Australian Government
Department of Health and Ageing
Therapeutic Goods Administration

# Australian Public Assessment Report for Ipilimumab

Proprietary Product Name: Yervoy/Winglore

Sponsor: Bristol-Myers Squibb Australia Pty Ltd

**August 2011**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The TGA is a division of the Australian Government Department of Health and Ageing, and is responsible for regulating medicines and medical devices.
- TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website.

# About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

# Contents

# I. Introduction to Product Submission

## Submission Details

| | |
|---|---|
| *Type of Submission* | New Biological Entity |
| *Decision:* | Approved |
| *Date of Decision:* | 27 June 2011 |
| | |
| *Active ingredient(s):* | Ipilimumab |
| *Product Name(s):* | Yervoy/Winglore |
| *Sponsor's Name and Address:* | Bristol-Myers Squibb Australia Pty Ltd,<br>556 Princes Highway Noble Park, Victoria 3174 |
| *Dose form(s):* | Concentrated solution for infusion |
| *Strength(s):* | 50 mg in 10 mL and 200 mg in 40 mL |
| *Container(s):* | Glass Vials |
| *Pack size(s):* | One 10mL glass vial containing 50mg ipilimumab<br>One 40mL glass vial containing 200mg ipilimumab |
| *Approved Therapeutic use:* | *As monotherapy, for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.* |
| *Route(s) of administration:* | Intravenous (IV) infusion |
| *Dosage:* | The recommended dose is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions. |
| *ARTG Number (s)* | 174319, 174322, 174327 and 174326 |

## Product Background

Ipilimumab is a monoclonal antibody directed against Cytotoxic T-Lymphocyte Antigen-4 (CTLA-4). CTLA-4 (or CD152) is a receptor found on the surface of activated T-lymphocytes. The natural ligands for the receptor are two glycoproteins, B7.1 (or CD80) and B7.2 (or CD86) which are found on the surface of antigen presenting cells. Binding of these ligands to CTLA-4 results in the delivery of an *inhibitory* signal to the activated T-lymphocyte. Such inhibition serves to limit the proliferative response of activated T-cells to an antigen.

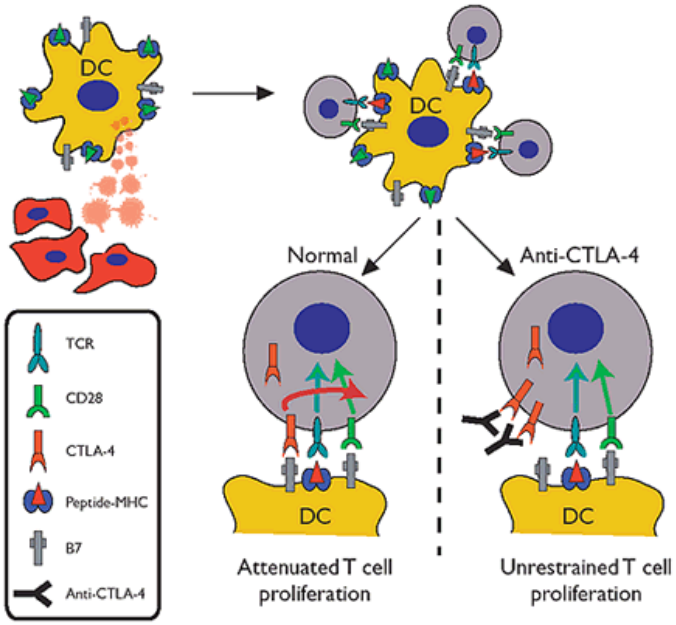
Binding of ipilimumab to CTLA-4 results in blockage of the inhibitory signal, and therefore enhances T-cell response to tumour antigens. This activity is summarised diagrammatically in Figure 1 below.

This AusPAR describes the evaluation of an application by Bristol-Myers Squibb Australia Pty Ltd (the sponsor) to register a new biological entity with two trade names, Yervoy and Winglore, containing ipilimumab, for the treatment of advanced melanoma in patients who have received prior therapy. Ipilimumab is the first agent in this class. In patients whose disease

progresses after an initial response or disease stabilisation following treatment, a repeat course of 4 doses is proposed.

Agents which are currently registered in Australia for the treatment of unresectable/metastatic melanoma include dacarbazine, temozolomide and fotemustine. There are no agents approved specifically for second line therapy.

**Figure 1. Potentiation of T cell activation by ipilimumab**




Source: Egen JG *et al.*, 2002. *Nat Immunol* 3:611-618.

## Regulatory Status

The following table (Table 1) summarises the overseas regulatory status of this product.

**Table 1. International Regulatory Status**

| Country | Date of submission | Date of Approval | Approved indication |
|---|---|---|---|
| **European Union** | 4 May 2010 | 13 July 2011 | Yervoy is indicated for the treatment of unresectable or metastatic melanoma |
| **USA** | 25 June 2010 | 25 March 2011 | Yervoy is indicated for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. |
| **Switzerland** | 18 June 2010 | Under evaluation | Under evaluation |
| **Canada** | 12 October 2010 | Under evaluation | Under evaluation |

## Product Information

The approved product information (PI) current at the time this AusPAR was prepared can be found as Attachment 1.

# II. Quality Findings

## Drug Substance

Ipilimumab is a fully human immunoglobulin (IgG1κ) consisting of four polypeptide chains; two identical heavy chains primarily consisting of 447 amino acids each with two identical kappa light chains consisting of 215 amino acids each linked through inter-chain disulfide bonds. The predominant product has a molecular formula of $C_{6572}H_{10126}N_{1734}O_{2080}S_{40}$ and predicted molecular weight of 147991 Da.

### Manufacture

This substance is manufactured by fermentation. After thawing a vial, various rounds of expansion steps and seed bioreactors are used to increase cell density before fermentation in the production bioreactor. Cells are then centrifuged and filtered before entering the downstream manufacturing steps. Three chromatography steps are performed and various filtration steps are performed, all of which remove host cell proteins, DNA, endotoxins and potential adventitious agents from the drug substance and concentrate and buffer exchange the ipilimumab protein.

### Physical and Chemical Properties

Each 1 mL contains 5 mg of ipilimumab and the inactive ingredients trometamol hydrochloride, sodium chloride, mannitol and polysorbate 80. At pH 7.0 it is a clear to slightly opalescent, colourless to pale yellow liquid.

### Specifications

Appropriate validation data have been submitted in support of the test procedures.

## Drug Product

### Formulation(s)

Ipilimumab Injection 50 mg/10 mL and 200 mg/ 40 mL (both 5 mg/mL) are sterile, non pyrogenic, single use, preservative free, isotonic aqueous solution for intravenous (IV) administration.

### Manufacture

The product is manufactured by simply filtering and filling the drug substance. The product is sterilised using filtration. Fill weight control is the single critical process parameter (CPP) for this step.

### Specifications

Appropriate validation data have been submitted in support of the test procedures.

### Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product. Photostability data show the product is not photostable. The proposed shelf life is 36 months when stored at 2°C to 8°C.

The following label has been added to the PI: T*o reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2-8°C for not more than 24 hours.*

The product is stable at -20°C for 3 months, but freeze/thaw cycling caused an increase in particulate matter. A '*Do Not Freeze*' statement will be included on the label.

### Biopharmaceutics

Biopharmaceutic data are not required for a product which is to be infused directly into the bloodstream.

### Quality Summary and Conclusions

The administrative, product usage, chemical, pharmaceutical, microbiological and biopharmaceutic data (as applicable) submitted in support of this application have been evaluated in accordance with the Australian legislation, pharmacopoeial standards and relevant technical guidelines adopted by the TGA.

#### Issues of concern

A number of issues requiring resolution before the product could be recommended for approval were identified during the evaluation. The sponsor responded to all the issues raised by the quality evaluators and Pharmaceutical SubCommittee (PSC) of the Advisory Committee on Prescription Medicines (ACPM) recommendations and the responses have been evaluated.

#### Conditions of Registration

Various batch release conditions of registration were recommended to the TGA Delegate.

## III. Nonclinical Findings

### Introduction

The proposed indication for ipilimumab is for the treatment of advanced melanoma. When conducting a risk assessment of the nonclinical safety of ipilimumab, it was assumed that the product was intended to treat patients with advanced *metastatic* melanoma

The submitted data comprised studies investigating the pharmacodynamics, repeat dose toxicity, toxicokinetics, immunotoxicity and local tolerance of ipilimumab. The relevant studies were Good Laboratory Practice (GLP)-compliant. The types of studies submitted were generally adequate for a biotechnology derived product. Several deficiencies and limitations were identified with different aspects of the nonclinical data, including the lack of reproductive toxicity studies, which are discussed separately under the relevant subheadings below.

Several studies used a developmental version of ipilimumab (referred to as ipilimumab-hyb), which was derived from a mouse hybridoma, rather than the CHO[1] cells used to produce the final drug product. Only one nonclinical study compared the toxicological profiles (including toxicokinetics) of the two products, following monthly administration of 10 mg/kg IV for three months. The pharmacokinetics of the two different forms of ipilimumab appeared to be generally similar following the first dose, although area under the concentration versus time curve (AUC) and maximum plasma concentration ($C_{max}$) based exposure was slightly lower with the hybridoma derived form. Likewise, their toxicological profiles appeared similar, although comparisons were difficult with testing of only one dosage level. The comparability of their pharmacological activity was uncertain, as the form of ipilimumab used in many pharmacodynamics studies was not specified. Whilst the two forms of ipilimumab cannot be considered equivalent from a regulatory perspective, any toxicity associated with ipilimumab-hyb may also be qualitatively relevant for the final drug product, particularly when related to exaggerated pharmacological effects. Thus, relevant findings for the developmental product are also discussed here, but should be interpreted with caution (the comparability of the two forms is also discussed on Page 26 of this AusPAR).

[1] CHO = Chinese hamster ovary

# Pharmacology

## Primary pharmacodynamics

Several *in vitro* studies investigated the mechanism of action of ipilimumab and characterised the receptor binding profile and cell, tissue and species specificity of ipilimumab. Interpretation of findings in many pharmacodynamics studies was difficult, as only limited discussion was often provided and data were often presented in the form of small graphs which were difficult to read.

## Mechanism of action

The binding of ipilimumab to human CTLA-4 and its mouse counterpart was investigated in several *in vitro* studies. Quantification and calculation of binding kinetics was limited in most studies. Where data were available, dissociation constants ($K_D$) were in the range 5.25–10.5 nM (or 0.8–1.6 µg/mL, compared to an extrapolated clinical steady state $C_{max}$ of 90.8 µg/mL at the recommended dose). Binding affinity between ipilimumab and mouse CTLA-4 was about 1000-fold lower, with $K_D$ values in the range 4.7–6.7 µM in one study. Another study reported binding of ipilimumab-hyb to cells constitutively expressing CTLA-4 from rhesus monkeys but the interaction was not quantified. Reports of binding of ipilimumab to CTLA-4 from Cynomolgus monkeys (with $K_D$ values of 8.2–20.1 nM) were cited in the sponsor's summary documents, but supportive data (quality or nonclinical) were not submitted. Concentration related decreases in the *in vitro* binding of B7-1 and B7-2 protein to cells expressing human CTLA-4 in the presence of ipilimumab was also observed. Results varied between studies with efficacious concentrations in the range starting at 0.5–148 µg/mL. One study reported a range of 50% inhibitory concentration ($IC_{50}$) values of 148–444 µg/mL for inhibition of B7-1 or B7-2 binding.

The species and tissue binding profile of ipilimumab was relatively restricted. Ipilimumab bound preferentially to activated human T lymphocytes, with 20–28% of lymphocyte populations binding to ipilimumab following incubation with appropriate T cell-specific stimuli in one study, rather than 5% binding without T cell stimulation. Ipilimumab binding to stimulated monkey lymphocytes was reported but supporting data were not provided. Binding of ipilimumab to unstimulated or stimulated rat lymphocytes was low (<2%).

Immunohistochemical analyses of frozen human tissues identified relatively specific binding of ipilimumab (1–10 µg/mL) to lymphocytes in different tissues (such as blood, lymphoid tissue, organs of the gastrointestinal tract, skin). The general pattern of ipilimumab binding was similar in Cynomolgus monkey tissue but with lower incidence and intensity; binding was only evident at the highest concentration of 10 µg/mL. Ipilimumab also bound to connective tissue in the placenta and ovaries from monkeys and the placenta from humans. Ipilimumab did not bind to spleen or lymph node tissue from mice, rats and rabbits under the conditions tested, consistent with a lack of CTLA-4 binding in these species.

