerably underestimated as there may be more inpatient hospital cost as well as greater costs associated with the PBS subsidised treatment of adverse events. There is also potential for use in the first-line setting, even if the listing mandates failure of a first line systemic therapy and that the higher dose (10mg/kg) used in the first-line setting may also be used. The PBAC noted that ipilimumab does not cross the blood brain barrier. However, patients with late stage melanoma are likely to have extensive brain metastases and this may lead to considerable pressure to use this therapy earlier in the disease course. The PBAC concluded that there is considerable uncertainty regarding the eligible population and that the costs associated with ipilimumab are likely to have been underestimated.

The PBAC therefore rejected the submission on the basis of uncertain extent of clinical benefit, uncertain clinical place of therapy, high and uncertain cost-effectiveness ratio and uncertain financial costs.

The PBAC noted the advice of the Highly Specialised Drugs Working Party which did not support the listing of ipilimumab as a Section 100 Highly Specialised Drug.

The PBAC also acknowledged and noted the consumer comments received in its consideration of ipilimumab.

Recommendation
Reject

13. Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the

medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

14. Sponsor's Comment

The Sponsor is committed to working with the PBAC to resolve any perceived uncertainties to ensure access is delivered to Australian patients through PBS listing.