Although monkeys represent a potentially relevant nonclinical model, limited quantitative data were provided regarding the relative activity of ipilimumab in monkeys compared to humans. Thus, it is unknown whether the safety profile of ipilimumab, as discussed under '**General Toxicity**' below, was adequately characterised in the primary nonclinical species. Extrapolation of findings in this species to the clinical setting was subsequently difficult. Several adverse effects, such as immune related hepatotoxicity and neurological effects, were reported in clinical trials, but not seen in nonclinical studies. This highlights the potential limitations of the nonclinical model.

## Efficacy

### *Effects in mouse models of tumorigenesis*

Several *in vivo* studies investigated the effects of anti-CTLA-4 antibodies on the growth of different tumour types implanted in mouse models. As ipilimumab does not bind to mouse CTLA-4, the use of standard mouse allograft or xenograft models of tumorigenesis was not feasible. Therefore, the majority of studies assessed the effect of mouse anti-CLTA-4 on the growth of tumours derived from murine tumour cell lines. These studies are considered to represent "proof of concept" studies for anti-CTLA-4 activity, rather than being directly supportive of efficacy of ipilimumab. One study investigated the effect of ipilimumab itself on the growth of murine carcinoma cells in transgenic mice lacking murine CTLA-4 but expressing human CTLA-4. Interpretation of the data in individual studies was often difficult, due to limited quantification of effects on tumour growth, limited dose ranging and complicated dosing regimens by intraperitoneal (IP) administration, not resembling the proposed clinical regimen. Evaluable data regarding the effects of murine anti-CTLA-4 mAbs on the growth of mouse melanoma were only available in one study. It was not possible to calculate the relative ipilimumab exposure associated with efficacy due to the use of a different product and different route of administration to that proposed clinically.

Mouse anti-CTLA-4 mAb demonstrated no significant effect on survival or growth of murine B16-F10 melanoma cells with four IP doses of 10 mg/kg administered every three days. In contrast, inhibition of tumour growth (≤100%) was seen at IP doses of 1–10 mg/kg in models of several other murine tumour types, including CT26 colon adenocarcinoma, MC38 colon carcinoma, SA1/N fibrosarcoma, P815 mastocytoma and EMT-6 mammary cell tumours. The sponsor also frequently reported cases of total tumour regression in ≤80% of anti-CTLA-4-treated mice, depending on the cell type and time point but this finding, identified by tumour palpation, was not confirmed by pathological analysis.

Ipilimumab (10 mg/kg IP) inhibited the growth of mouse MC38 colon carcinoma cells in transgenic mice expressing human CTLA-4. The level of inhibition varied from 0–80%, depending on the dosage regimen and number of tumour cells injected. A minimum of four ipilimumab doses over a 10–13 day period appeared to be required for efficacy. The relevance of this finding to the effect on established tumours was uncertain, as all mice received their first ipilimumab dose on the same day as tumour cell injection.

The sponsor provided evidence from published literature (not shown) indicating that the anti-CTLA-4 mAb may only be efficacious against inherently immunogenic tumours. Based on the nature of the models utilised and other limitations described above, the submitted data do not adequately address the efficacy of ipilimumab in suitable nonclinical (*in vitro* or *in vivo*) models of melanoma.

### *Immunological effect in repeat dose studies in monkeys*

Detailed analysis of the immunological response in monkeys that received injections of ipilimumab and human SK-Mel melanoma cells was conducted in three repeat dose toxicity studies. Monthly IV doses of either 10 mg/kg ipilimumab or ipilimumab-hyb augmented the development of antibodies to SK-Mel cells, with ≤5-fold increases in antibody titre compared to control groups; an increased effect was generally apparent after the second dose. No treatment related increase in antibody titre was seen at ipilimumab doses ≤1 mg/kg (respective AUC- and mg/kg-based exposure after a single dose were 5- and 3-fold less than the clinical exposure at steady state). A dose related increase in the levels of antibodies to hepatitis B surface antigen (HBsAg, which was also given to monkeys on the day of ipilimumab treatment) was also seen in these studies, which is indicative of a general enhancement of the immune response, rather than an SK-Mel-specific response.

The relative expression of different lymphocyte subsets, particularly T cells, in response to ipilimumab treatment was investigated in several repeat dose toxicity studies in monkeys. Results varied between different studies (that is, altered proportions of various subsets was seen in some studies but not in others), without any clear causative factor such as dosage level or dosing frequency. Table 2 below summarises the general findings seen in each study. Increased numbers of memory T cells, which is theoretically relevant for efficacy against melanoma, was seen in the most comprehensive study of the immunological effects of ipilimumab (study no. SUV00006). Increased levels of activated T cells appeared to be the only other consistent treatment related effect, which appeared to be associated with more frequent ipilimumab dosing, that is, three doses in one week, compared to weekly or monthly dosing. Memory T cells and activated T cells express CTLA-4, thus the results may be pharmacologically relevant [2]. It was not possible to determine whether coadministration of human SK-Mel cells in some studies (underlined in the table) influenced the effect of ipilimumab on the immune system.

Plasma from monkeys that received two doses of 10 mg/kg ipilimumab, one month apart, in conjunction with injection of SK-Mel cells demonstrated significantly increased binding to several human melanoma cell lines *ex vivo*, compared to human non-melanoma tumour cells (1.4- to 5-fold greater) and non-human cells (7- to 25-fold greater). This was associated with increased *in vitro* cytotoxicity of human melanoma cells, as discussed under '***Mechanism of action***' above. Additionally, incubation of serum from ipilimumab-hyb (two 10 mg/kg doses, one month apart) and SK-Mel cell-treated monkeys with human mononuclear cells increased the cytotoxicity of three human melanoma cell lines (SK-Mel-3, A375 and WM 266-4) *in vitro*, according to a published study. Cytotoxicity ranged from 16–35% in treated monkeys, compared to 3–14% in a group administered SK-Mel cells only.

Thus, ipilimumab demonstrated some immunomodulatory ability in monkeys although it was difficult to identify consistent effects. This was associated with increased cytotoxicity of human melanoma cells *ex vivo* but the relevance of these effects to the *in vivo* proliferation of melanoma cells, in monkeys or in humans, is unknown.

### *Effects in mouse models of autoimmunity*

Three studies investigated the effects of mouse anti-CTLA-4 on disease progression in three mouse models of autoimmunity, namely non-obese diabetic mice given anti-PD-1 mAb, chemically induced colitis and transgenic mice lacking FcγRIIb[3]. Anti-CTLA-4 mAb appeared to accelerate and exacerbate the effects of the first two models. Data in the model of diabetes indicated that anti-CTLA-4 potentiated the destructive T cell responses to pancreatic islets elicited by anti-PD-1. Anti-CTLA-4 demonstrated no clear effect in FcγRIIb-deficient mice, although one treated mouse was euthanised due to clinical signs possibly consistent with renal toxicity. These findings are consistent with the primary pharmacology of ipilimumab (that is, an immune system activator) and are potentially clinically relevant.

[2] Jago CB *et al*. (2004) Differential expression of CTLA-4 among T cell subsets. *Clin Exp Immunol* 136:463–471.

[3] These mice reportedly develop an autoimmune disorder characterised by kidney pathologies such as hydronephrosis when bred with PD-1-deficient mice.

**Table 2. Immunological effects of ipilimumab in repeat dose studies in monkeys.**

| Study no. | Dose (mg/kg) | Treatment regimen | Immunological effect |
|---|---|---|---|
| 0919-128 | 3, 10 (ipi-hyb) | Days 1, 4 & 7 | • Increase in activated helper T cells ($CD4^+$ cells expressing CD25, CD29, CD69 or HLA-DR).<br>• Decrease in cytotoxic T cells ($CD8^+$) at the HD.<br>• No effect on B cells ($CD20^+$). |
| 7114-100 | 3, 30 (ipi-hyb) | Days 1, 4 & 7 | • Increase in activated helper T cells expressing CD29, but not CD25 or CD69.<br>• Decrease in cytotoxic T cells at the HD.<br>• No effect on B cells. |
| 0992-128 | 10 (ipi-hyb) | Days 1 & 29 | • No effect on levels of activated T cells ($CD4^+$ or $CD8^+$ cells expressing CD25, CD29, CD69 or HLA-DR). |
| TIB-06-001 | 10 (ipi) | Days 4, 9, 30, 32, 58, 60, 86 & 88 | • Increase in helper T cells expressing PD-1 or CCR5, and certain naive T cells ($CD4^+CD45RA^+CCR7^+$) and memory T cells ($CD4^+CD45RA^-CCR7^+$). |
| SUV00006 | 10 (ipi) | Days 1, 29, 57 & 140 | • Increase in circulating memory T cells ($CD45RO^+$ or $CD45RA^-$), central memory T cells ($CD28^+CD95^+$) & effector memory T cells ($CD28^-CD95^+$).<br>• No consistent effect on circulating levels of B cells, dendritic cells, monocytes, activated T or B cells, naive T cells or regulatory T cells.<br>• No consistent effect on the same cell types in lymphoid tissue from colon, inguinal lymph node or spleen at necropsy (Day 167).<br>• No effect on the proportion of helper T cells expressing TNF-α or IFN-γ following *ex vivo* stimulation.<br>• Increased intra-cellular expression of CTLA-4 in central memory T cells from blood & spleen, but not in regulatory, naive or effector memory T cells from these tissues. No effect on FoxP3 expression in the same tissues. |
| DS06064 | 10 (ipi) | Days 1, 8, 15 & 22 | • Increase in B cells ($CD2^-CD20^+$), T cells/NK cells ($CD2^+CD20^-$) & helper T cells.<br>• No effect on the proportion of cytotoxic T cells and NK cells. |
| 1416-128 | 0.1, 1, 10 (ipi)<br>10 (ipi-hyb)<br>1 | Days 1, 29 & 57<br>As above<br>Weekly to Day 64 | • No effect on levels of activated T cells ($CD69^+$, $CD25^+$ or $HLA\text{-}DR^+$).<br>• No effect on the proportion of T cells producing TNF-α or IFN-γ. |
| 01-3460 | 10 (ipi-hyb) | Days 0, 28, 56, 84 & 140 | • No effect on levels of activated T cells ($CD69^+$, $CD25^+$ or $HLA\text{-}DR^+$). |

CCR-5 = a chemokine possibly involved in the inflammatory response to infection; CCR-7 = a chemokine secreted by central memory T cells

Ipi = ipilimumab; ipi-hyb = ipilimumab-hyb. Studies in which monkeys also received injections of human SK-Mel cells are underlined.

### Secondary Pharmacodynamics

One *in vitro* study investigated the binding of ipilimumab to three human Fc gamma receptors (FcγR), namely FcγRI/CD64, FcγRIIA/CD32A and FcγRIII/CD16. As expected for an immunoglobulin G 1 (IgG1) protein, ipilimumab bound to FcγRI (high affinity IgG1 receptor) in a concentration related manner in the range $2x10^{-4}$ to 200 µg/mL, with an 50% effective dose ($EC_{50}$) value (0.27 µg/mL) comparable to that of non-specific human IgG1 (0.60 µg/mL). In contrast, some binding of ipilimumab to low affinity IgG1 receptors FcγRIIA and FcγRIII was observed in the range 10 to 800 µg/mL but $EC_{50}$ values were not reached. The sponsor did not investigate the potential of ipilimumab to bind to other human Fc receptors.

Consistent with ipilimumab binding to FcγRIII (, increased antibody dependent cellular cytotoxicity (ADCC) was seen in *in vitro* studies. Increased cytotoxicity of activated human T cells in the presence of effector human peripheral blood mononuclear cells occurred with ipilimumab concentrations ≥0.01 µg/mL. Cytotoxicity was variable, both between and within studies, and ranged from 0–55%. It was usually ≤1.5 fold lower than positive control values. There was no consistent depletion of T cells in *in vivo* studies of Cynomolgus monkeys but effects may have been confounded by anti-CTLA-4 activity.

There was no evidence of complement dependent cytoxicity in response to ipilimumab (≤50 µg/mL, compared to clinical $C_{max}$ of 90.8 µg/mL) incubation with human T cells under appropriate reaction conditions *in vitro*.

### Safety Pharmacology

No standard safety pharmacology studies were conducted, which was considered acceptable for a biotechnology derived product. The cardiovascular safety of ipilimumab was investigated in two one month repeat dose toxicity studies in monkeys, one of which involved coadministration of ipilimumab and anti-PD-1 mAbs. There were no clear, treatment related effects on electrocardiogram (ECG) parameters, including QT interval[4], at 10 mg/kg IV ipilimumab. Steady state $C_{max}$ values were 4-fold greater than the steady state $C_{max}$ at the recommended clinical dose. Respiratory rate was significantly reduced in treated females on one occasion post-dose. The clinical relevance of this finding was unclear.

## Pharmacokinetics

### Toxicokinetics

The toxicokinetics of ipilimumab were investigated following single and repeated IV dosing in three toxicity studies in Cynomolgus monkeys. Toxicokinetics were calculated following weekly dosing for three weeks in monkeys, rather than in a study approximating the clinical dosing regimen. The pharmacokinetics of ipilimumab were generally similar in monkeys and humans, and consistent with the properties expected from a monoclonal antibody, that is, long half-life and slow plasma clearance. The volume of distribution was consistent with ipilimumab remaining primarily in the vasculature. There was evidence of accumulation in both species with repeated dosing. Standard distribution, metabolism and excretion studies were not conducted, which was acceptable for a biotechnology derived product. Some distribution data were obtained in two *in vitro* tissue binding specificity studies, as discussed in '***Mechanism of action***' above.

[4] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death.

**Relative exposure**

Exposure levels (plasma AUC and $C_{max}$-based) of ipilimumab in the submitted toxicity studies were compared with exposure data from human melanoma patients (n=3–13) obtained in clinical trials with ipilimumab, as summarised in Table 3. The recommended clinical dosage regimen of ipilimumab is 3 mg/kg, administered as an IV infusion or bolus, every three weeks for four doses. Pharmacokinetic data were obtained in several clinical trials with ipilimumab, although data were not obtained using the final drug product at the proposed dose of 3 mg/kg.

For calculation of AUC-based exposure margins, three clinical studies (Study nos. CA184008, CA184007 and MDX010-15) were considered suitable, as they involved analysis of repeat dose pharmacokinetic data following administration of ipilimumab, rather than ipilimumab-hyb, according to the proposed clinical dosage regimen of once every three weeks. However, a higher dose, 10 mg/kg ipilimumab, was administered in these studies, rather than the proposed 3 mg/kg. Thus, a mean steady state $AUC_{0\text{-}21\ days}$ value of 51956 µg.h/mL was calculated from the means from each study (52713 µg.h/mL, 47722 µg.h/mL and 55433 µg.h/mL, respectively). This value was scaled to the proposed clinical dose of 3 mg/kg, to give an estimated steady state $AUC_{0\text{-}21\ days}$ of 15602 µg.h/mL, which was used for relative exposure calculations. Similarly a mean $C_{max}$ value of 302.3 µg/mL was determined for a 10 mg/kg IV dose, which, assuming linear pharmacokinetics, would correspond to an extrapolated $C_{max}$ of 90.8 µg/mL at 3 mg/kg.

AUC-based exposure comparisons were made based on nonclinical exposure values calculated from time zero to the last quantifiable concentration (0-t), normalised to a dosing interval of 21 days; the values for t in each study are specified in Table 3. Values for males and females were combined where applicable. Some accumulation was noted with repeated dosing in monkeys and humans; accumulation factors were about 2-fold for AUC and 1.7-fold for $C_{max}$ in one repeat dose toxicity study. Exposure margins in nonclinical studies with single dose toxicokinetic data would be increased by about 50% if this was taken into account. In Study no. DS06064, the sponsor calculated combined mean exposure (AUC and $C_{max}$) for males and females from both ipilimumab and combination treatment groups. However, it was considered more appropriate to calculate mean exposure for monkeys treated with ipilimumab alone.

AUC-based relative exposure calculations for ipilimumab must be interpreted with caution, as they may represent an overestimation of exposure to pharmacologically active antibody due to the potential *in vivo* binding of neutralising antibodies following repeated ipilimumab dosing. Anti-ipilimumab antibodies developed in about 8% of treated monkeys (refer to '***Immunotoxicity***' below). As a consequence, calculations of relative exposure based on dose per body weight (the most relevant unit of calculation for a large protein expected to remain largely in the vasculature) in nonclinical studies are also included in Table 3 below.

No Observable Adverse Effect Levels (NOAELs) could not be established in the majority of nonclinical studies due to the lack of dose ranging. The NOAEL in one applicable study is highlighted in bold.

**Table 3. Relative exposure (AUC, $C_{max}$ & mg/m²) in repeat dose toxicity studies in monkeys.**

| Study no. | Species | Treatment frequency | Dose (mg/kg) | Dose (mg/kg/ 21 days) | $AUC_{0-t}$ (µg.h/mL) | t (days) | Dose-normalised AUC (0–21 days) | $C_{max}$ (µg/mL) | Relative exposure (0-21 days) | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | | AUC | $C_{max}$ | mg/kg |
| 1416-128 | Monkey | First dose (monthly) | 1 | 1 | 1670 | 13 | 2672 | 24.7 | 0.2 | 0.3 | 0.3 |
| | | | **10** | **10** | **50600** | 28 | **37950** | **532** | **2.4** | **5.9** | **3** |
| | | | 10 (ipi-hyb) | 10 | 45100 | 28 | 33825 | 440 | 2.2 | 4.8 | 3 |
| DS06064 | | Weekly | 10 | 30 | 34200 (Day 22) | 7 | 102600 | 360 | 6.6 | 4.0 | 10 |
| CA184008, CA184007, MDX010-15 | Human | q3w | 3 | 3 | 51956 (10 mg/kg) | 21 | 15602[a] | 90.8[a] | NA | NA | NA |

[a]Extrapolated from the mean value (AUC or $C_{max}$) at 10 mg/kg to give an estimated value at the proposed clinical dose

A = ipilimumab; B = developmental batch of ipilimumab; NA = not applicable; q3w = every 3 weeks; NOAELs are highlighted in bold.

## Toxicology

The repeat dose toxicity of ipilimumab was investigated in studies of up to 23 weeks duration by the IV route in Cynomolgus monkeys. Several studies were submitted, although interpretation of findings in many was difficult, due to the lack of concurrent control groups, combination treatment with other products and/or limited documentation. As ipilimumab-hyb was administered in the 23 week study, the toxicity of ipilimumab drug product has only been investigated in adequate studies of up to three months duration. This was considered acceptable for an anticancer product, although it should be noted that the number of doses was lower than that intended clinically (3 rather than 4) with a longer period between the doses (4 weeks instead of 3). This indicates that the full toxicological profile of ipilimumab may not have been revealed. Dose ranging was not conducted in most studies and NOAELs were subsequently not established. Ipilimumab was administered as a bolus injection in all studies, rather than the proposed clinical route of IV infusion. This was not expected to raise additional safety concerns. Any findings in monkeys must be interpreted with caution as the relative activity of ipilimumab in monkeys compared to humans was not adequately quantified, as discussed under '**Primary Pharmacodynamics**' above.

Three GLP-compliant studies (the 23 week study with ipilimumab-hyb, and one and three month studies with ipilimumab) comprised the primary basis for this assessment, based on their study design and general adequacy. Ipilimumab or ipilimumab-hyb was administered as a bolus injection weekly or every four weeks in these studies, rather than the clinical dosing regimen of IV infusion every three weeks. Necropsy was often conducted several weeks after the final dose, particularly in the two primary longer term studies. As a consequence, some treatment related findings might not have been identified. Limited in-life data were also obtained in a single dose toxicity study with ipilimumab and a developmental version of CHO-derived ipilimumab. Plasma ipilimumab concentrations were determined in most toxicity studies, although toxicokinetic parameters were not calculated in the majority of studies due to limited blood sampling.

Ipilimumab and ipilimumab-hyb were generally well tolerated in monkeys at IV doses of 0.1–30 mg/kg (equivalent to steady-state IV exposures 0.2- to 7-fold greater than the recommended clinical dose, based on AUC and adjusted for the difference in dosing frequency) with dosing frequencies ranging from about monthly to three times per week. Exposure margins based on dose per body weight were 0.3–10, adjusted for dosing frequency. Reduced body weight gain or body weight loss was frequently observed at doses ≥3 mg/kg but there were no consistent effects. There was evidence for a low incidence of inflammatory effects due to ipilimumab treatment. One female was euthanised due to severe colitis after receiving two 10 mg/kg ipilimumab doses 4 weeks apart. The inflammatory response in the colon (mucosal pockets of mixed to suppurative inflammation, crypt abscesses and mucosal erosion) was consistent with inhibition of CTLA-4 regulation of immune self-tolerance. Another female monkey administered 10 mg/kg ipilimumab and anti-CD137 mAb developed severe dermatitis after the first dose but it was unclear which treatment was responsible. Increased white blood cell (WBC) counts and lymph node hypercellularity, as well as inflammatory changes in the intestine were frequently seen in one study in which ipilimumab (3–10 mg/kg IV) was coadministered with anti-PD-1 weekly for four doses. Two cases of lymphoid hyperplasia were seen after three doses of 30 mg/kg given in one week. This was consistent with findings in mice lacking CTLA-4[5].

One female dosed with 10 mg/kg ipilimumab at irregular intervals during a 2 month period was treated for signs of circulatory shock, consistent with an infusion reaction, immediately after the fifth dose. This effect was not seen upon rechallenge after about five months. The adverse reaction could not be conclusively attributed to ipilimumab treatment and its significance is

[5] Tivol EA *et al.* (1995) *Immunity* 3:541-547 and Waterhouse P *et al.* (1995) *Science* 270:985–988

unknown. However, the occurrence of rare infusion reactions in human patients has been noted in the proposed Australian PI and included in the final Australian PI.

Two monkeys treated with ipilimumab-hyb-treated and SK-Mel cells monthly for six months showed *in vitro* cross reactivity of anti-SK-Mel antibodies with iris tissue which is rich in melanocytes. The response was 8- to 10-fold greater than pre-treatment values. Reactivity was also reported for brain and kidney tissue but not for the stomach. Thus, there is a theoretical potential for enhanced autoimmune responses with repeated ipilimumab dosing, which is consistent with rare clinical findings reported in the proposed Australian PI and included in the final Australian PI.

**Genotoxicity and carcinogenicity**

Nonclinical studies investigating the genotoxicity and carcinogenicity of ipilimumab were not submitted. This was considered acceptable for a biotechnology derived product[6], and for the intended patient population.

**Reproductive toxicity**

No studies investigating the reproductive toxicity of ipilimumab were submitted. As a justification, the sponsor stated that standard reproductive toxicity studies in rodents or rabbits would not be relevant due to the species specificity of ipilimumab binding together with the short life expectancy and physiologic status of advanced melanoma patients does not warrant formal investigation of effects on reproduction. While it was acknowledged that reproductive toxicity studies with ipilimumab in rodents and rabbits would be of limited value, studies in non-human primates would be applicable, and are routinely conducted for other mAb products with anti-neoplastic indications. Indeed, an embryofetal development study has reportedly been conducted for tremelimumab, another anti-CTLA-4 mAb[7].

Additionally, indirect evidence suggestive of pharmacological effects of ipilimumab on reproductive organs in both male and female monkeys, which may theoretically adversely affect fertility and possibly embryofetal survival, warrants further investigation. Specific binding of ipilimumab to connective tissue of the ovary and placenta in monkeys and to the placenta in humans was seen in one *in vitro* tissue binding study (refer to '**Primary Pharmacodynamics**' above). There was no evidence of toxicity to the ovaries in the submitted repeat dose toxicity studies. However, published *in vitro* studies indicated that the *CTLA4* gene is expressed in placental fibroblasts[8], and that CTLA-4 may be involved in maintaining maternal-fetal tolerance during pregnancy[9]. Whether by CTLA-4 or Fc receptor binding, placental transfer of ipilimumab was considered likely. The potential effect on the developing fetus has not been established.

In males, reduced relative weights of the testes, epididymides and prostate were seen in three repeat dose toxicity studies with 10 mg/kg ipilimumab or ipilimumab-hyb, which included the 23 week study. There were no correlating histopathology findings. Steady state ipilimumab exposure (AUC) in one of these studies with weekly dosing was 7-fold higher than exposure at the recommended clinical dose; exposure margins based on body weight were 10. However, it was not possible to determine a No Observable Effect Level (NOEL) dose for this finding, due to the differences in study design and lack of dose ranging in most studies. Taken together, the potential for effects on male fertility at clinically relevant doses cannot be excluded.

[6] CPMP/ICH/302/95: ICH Topic S6: Preclinical safety evaluation of biotechnology-derived pharmaceuticals.
[7] MSDS for tremelimumab (www.pfizer.com).
http://www.pfizer.com/files/products/material_safety_data/PZ00158.pdf
[8] Kaufman KA *et al*. (1999) *Mol Hum Reprod* 5:84–87.
[9] Tsai AF *et al*. (1998) *J Reprod Immunol* 40:147–157; Jin LP *et al*. (2009) *Clin Immunol* 133:402–410.

Nonclinical reproductive toxicity studies are not necessarily expected for products indicated for patients with advanced cancer[10]. However, the discussion in the sponsor's *Clinical Overview* was indicative of improved patient survival with ipilimumab compared to other available treatments. As melanoma commonly occurs in patients with child bearing potential, the likelihood of subsequent pregnancies in successfully treated patients is increased. Thus, investigation of the potential reproductive toxicity of ipilimumab was justified, and the lack of reproductive toxicity studies was considered to be a deficiency. The sponsor was therefore encouraged to conduct appropriately designed studies, including studies for effects on fertility, in a relevant species (that is, a non-human primate) as a postmarketing commitment, should ipilimumab be approved for registration in Australia.

**Pregnancy classification**

The sponsor proposed a Pregnancy Category C for ipilimumab. This was considered acceptable as the primary potential effect, that is, increased embryofetal loss due to effects on the placenta, represents a pharmacological effect. The proposed statement in the proposed Australian PI (which was included in the final Australian PI) adequately reflects the lack of available relevant data for ipilimumab.

**Use in children**

Ipilimumab is not indicated for use in children. Nonclinical studies in juvenile animals were not conducted, which was considered acceptable.

**Local tolerance**

No specific local tolerance studies were conducted with ipilimumab. There was no evidence for ipilimumab related effects at the IV injection site in most repeat dose toxicity studies in monkeys. Injection rates in nonclinical studies were typically ≥15 mg/min. The proposed clinical infusion rate of ipilimumab is about 1.7 mg/min[11], resulting in a safety factor of ≥9. An increased incidence of subacute inflammation of the injection site was seen with weekly administration of 10 mg/kg ipilimumab (alone or in combination with anti-CD137) for one month in one study. This was considered unlikely to be toxicologically significant given the lack of similar effects in other studies with more frequent dosing.

**Immunotoxicity**

Ipilimumab is expected to have effects on the immune system. Some findings were indicative of a positive pharmacological effect and are discussed in '**Primary Pharmacodynamics**' above. However, toxicities consistent with exaggerated pharmacology may also be expected, as discussed below. Effects were observed in several studies, although results were often inconsistent across studies and/or confounded by concomitant administration of other products.

Increased white blood cell counts were seen in three studies at doses ≥10 mg/kg (irrespective of dosing frequency; steady state exposures 7-fold greater than the recommended clinical dose, based on AUC, and mg/kg-based exposure margins were 10). This was associated with lymphoid hyperplasia of the mandibular lymph node in two females administered 30 mg/kg three times in one week. Relative weights of other lymphoid organs were also affected in these studies, without a consistent response or any correlating histopathology findings. Due to limitations in study design and the inconsistency of findings across studies, it was unclear if these findings occurred at clinically relevant doses. Excessive lymphocyte proliferation is consistent with the expected pharmacology of ipilimumab and is consistent with findings in CTLA-4 knockout mice.

[10] EMEA/CHMP/ICH/646107/2008: ICH Topic S9: Note for guidance on nonclinical evaluation for anticancer pharmaceuticals.
[11] 150 mg per 3 mg/kg dose for a 50 kg adult, over a 90-min period.

The potential for increased delayed type hypersensitivity (DTH) reactions was investigated in two repeat dose studies in monkeys with monthly dosing. Monkeys received intramuscular (IM) injections of hepatitis B surface antigen (HBsAg) and subcutaneous (SC) injections of SK-Mel cells in conjunction with ipilimumab treatment. The potential for DTH was investigated by intradermal injection of both antigens and scoring of the resulting erythema. In both studies, a trend towards increased DTH scores in ipilimumab treated monkeys was seen for HBsAg and increased DTH scores for SK-Mel was seen in one study. The response was approximately dose related in the range 0.1–10 mg/kg in one study (extrapolated AUC- and mg/kg-based exposure to ipilimumab at the lowest dose was 0.02 and 0.03 times exposure at the recommended clinical dose, respectively). The clinical relevance of this finding was uncertain.

*In vitro* data were suggestive of increased ADCC with ipilimumab treatment, as discussed under '**Secondary Pharmacodynamics**'. However, there was no evidence for this effect in toxicity studies in monkeys.

The sponsor reported an incidence of anti-ipilimumab antibodies across all repeat dose studies of around 8%. The development of anti-ipilimumab antibodies was associated with rapid clearance of plasma ipilimumab which has implications for its efficacy and potentially clinically relevant.

Evidence for a low incidence of treatment related inflammatory responses was seen in monkeys, as discussed under '**General toxicity**' above. This finding is consistent with the primary pharmacology of ipilimumab and likely to be clinically relevant. This and other adverse immune effects are reported in the proposed Australian PI and included in the final Australian PI.

**Potential for increased cytokine release**

Two *in vitro* studies investigated the potential for cytokine release from human peripheral blood mononuclear cells (PBMCs) in response to ipilimumab. Two of the three assays conducted in these studies were similar in design to those developed for the retrospective analysis of TGN1412, an agonistic CD28-specific mAb which induced severe pro-inflammatory cytokine release in healthy human volunteers in a clinical trial. In previous *in vitro* assays with TGN1412, when it was added to human WBCs, or when it was cross linked via its Fc region in aqueous solution, no response was observed. However, positive results consistent with those seen clinically were observed for TGN1412 for the first two assay methods described below.

Low levels of interleukin (IL)-2, IL-6, IL-8 and tumour necrosis factor-alpha (TNF-α) (stimulation index (SI) of 2.2–6.3 with 2 μg/mL ipilimumab) were detected with a generally low incidence in peripheral blood mononuclear cells (PBMCs) in the presence of ipilimumab using a captured mAb assay, in which ipilimumab was immobilised by binding to anti-human antibody previously applied to assay plates. There was no increase in the levels of IL-4, IL-5, IL-12 or IFN-γ. A marked increase in levels of all cytokines except for IL-12 (SI of 4–124 at the $C_{max}$) was seen at high incidence in response to the positive control, mouse anti-CD28. Similar results were seen with ipilimumab which was immobilised by dry coating onto assay plates, although mean values were not calculated. A minimal proliferative response was observed for ipilimumab in both assays (SI 4.4–12), compared to a marked proliferative response with anti-CD28 (SI 34–139). No cytokine release was detected in an assay in which free ipilimumab was incubated with human PBMCs.

The results indicate that ipilimumab presents some potential for cytokine release from PBMCs, consistent with its primary pharmacology. However, the effects were considerably less pronounced than seen concurrently with anti-CD28 mAb. There was possibly some evidence of increased cytokine release in one treated monkey but the presence of several confounding factors (discussed under '**General Toxicity**') means the relationship with ipilimumab treatment was difficult to determine. Thus, the risk of severe pro-inflammatory cytokine release in patients taking ipilimumab, based on the available nonclinical data was considered to be low.

The potential for increased cytokine release is mentioned in the proposed Australian PI and included in the final Australian PI.

## Nonclinical Summary and Conclusions

- The submitted data comprised studies investigating the pharmacodynamics, repeat dose toxicity, toxicokinetics, immunotoxicity and local tolerance of ipilimumab. The relevant studies were Good Laboratory Practice (GLP)-compliant. Several studies used a developmental version of ipilimumab (ipilimumab-hyb). Only one nonclinical study compared the toxicological profiles (including toxicokinetics) of the two products. The comparability of their pharmacological activity and resulting safety profile was uncertain, but any toxicity associated with hybridoma-derived ipilimumab may also be qualitatively relevant for the final drug product. As there was limited quantitative data regarding the relative activity of ipilimumab in monkeys compared to humans, it was not known whether the nonclinical safety profile of ipilimumab was adequately characterised.

- Ipilimumab bound to human CTLA-4 *in vitro*, with $K_D$ values in the range 5.25–10.5 nM (or 0.8–1.6 μg/mL, compared to a steady state $C_{max}$ of 90.8 μg/mL at the clinical dose). Ipilimumab exerted its effects through inhibition of binding of natural CTLA-4 ligands, B7-1 and B7-2 ($IC_{50}$ values 148–444 μg/mL). The species and tissue binding profile of ipilimumab was restricted with binding generally limited to lymphocytes in most tissues from humans and monkeys. Ipilimumab binding to connective tissue in the placenta and ovary from monkeys and the placenta from humans was also seen. Binding affinity between ipilimumab and mouse CTLA-4 was about 1000-fold lower than that of the human protein.

- As expected for an IgG1 protein, ipilimumab bound to the high affinity IgG1 receptor, FcγRI, with an $EC_{50}$ value (0.27 μg/mL) comparable to that of non-specific human IgG1 (0.60 μg/mL). Consistent with this, increased antibody dependent cellular cytotoxicity of activated T cells was seen with ipilimumab *in vitro* but there was no evidence for T cell depletion in ipilimumab treated monkeys. Binding of ipilimumab to low affinity IgG1 receptors FcγRIIA and FcγRIII was also observed but $EC_{50}$ values were not reached. There was no evidence of complement dependent cytoxicity in response to ipilimumab (≤50 μg/mL, compared to the clinical $C_{max}$ of 90.8 μg/mL) *in vitro*.

- Several *in vivo* studies investigated the effects of a surrogate mouse anti-CTLA-4 mAb on the growth of mouse tumour cell lines. These studies are considered to represent "proof of concept" studies for anti-CTLA-4 activity, rather than being directly supportive of efficacy of ipilimumab. The studies were indicative of a general inhibitory effect on mouse tumour cells, although no inhibition of a mouse melanoma cell line was seen with IP dosing every three days for four doses. Ipilimumab (10 mg/kg IP) inhibited the growth of mouse MC38 colon carcinoma cells by 0–80% in transgenic mice expressing human CTLA-4, depending on the dosage regimen and number of tumour cells injected; at least four ipilimumab doses over a 10–13 day period commencing on the day of tumour injection appeared to be required for an anti-tumour effect.

- Ipilimumab demonstrated some immunomodulatory ability in monkeys, although results were inconsistent. Ipilimumab treatment in conjunction with injection of human SK-Mel melanoma cells in monkeys augmented the development of anti-SK-Mel antibodies by ≤5-fold. Similar results were seen with injection of Hepatitis B surface antigen, indicative of a general enhancement of the immune response. Increased numbers of memory T cells were seen in one comprehensive immunological study with monthly dosing in monkeys and increased levels of activated T cells was associated with dosing three times in one week. No

studies were conducted to link the enhanced immune response with a reduction in melanoma progression.

- Mouse anti-CTLA-4 antibodies accelerated and exacerbated disease progression in three mouse models of autoimmunity consistent with an enhancement of immune related activities. This finding may be clinically relevant.

- Specialised safety pharmacology studies were not conducted, which was acceptable for a biotechnology derived product. There was no evidence of effects on the cardiovascular system in monkeys with repeated ipilimumab dosing at $C_{max}$ values 4-fold greater than the $C_{max}$ at the recommended clinical dose.

- The pharmacokinetics of ipilimumab were generally similar in monkeys and humans, and consistent with the properties expected from a monoclonal antibody, that is, long half-life and slow plasma clearance. There was evidence of accumulation in both species, which was dependent on the dosage regimen.

- The repeat dose toxicity of ipilimumab by the IV route was investigated in only one study (3 months), whereas ipilimumab-hyb was investigated in studies of up to 23 weeks duration in Cynomolgus monkeys. Interpretation of findings in most studies was difficult, due to the lack of concurrent control groups, combination treatment with other products and/or limited documentation. Dose ranging was not conducted in most studies and NOAELs were subsequently not established. Treatment was generally less frequent than the proposed clinical regimen and the number of doses given was lower than that expected clinically. Necropsy was often conducted several weeks after the final dose. As a consequence, some treatment related findings might not have been identified.

- Ipilimumab was generally well tolerated in monkeys at IV doses which were equivalent to steady state IV exposures 0.2- to 7-fold greater than the recommended clinical dose, based on AUC and adjusted for the difference in dosing frequency (exposure margins based on body weight were 0.3–10). Isolated incidences of severe toxicities consistent with exaggerated pharmacological effects of ipilimumab were seen, including inflammatory colitis, dermatitis and an infusion reaction. Evidence for increased lymphocyte proliferation, including two cases of lymphoid hyperplasia was also seen at high doses in some studies.

- Nonclinical studies investigating the genotoxicity and carcinogenicity of ipilimumab were not submitted. This was considered acceptable for a biotechnology derived product and considering the intended patient population.

- No studies investigating the reproductive toxicity of ipilimumab were submitted. Indirect evidence was suggestive of pharmacological effects of ipilimumab on reproductive organs in both male and female monkeys which may theoretically adversely affect fertility and possibly embryofetal survival. Together with the potential for increased patient survival with ipilimumab treatment this was considered a deficiency. The sponsor was therefore encouraged to conduct appropriately designed studies in non-human primates, should ipilimumab be approved for registration.

- There was no ipilimumab related local toxicity at the IV injection site in monkeys with IV infusion rates about 9-fold greater than that proposed clinically.

- Ipilimumab was slightly antigenic in monkeys; around 8% of treated monkeys developed anti-ipilimumab antibodies.

- Ipilimumab induced the release of some cytokines (IL-2, IL-6, IL-8 and TNF-α) from human mononuclear cells *in vitro* but to a lesser extent than mouse anti-CD28[12]. Evidence for increased *in vivo* cytokine release in monkeys was inconclusive. Thus, the nonclinical data indicate a minimal risk for severe pro-inflammatory cytokine release in ipilimumab treated patients.

### Conclusions and Recommendations

Ipilimumab induced its pharmacological effects through binding to CTLA-4 and displacement of its natural ligands. Immunomodulatory effects in monkeys were inconsistent but increased memory T cells were observed and increases in activated T cells with frequent dosing were noted. A mouse surrogate for ipilimumab inhibited tumour growth in mice, but exerted no effects on the growth of mouse melanoma. The effect of ipilimumab itself on the proliferation of melanoma cells was not investigated in nonclinical studies. Thus, the assessment of the efficacy of ipilimumab for the treatment of advanced melanoma will rely on the clinical data.

It was unclear whether the nonclinical safety profile of ipilimumab was adequately characterised, as its relative activity in monkeys and humans was not quantified. The observed toxicities were consistent with exaggerated pharmacological effects and included exacerbated disease progression in mouse models of auto-immunity, severe inflammatory colitis and dermatitis, and an infusion reaction. Evidence for increased lymphocyte proliferation, including a low incidence of lymphoid hyperplasia, was seen at high doses. All are considered potentially clinically relevant.

No studies investigating the reproductive toxicity of ipilimumab were submitted. Given the indirect evidence for pharmacological effects of ipilimumab on reproductive organs in both males and females which may theoretically adversely affect fertility and possibly embryofetal survival and the potential for increased patient survival with ipilimumab treatment, this was considered a deficiency. The sponsor was therefore encouraged to conduct appropriately-designed studies in non-human primates as a post-marketing commitment, should ipilimumab be approved for registration.

The observed toxicities have been identified in the Australian Product Information document, and should be manageable clinically. The treatment of advanced metastatic melanoma represents an unmet clinical need and the severity of the illness should be considered when making a risk analysis of ipilimumab. Thus, there are no nonclinical objections to the registration of ipilimumab, provided the clinical data adequately address its efficacy.

# IV. Clinical Findings

## Introduction

The sponsor's clinical development program for Yervoy is summarised in Figure 2.

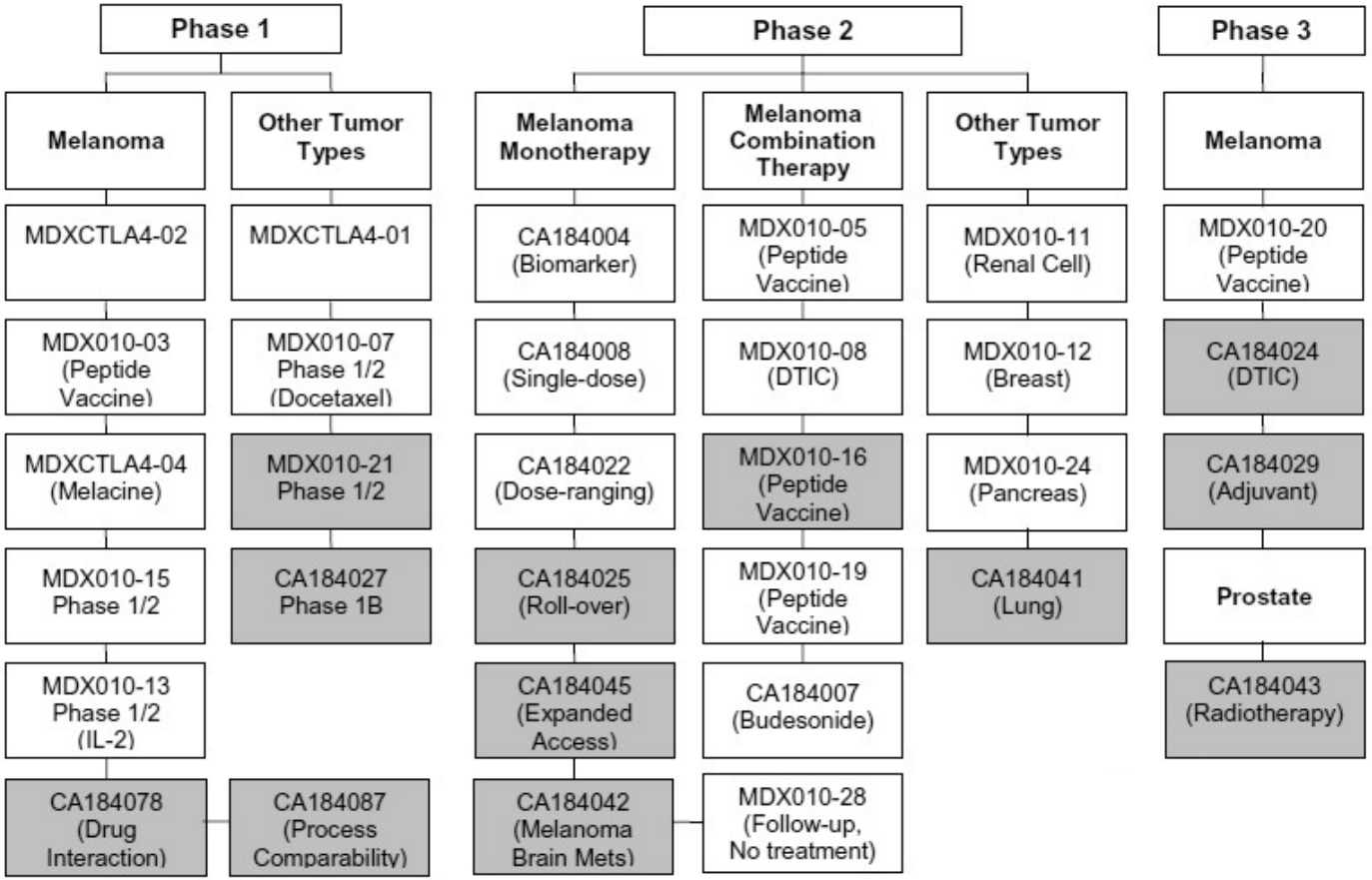
### Formulations used in the clinical studies

Two manufacturing processes were used in the development of the ipilimumab drug substance.

The first process, Process A, involved manufacture of ipilimumab in a hybridoma cell line (10D1.3/3.6). The second process, Process B, refers to the manufacturing process in a recombinant Chinese Hamster Ovary (CHO) cell line. Ipilimumab produced by Process B was used in MDX010-20. Process B was also used in the four Phase II clinical studies (CA184004, CA184007, CA184008, CA184022) carried out by the sponsor and was proposed for commercial launch.

[12] A human anti-CD28 mAb (TGN1412) was associated with severe cytokine-related adverse effects in a clinical trial.

**Figure 2. Clinical development program.**



Comparability of the drug substance produced using the Process B from CHO cells to the drug substance produced using Process A from hybridoma cells was demonstrated primarily through analytical characterisation of the drug substance and also through PK studies in Cynomolgus monkeys. Similarly, comparability of the drug substance produced using the two different Process B's was demonstrated through analytical characterisation.

**Ethics and Good Clinical Practice (GCP) certification included in report**

MDXCTLA4-01, MDXCTLA4-02, MDX-010-15, CA184004, CA184007, CA184008, CA184022, MDX010-20, MDX010-08, MDX010-28, CA184042, MDX010-19,

MDX010-13, MDX010-05, MDXCTLA4-04, MDX010-03, MDX010-07, MDX010-17,

MDX010-12, MDX010-24

**GCP but not ethics certification included in report**

MDX010-11, MDX010-23

**Neither ethics nor GCP certification included in report**

MDX010-21.

## Pharmacokinetics

### Introduction

The main studies of pharmacokinetics are summarised in Table 4. Pharmacokinetic measurements were also made in some of the other studies (see below).

### Analytic methods

Two validated, quantitative enzyme-linked immunosorbent assays (ELISAs) were developed to quantify ipilimumab levels to support the nonclinical and clinical ipilimumab programs.

### Distribution

Animal studies suggest that ipilimumab does not distribute out of the plasma compartment. The apparent volume of distribution at steady state is about 4.5 - 6.5 L.

### Elimination

From Study MDX010-15 it was deduced that the mean clearance in the steady state was about 12-14 mL/h.

**Table 4. Pharmacokinetics studies (table continued across five pages).**

| Study<br>Year finished<br>Location | Design | Treatments | Subjects entered | Pharmacokinetics<br>Mean (sd) |
|---|---|---|---|---|
| MDXCTLA4-01<br><br>Jun 2000 - Jul 2001<br><br>USA | Phase I, open, single dose. After day 28, follow-up monthly until disease progression. A 2nd dose option after 6 months. | Ipi[1] , dose 3mg/kg. Test dose 0.2mg over 10 min, then observation 30 min, then remainder of dose over 90 min.<br><br>2 patients received a 2nd dose after 6 months, but subsequently withdrew consent. | 14 patients with metastatic adenocarcinoma prostate treated:<br><br>mean age 69.4 (range 56-79); mean weight 85.6 kg (range 62-121).<br><br>10 completed 28 days follow-up. During further follow-up, 2 died and 2 withdrew consent. | $C_{max}$ (µg/mL) 155.44 (64.81)<br>$T_{max}$ (h) 3.24 (1.40)<br>$t_{½}$ (h) 317 (123)<br>$AUC_{0-\infty}$ (h.µg/mL) 223926 (9237)<br>Vz (L) 4.10 (1.14)<br>Vs (L) 4.40 (1.84)<br>Cl (L/h) 0.0095 (0.0033)<br>MRT (h) 474 (164) |

Cmax=maximum plasma concentration. Tmax=Time of maximal plasma concentration. $t_{1/2}$=half-life. $AUC_{0-\infty}$: area under the plasma concentration time curve from time zero to infinity. Vz=apparent volume of distribution. Vs= volume of distribution. Cl=clearance. MRT=mean residence time. Sd=standard deviation.

**Table 4. (continued)**

| | | | | | |
|---|---|---|---|---|---|
| MDXCTLA4-02<br><br>Aug 2000 - Apr 2002<br><br>USA | Phase I, open, single dose. After day 28, follow-up monthly for 6 months or until disease progression (whichever is later). A 2nd dose option after 3 months. | Ipi[1] , dose 3mg/kg as in Study 01 above, on Day 1.<br><br>2 patients received a 2nd dose. | 17 patients with unresectable melanoma stage III or IV treated: 11M, 6F; mean age 59.1 (sd 14); mean weight 80.4 kg (sd 15).<br><br>11 completed 28 days follow-up. During further f/u, 4 died, 1 withdrew consent and 1 was lost to f/u. | $C_{max}$ (µg/mL)<br>$T_{max}$ (h)<br>$t_{½}$ (h)<br>$AUC_{0-\infty}$ (h.µg/mL)<br>Vz (L)<br>Vs (L)<br>Cl (L/h)<br>MRT (h) | 160.61 (52.1)<br>3.22 (1.16)<br>371 (194)<br>28350 (15200)<br>4.96 (2.03)<br>4.44 (1.83)<br>0.0100 (0.0040)<br>478 (219) |

**Table 4. (continued )**

| | | | | $C_{max}$ (µg/mL) G. Mean (CV) | $T_{max}$ (h) Median (range) | $AUC_{0-504h}$ (h.µg/mL) G. Mean (CV) | $AUC_{0-\infty}$ (h.µg/mL) G. Mean (CV) | CL (mL/h) A. Mean (sd) | Vdss (mL) A. Mean (sd) | $t_{½}$ (h) A. Mean (sd) |
|---|---|---|---|---|---|---|---|---|---|---|
| MDX010-15<br><br>Dec 2003 - Aug 2006<br><br>USA (5 sites) | Phase I, open, single and multiple dose. | **Group A-MD**<br>Cohort a (n=12)<br>Ipi[2], 2.8 mg/kg<br>x3 doses (Days 1, 57, 85) | 88 patients with unresectable melanoma stage III or IV treated: 57M, 31F; mean age 59 (range 29-87); mean weight 84.1 kg (sd 22).<br><br>PP population 87 (in 1 pt lung lesions found to be adenocarcinoma).<br><br>In 68 pts, sufficient drug concentration values were obtained for full pharmacokinetic analyses. | | | | | | | |
| | | | | **Day 1 (13)[4]** | | | | | | |
| | | | | 79.9 (24%) | 2.5 (1.5-5.5) | 12081 (44%) | 19583 (74%) | 12.8 (6.8) | 5505 (2073) | 385 (227) |
| | | | | **Day 57 (7)** | | | | | | |
| | | | | 108 (38%) | 2.5 (1.33-4.0) | 15206 (29%) | - | - | - | 270 (64) n=6 |
| | | | | **Day 85 (4)** | | | | | | |
| | | | | 257 (51%) | 2.3 (1.33-4.0) | 25707 (42%) | - | - | - | 700, 475 n=2 |
| | | Cohort b (n=12)<br>Ipi[3], 3 mg/kg<br>x3 doses (Days 1, 57, 85) | | | | | | | | |
| | | | | **Day 1 (12)** | | | | | | |
| | | | | 84.5 (38%) | 1.75 (1.5-4.0) | 12383 (32%) | 19596 (68%) | 13.8 (8.1) | 5878 (1609) | 414 (264) |
| | | | | **Day 57 (5)** | | | | | | |
| | | | | 103 (68%) | 3.0 (1.5-24.0) | 18396 (33%) | - | - | - | 321 (225) n=4 |
| | | | | **Day 85 (2)** | | | | | | |
| | | | | 184, 96.7 | 5.0, 2.5 | 27581 n=1 | - | - | - | 447, 70.0 |

**Table 4. (continued )**

| | | | | $C_{max}$ (µg/mL) G. Mean (CV) | $T_{max}$ (h) Median (range) | $AUC_{0-504h}$ (h.µg/mL) G. Mean (CV) | $AUC_{0-\infty}$ (h.µg/mL) G. Mean (CV) | CL (mL/h) A. Mean (sd) | Vdss (mL) A. Mean (sd) | $t_{½}$ (h) A. Mean (sd) |
|---|---|---|---|---|---|---|---|---|---|---|
| MDX010-15 | | Cohort c (n=10) Ipi[2], 5 mg/kg x3 doses (Days 1, 57, 85 | | | | | **Day 1 (10)** | | | |
| | | | | 162 (28%) | 3.5 (1.5-5.5) | 26875 (23%) | 42337 (32%) | 11.6 (5.2) | 5381 (1859) | 384 (261) |
| | | | | | | | **Day 57 (3)** | | | |
| | | | | 213 (60%) | 2.0 (1.7-4.8) | 32136 (15%) | - | - | - | 284 n=1 |
| | | | | | | | **Day 85 (3)** | | | |
| | | | | 237 (32%) | 2.5 (1.6-5.5) | 37670 (30%) | - | - | - | 423, 384 n=2 |

CV= coefficient of variation, Vdss=volume of distribution at steady state.

**Table 4. (continued )**

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | **Group A-SD** | | **Day 1** | | | | | | |
| | | | | $C_{max}$ (µg/mL) G. Mean (CV) | $T_{max}$ (h) Median (range) | $AUC_{0-504h}$ (h.µg/mL) G. Mean (CV) | $AUC_{0-\infty}$ (h.µg/mL) G. Mean (CV) | CL (mL/h) A. Mean (sd) | Vdss (mL) A. Mean (sd) | $t_{½}$ (h) A. Mean (sd) |
| | | Cohort d (n=6) Ipi[2], 7.5 mg/kg x1 dose | | 292 (23%) | 2.0 (1.5, 2.5) | 44853 (22%) | 70847 (19%) | 8.90 (2.1) | 4658 (1103) | 387 (161) |
| | | Cohort e (n=7) Ipi[2], 10 mg/kg x1 dose | | 300 (24%) | 2.0 (1.5, 7.0) | 37706 (24%) | 60099 (43%) | 15.7 (6.2) | 6664 (2310) | 366 (200) |
| | | Cohort f (n=6) Ipi[2], 15 mg/kg x1 dose | | 440 (7%) | 3.25 (1.5, 22) | 67107 (11%) | 98325 (23%) | 13.6 (2.2) | 6146 (1929) | 395 (143) |
| | | Cohort g (n=11) Ipi[2], 20 mg/kg x1 dose | | 533 (33%) | 3.0 (1.4, 5.5) | 64808 (23%) n=9 | 78258 (46%) | 21.9 (11) | 6080 (1840) | 297 (198) |
| | | **Group B** (n=24) | | **Day 64 (13)** | | | | | | |
| | | Ipi[2], 10 mg/kg x4 doses (Days 1, 22, 43, 64) | | 441 (36%) | 2.5 (1.2, 48) | 55433 (35%) | - | - | - | 359 (225) n=12 |

[1] Hybridoma-derived, formulated at protein concentration 5 mg/mL. For administration, diluted in normal saline to 2.5 mg/mL.
[2] Transfecta-derived, formulated at protein concentration 5 mg/mL and provided in 5 or 10 mL vials. Administered IV over 90 min.
[3] Hybridoma-derived, formulated at protein concentration 5 mg/mL and provided in 5 or 10 mL vials. Administered IV over 90 min. [4] Value of n.

**Pharmacokinetic measurements made in studies beyond Phase I**

***CA184007***

Serum samples were collected to measure levels of ipilimumab over time. Data from this study were used in conjunction with data from other ipilimumab studies as part of a population PK evaluation. An interim PK-oriented database lock for dosing times, dose amounts, PK sampling times, and for various covariates including, but not limited to, subject age, sex, and weight, was performed to include approximately 125 to 150 subjects across other CA184 studies.

Blood for pharmacokinetic analysis was sampled Pre dose (Days 1, 22, 43 and 64) and at intervals post dosing. The samples taken between Days 45 and 57 were specifically for use in the population analysis. The protocol did not stipulate any randomised procedure for selecting patients for pharmacokinetic sampling – rather, the plan formally involved samples from all patients. In the event, few patients provided sufficient data for non-compartmental pharmacokinetic analysis:

> "Of 115 treated subjects, only 15 had intensive PK sampling and were included in the PK dataset. Among these 15 subjects, 14 had sufficient data to calculate terminal half life and 12 had sufficient data for non-compartmental PK analysis."

Results derived from these 14 patients are tabulated below.

**Table 5. PK results from Days 1 and 43.**

| Study Day | $C_{max}$ (µg/mL) G. Mean (CV) | $AUC_{0-21d}$ (h.µg/mL) G. Mean (CV) | $AUC_{0-\infty}$ (h.µg/mL) G. Mean (CV) | $t_{½}$ (d) A. Mean (sd) | CL (mL/h) A. Mean (sd) | Vs (L) A. Mean (sd) |
|---|---|---|---|---|---|---|
| Day 1 (n=11) | 206 (21%) | 33498 (18%) | 42844 (23%) | 9.6[1] (3.5) | 19.1 (6.6) | 6.0 (1.9) |
| Day 43 (n=12) | 215 (24%) | 47722 (27%) | N/A | 15.2[1] (7.1) | N/A | N/A |

[1] n=14

Sponsor response:

*In CA184007, extensive PK sampling was obtained from a subset of patients (N = 15) not only after the third dose (between Days 43 and 57) but also after the first dose (between Days 1 and 21). These data were used to characterize the PK of ipilimumab by non compartmental PK analysis (NCA) following both of these doses. In addition, sparse PK samples were obtained from the majority of patients in the study (N = 112) such that all post-dose PK samples from the study as well as from other studies (CA184008, CA184022) were used for a comprehensive population PK (PPK) analysis. The PPK analysis was externally validated using data from CA184004 (see Sponsor's Response below).*

***CA184008***

Only five patients were intensively studied, the arrangements being similar to those for Study CA184007 (see above). Results are summarised below. As for Study CA184007, data from this study were used in conjunction with data from other ipilimumab studies as part of a population PK evaluation.

**Table 6. PK results from Days 1 and 43.**

| Study Day | $C_{max}$ (µg/mL) G. Mean (CV) | $AUC_{0-21d}$ (h.µg/mL) G. Mean (CV) | $AUC_{0-\infty}$ (h.µg/mL) G. Mean (CV) | $t_{½}$ (d) A. Mean sd) | CL (mL/h) A. Mean (sd) | Vs (L) A. Mean (sd) |
|---|---|---|---|---|---|---|
| Day 1 (n=4) | 200 (16%) | 36110 (24%) | 45547 (32%) | 8.9 (2.1) | 16.2 (3.1) | 5.0 (0.5) |
| Day 43 (n=4) | 251 (24%) | 52713 (17%) | N/A | 16.9 (7.1) | N/A | N/A |

### *CA184004*

Serum ipilimumab concentration data collected in this study were not used for non compartmental PK analysis. These data were used in conjunction with samples from other studies as part of a population PK assessment and specifically in an assessment of external validity.

### *CA184022*

Serum ipilimumab concentration data collected in this study were not used for non compartmental PK analysis. As for Study CA184007, these data were used in conjunction with samples from other studies as part of a population PK assessment.

### Evaluator's overall conclusions on pharmacokinetics

A minimal set of estimates of PK parameters has been obtained from the studies listed in Table 4. The clinical evaluator has reservations about the reliability of estimates obtained from the population pharmacokinetic modelling (see below).

## Pharmacodynamics

No specific pharmacodynamic studies were presented, other than Study MDXCTLA4-01, whose primary objective was to determine whether administration of ipilimumab causes nonspecific T-cell activation. The result was negative.

**Sponsor response:**

*Pharmacodynamic biomarkers of ipilimumab were investigated as secondary endpoints in a number of Phase II studies. A summary of these findings were presented in the* ***Summary of Clinical Pharmacology Studies****. The sponsor agreed that none of the candidate biomarkers evaluated in these studies were shown to be viable predictors of clinical outcome.*

## Efficacy

### Introduction

The main clinical evidence for efficacy relies upon a single Phase III study (MDX010-20) supported by two late Phase II studies (CA184004 and CA184022). Some additional data are contributed by Phase II studies in which the treatment with Yervoy was uncontrolled (CA184007, CA184008 and MDX010-08).

**Dose-response studies (see Table 7)**

***Study CA184022***

*Methods*

Following screening, there was an induction period (Weeks 1 to Week 24), a maintenance period (Week 24 dose visit until progression or study closure) and a follow up period. Four tumour assessments (Tas) (radiologic and photographic) were performed at Weeks 12, 16, 20 and 24.

The maintenance period included two categories of patients:

(1) On-treatment.

Patients without progressive disease (PD) who continued to tolerate Yervoy continued treatment in 12 week intervals until PD, withdrawal of consent or study closure.

(2) TAs only.

Patients without PD who discontinued Yervoy treatment due to toxicity continued with TAs in the maintenance period and study procedures until PD but received no further dosing. All patients in the maintenance period had TAs performed every 6 weeks (Weeks 30, 36, 42 and 48). After Week 48, TAs were performed every 12 weeks.

Any patient who did not qualify for entry into the maintenance period was moved into the follow up period or into a separate study, CA184025. Patients in Study CA184022 were eligible to enter CA184025 as follows:

- If patients exhibited PD at anytime during induction or maintenance in Study CA184022, they could be re-induced in Study CA184025 at 10 mg/kg of Yervoy irrespective of their dose in Study CA184022.
- If patients enrolled into CA184025 when CA184022 closed, they could continue to receive their CA184022 blinded dose in CA184025 maintenance period.
- If patients who did not progress in CA184022 but discontinued treatment due to an immune related adverse event (irAE) and were subsequently enrolled into CA184025 maintenance period for TAs only, they could be re-induced upon progression at 3 mg/kg of Yervoy.

The follow up period began for all patients with PD who did not meet the criteria for entry into Study CA184025 for re-induction, or chose not to enrol in Study CA184025.

*Study Participants:*

Patients aged ≥ 16 with histological diagnosis of malignant melanoma;

Measurable unresectable Stage III or IV disease;

Must have demonstrated 1 of the following in response to ≥ 1 regimen other than a CD137 agonist or CTLA-4 inhibitor or agonist:

1) PD; or

2) failed to demonstrate an objective response based on an assessment period of ≥ 12 weeks from prior regimen start; or

3) inability to tolerate treatment due to unacceptable toxicity.

At least 30 days since treatment with other investigational products.
Life expectancy ≥ 16 weeks; ECOG PS 0-1[13];

Required values for initial laboratory tests: WBC ≥ 2500/μL; platelets ≥ 75 x $10^3$/μL; haemoglobin ≥ 9 g/dL; creatinine ≤ 2.5 x upper limit of normal (ULN); aspartate aminotransferase (AST) ≤ 3 x ULN (except patients with AST ≤ 5 x ULN that is attributed to liver metastases); bilirubin ≤ 3 x ULN.

*Randomisation*: Patients enrolled into the study were stratified on the basis of prior treatment received (interleukin-2 (IL-2), fotemustine, dacarbazine (DTIC) or temozolomide versus other treatments), then randomised 1:1:1 to Yervoy dosage.

*Prohibited therapy:* Subjects could not use any of the following therapies during the screening period, within 1 month of their first dose of Yervoy or during the induction and maintenance periods:

- Any anticancer agent;
- Immunosuppressive agents;
- Any other CTLA-4 inhibitors or agonists not associated with Study CA184022;
- CD137 agonist;
- Investigational therapies;
- Any non-oncology vaccine therapy used for prevention of infectious disease for up to one month pre and post dosing with Yervoy;
- Chronic systemic steroids; or (except in certain limited circumstances)
- Surgery or radiotherapy.

[13] ECOG Performance Status. The Eastern Cooperative Oncology Group (ECOG) has developed criteria used by doctors and researchers to assess how a patient's disease is progressing, assess how the disease affects the daily living abilities of the patient, and determine appropriate treatment and prognosis. The following are used: 0 - Fully active, able to carry on all pre-disease performance without restriction, 1- Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, such as light house work, office work, 2 - Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours, 3 - Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours, 4 - Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair, 5 – Dead.

**Table 7. Dose-response studies.**

| Study ID<br>Study period | Centres | Design | Posology | Objective | Subjects by arm: treated (response evaluable) | Duration | Gender<br>(Age) | Diagnosis and main inclusion criteria | Primary outcome variable |
|---|---|---|---|---|---|---|---|---|---|
| CA184 022<br><br>Apr 2006-Dec 2007 | 66 in 13 countries | Phase2, randomised, double-blind, multiple dose study of 3<br>dose levels | (A) Yervoy 0.3mg/kg[1].<br>(B) Yervoy 3mg/kg[1].<br>(C) Yervoy 10mg/kg[1]. | Estimate BORR at 3 dose levels. | 72 (54)<br>71 (55)<br>71 (54) | Induction, wks 1-24; Maintenance, wks 24 - progression or end of study. | 217 patients randomised: 144M, 73F; mean age 57.2 (sd 14); mean weight 80.9kg (sd 17). | Patients with measurable, stage III (unresectable) or IV melanoma, who had progressed on previous chemotherapy. | BORR |

BORR=Best Objective Response Rate.

[1] Administered as a 90 minute IV infusion, every 3 weeks at Weeks 1, 4, 7 and 10, for a total of 4 separate doses in the induction period, followed by maintenance period with administration every 12 weeks from Week 24 "until progression, study drug-related toxicity leading to discontinuation of ipilimumab dosing, withdrawal of consent or study closure". [2] The assessment of tumour response was based on measurable index and non-index lesions, and the presence or absence of new lesions. [3] "Until toxicities requiring discontinuation ... tumour progression or consent withdrawal."

[4] It is not clear whether this was the date of database lock. "All treated subjects were off study-drug treatment at database lock" (*CSR* ); "The primary analysis will be performed when the last randomized patient has been followed to the tumour re-staging assessment at Week 24. The end of the study will occur at the same time as the primary analysis."

[5] At the time of progression, subjects with SD or better at Week 12 were offered entry into CA184025 at the investigator's discretion, where subjects could receive 3 mg/kg or 10 mg/kg ipilimumab depending on eligibility. Subjects with documented PD during the induction or maintenance periods who did not meet the criteria for re-induction or chose not to enrol in CA184025 were to continue in a follow-up period. Tumour assessments were performed every 4 weeks from Weeks 12 - 24 and every 12 weeks thereafter.

**Table 7. Dose-response studies (continued).**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects by arm: Treated (Completed *per* protocol) | Duration | Gender, age, weight | Diagnosis and main inclusion criteria | Primary outcome variables |
|---|---|---|---|---|---|---|---|---|---|
| CA184004 (Nov 2005-Oct 2007) | 14 sites in Europe, North America, and South America | Phase II, randomised, double-blind. | **Induction period (Weeks 1-24)**<br>(A) Yer 3 mg/kg IV over 90min at weeks 1, 4, 7, 10.<br>(B) Yer 10 mg/kg IV over 90min at weeks 1, 4, 7, 10.<br>**Maintenance period**<br>(A) Yer 3 mg/kg IV over 90min at week 24 then every 12 weeks[3].<br>(B) Yer 10 mg/kg IV over 90min at week 24 then every 12 weeks[3]. | To analyse pre-treatment characteristics of the patient or tumour and clinical tumour response in patients with unresectable Stage III and IV melanoma, in order to identify candidate markers predictive of response or serious toxicity.[6] | | "Last subject last visit for [the CSR] 30 Oct 2007." [4,5] | 82 randomised and treated with Yer: 52M, 30F; mean age 55.0 (sd 15); mean weight 79.2 kg (sd 17).<br>Patients were randomised 1:1 to (A) or (B), stratified by use of prior immunotherapy for melanoma. | Measurable, stage III or IV melanoma; life expectancy ≥ 4 months; ECOG PS 0 or 1. | BORR[2]; others. |

[6] This objective was of minor importance to the dossier. The study is included in this section of the clinical evaluation report (CER) on the basis of the secondary objectives relating to efficacy and safety of the dosages tested.

*Primary efficacy endpoint: Best Objective Response Rate (BORR).*

It was stipulated that tumour response would be based on Independent Review Committee (IRC) assessment of imaging studies of index and non-index lesions. Other listed response endpoints were: Duration of Best Objective Response (BOR); Time to BOR; Disease Control Rate (defined for each arm as the total number of randomised patients in the arm with BOR of complete response (CR), partial response (PR) or stable disease (SD), divided by the total number of randomised patients in the arm); progression free survival (PFS); overall survival (OS).

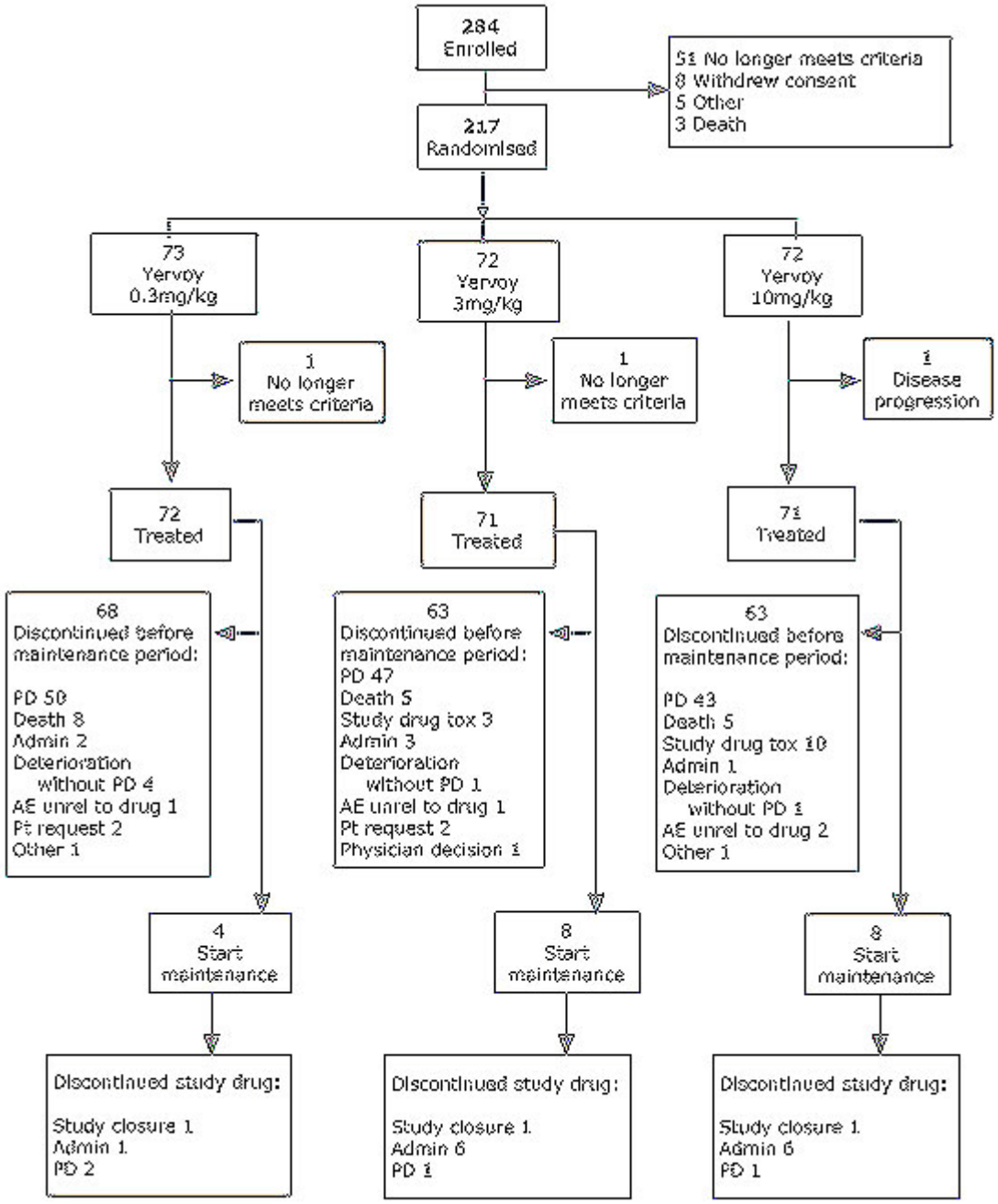
*Statistical methods*: The planned analyses included the following:

- Efficacy analyses to be performed when the last randomised patient has been followed to Week 24.
- BORR to be estimated in each randomised arm, and the corresponding exact two-sided 95% confidence interval to be computed using the method of Clopper and Pearson.
- Two-sided 95% confidence intervals (CIs) for all pairwise differences in BORR (3 versus 0.3 mg/kg, 10 versus 0.3 mg/kg and 10 versus 3 mg/kg) to be computed using the method of DerSimonian and Laird.
- A one-sided exact Cochran-Armitage trend test using 0.05 significance level to be used to assess the existence of a positive dose-response relationship based on the BORRs.
- Survival rate at one year to be calculated in each randomised arm using the Kaplan-Meier method with a corresponding two-sided 95% confidence interval.
- PFS, OS, time to BOR and duration of BOR to be calculated using Kaplan-Meier estimates, and medians with corresponding two-sided 95% confidence intervals will be reported.

*Participant Flow*

The participant flow is shown in Figure 3.

**Figure 3. Participant flow, Study CA184022.**




**Note:** Discontinuation of study drug relates to discontinuation in this study; a patient may have transferred to Study CA184025. "Admin" as the reason for discontinuation relates to those patients who transferred to Study CA184025 for reasons other than PD.

### *Outcomes*

The primary endpoint is shown in Table 8.

**Table 8. Primary endpoint (BORR) data – all randomised patients.**

| | Yervoy | | |
|---|---|---|---|
| | **0.3 mg/kg N=73** | **3 mg/kg N=72** | **10 mg/kg N=72** |
| **BORR[1], n (%)** | 0 | 3 (4.2) | 8 (11.1) |
| 95% CI | (0, 4.9) | (0.9, 11.7) | (4.9, 20.7) |
| **BOR, n (%)** | | | |
| CR | 0 | 0 | 2 (2.8) |
| PR | 0 | 3 (4.2) | 6 (8.3) |
| SD | 10 (13.7) | 16 (22.2) | 13 (18.1) |
| PD | 43 (58.9) | 41 (56.9) | 36 (50.0) |
| Unknown | 20 (27.4) | 12 (16.7) | 15 (20.8) |
| Reason for Unknown | | | |
| Early censoring therapy | 1 (1.4) | 0 | 4 (5.6) |
| No post-baseline assessments | 17 (23.3) | 11 (15.3) | 10 (13.9) |
| No Week 12 assessment | 2 (2.7) | 1 (1.4) | 1 (1.4) |

[1] (Number with CR or PR)/N

Two OS assessments were performed. The initial assessment was at database BORR reporting (at the last treated subject's Week 24 assessment), at which time 25/73 subjects in the 0.3 mg/kg, 25/72 subjects in the 3 mg/kg, and 24/72 subjects in the 10 mg/kg group had died. After database lock, an updated analysis was conducted using data available from additional follow up. At the time of this updated analysis, 42/73 subjects in the 0.3 mg/kg, 43/72 subjects in the 3 mg/kg, and 33/72 subjects in the 10 mg/kg group had died. Results of both assessments are tabulated below.

**Table 9. OS (Initial assessment).**

| | Yervoy | | |
|---|---|---|---|
| | **0.3 mg/kg N=73** | **3 mg/kg N=72** | **10 mg/kg N=72** |
| Median follow-up (months)[1] | 5.06 | 5.70 | 5.55 |
| Interquartile range (25% to 75%), months | (3.25, 6.65) | (3.78, 7.78) | (3.29, 7.44) |
| Number of subjects censored prior to median | 42 | 42 | NA[2] |
| Median OS (months) | 7.95 | 9.07 | NA[2] |
| 95% CI | (6.51, NA[2]) | (8.57, 12.25) | (9.26, NA[2]) |
| Projected 1-year survival rate (%) | 49.30 | 48.79 | 57.83 |
| 95% CI | (33.71, 69.63) | (25.88, 70.09) | (37.67, 73.05) |

[1] Per-protocol follow-up period is period from randomisation date to death or last known alive date per protocol follow-up.

[2] Reason: median was not reached, or censored observations.

**Table 10. OS (Updated assessment).**

| | Yervoy | | |
|---|---|---|---|
| | **0.3 mg/kg N=73** | **3 mg/kg N=72** | **10 mg/kg N=72** |
| Median follow-up (months)[1] | 7.92 | 8.05 | 8.92 |
| Interquartile range (25% to 75%), months | (3.29, 10.78) | (3.91, 11.48) | (3.24, 12.07) |
| Number of subjects censored prior to median | 8 | 4 | 34 |
| Median OS (months) | 8.57 | 8.64 | 14.59 |
| 95% CI | (7.69, 14.49) | (6.87, 12.25) | (6.90, NA[2]) |
| Projected 1-year survival rate (%) | 40.38 | 38.16 | 53.39 |
| 95% CI | (27.06, 53.79) | (25.32, 50.94) | (41.17, 63.71) |

[1] Total follow-up period is period from randomisation date to extended follow-up death or last known alive date where available, otherwise to per-protocol death or last known alive date. End date per extended follow-up may be earlier than per protocol follow-up.

[2] Reason: median was not reached, or censored observations.

***CA184004***

*Methods*

Following screening, there was an induction period (Weeks 1 to Week 24), a maintenance period (Week 24 dose visit until progression or study closure), and a follow up period. Four tumour assessments (radiologic and photographic) were performed at Weeks 12, 16, 20 and 24.

*Study Participants*

Patients aged ≥ 18 with histological diagnosis of malignant melanoma with;

- Measurable unresectable Stage III or IV disease;
- Life expectancy ≥ 4 months; ECOG PS 0-1;
- Adequate renal, hepatic, and haematologic function.

At least four weeks must have elapsed since the last chemotherapy, immunotherapy, hormonal therapy, radiotherapy, or major surgery and the beginning of protocol therapy. At least six weeks must have elapsed for treatment with nitrosoureas, mitomycin C and liposomal doxorubicin;

Toxicity related to prior therapy must either have returned to Grade ≤ 1, baseline or been deemed irreversible

*Randomisation:* Patients were randomised 1:1 to 3 mg/kg or 10 mg/kg Yervoy, stratified by use of prior immunotherapy for malignant melanoma.

*Prohibited therapy:* Patients could not use any of the following therapies during the study:

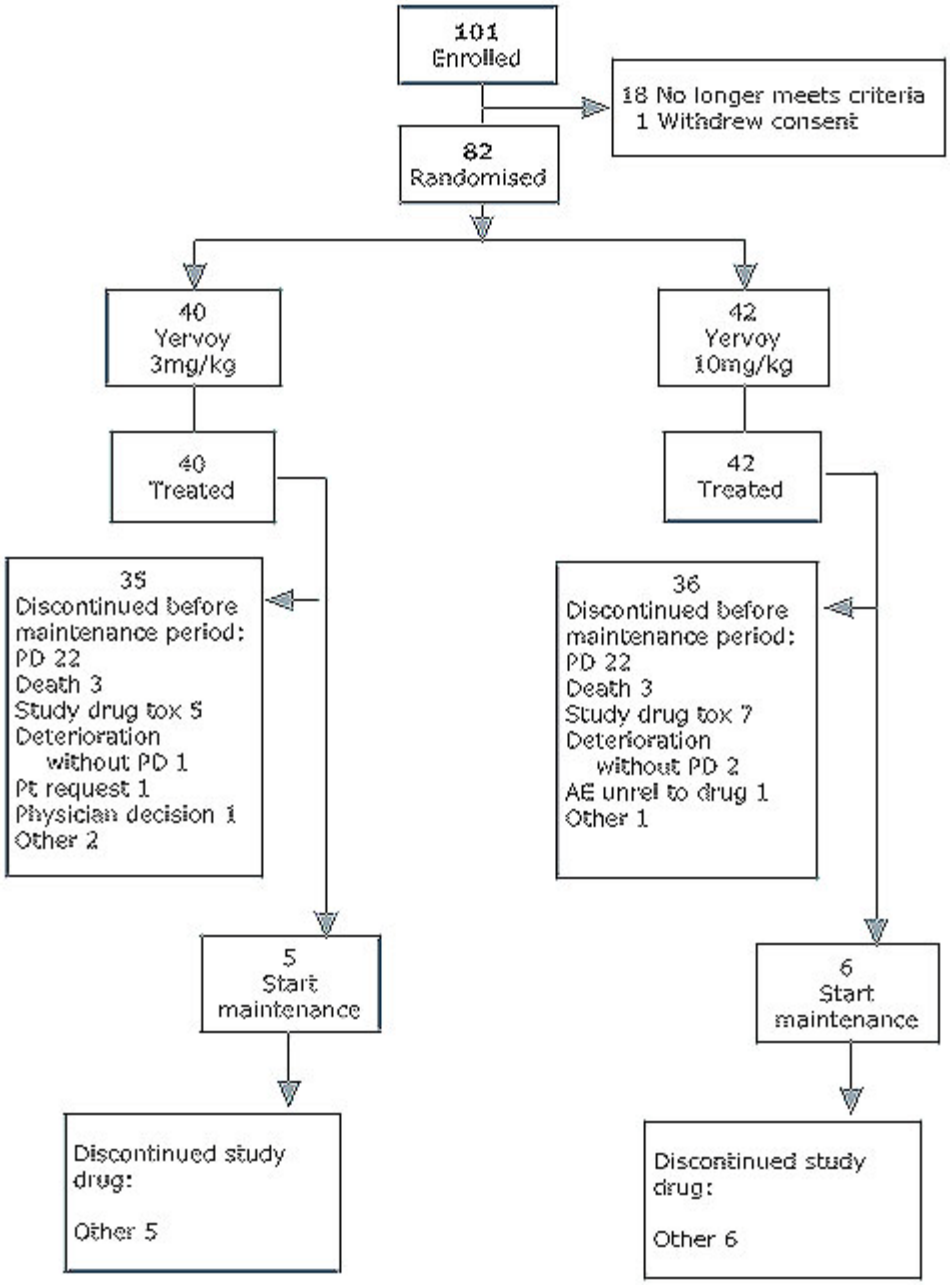
- interleukin-2, interferon, or other non-study antimelanoma immunotherapy regimens;
- cytotoxic chemotherapy;
- immunosuppressive agents; CTLA-4 agonists or antagonists; investigational therapies;
- chronic systemic steroids (except stable doses of hormone replacement therapy), including corticosteroids (unless for Grade 2-4 diarrhoea or Grade 3-4 other immune related adverse event (irAE), in which case treatment with blinded oral study medication was discontinued);
- surgery or radiotherapy;
- drugs generally accepted to have a risk of causing torsades de pointes.

*Primary efficacy endpoint:* BORR, based on investigator assessment of tumour response. Other stipulated efficacy variables included OS, survival rate at 1 year and PFS.

*Statistical methods:* For the objectives of principal interest here, the statistical methods were similar to those used in Study CA184022 above.

*Participant Flow:* The participant flow is shown in Figure 4.

**Figure 4. Participant flow, Study CA184004**




**Note:** Discontinuation of study drug relates to discontinuation in this study; a patient may have transferred to Study CA184025. "Other" as the reason for discontinuation relates to study closure.

*Outcomes*

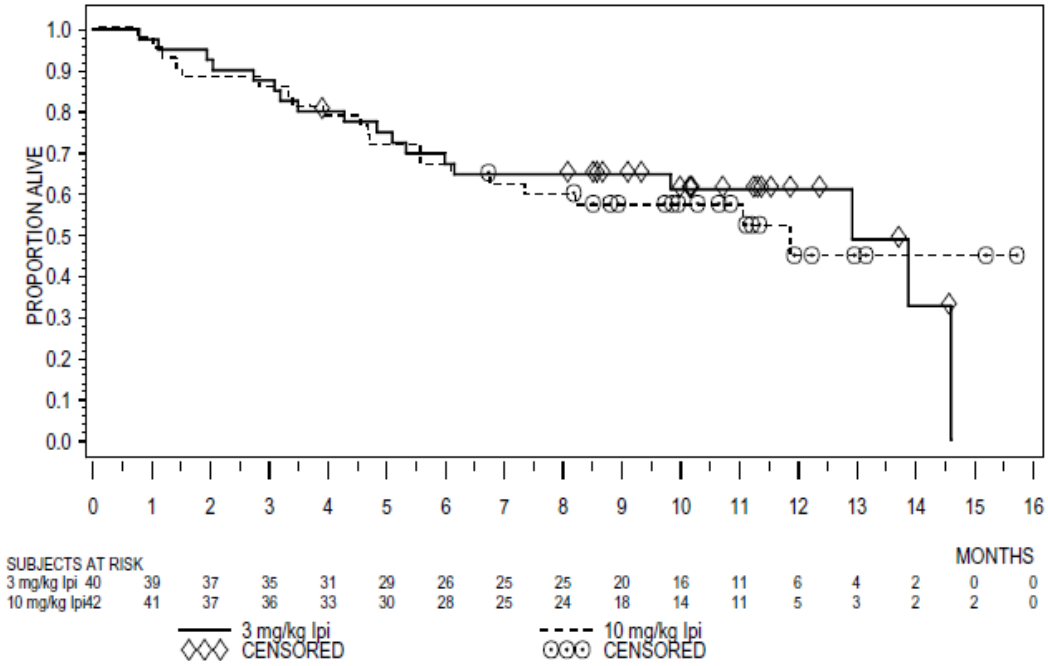
BORR, PFS and OS for randomised subjects by treatment group are shown in Table 11 below with OS shown in Figure 5.

**Table 11. BORR, BOR, PFS and OS**

| | Yervoy | |
|---|---|---|
| | **3 mg/kg N=40** | **10 mg/kg N=42** |
| **BORR, n (%)** | 3 (7.5) | 5 (11.9) |
| 95% CI[1] | (1.6, 20.4) | (4.0, 25.6) |
| **BOR, n (%)** | | |
| CR | 0 | 1 (2.4) |
| PR | 3 (7.5) | 4 (9.5) |
| SD | 10 (25.0) | 3 (7.1) |
| PD | 19 (47.5) | 24 (57.1) |
| Unknown | 8 (20.0) | 10 (23.8) |
| Reason for Unknown | | |
| Censored due to surgical treatment of index lesions | 4 | 5 |
| No post-baseline assessments | 4 | 5 |
| **PFS** | | |
| Progressed or died, n(%) | 28 (70.0) | 32 (76.2) |
| Median (months) (95% CI) | 2.63 (2.56, 3.88) | 2.56 (2.50, 2.66) |
| PFS accounting for subsequent therapy prior to progression[2] | | |
| Progressed or died, n(%) | 28 (70.0) | 32 (76.2) |
| Median (months) (95% CI) | 2.63 (2.56, 3.88) | 2.56 (2.50, 2.66) |
| PFS rate truncated at Week 12 (%) | 57.64 | 40.54 |
| PFS rate truncated at Week 24 (%) | 21.43 | 12.97 |
| PFS rate at 1 year (%) | 22.22 | 13.51 |
| PFS rate truncated at Week 12 accounting for early progression (%)[3] | 61.11 | 40.54 |
| **OS** | | |
| Median survival, months | 12.9 | 11.8 |
| Estimated 1-year survival rate, % (95% CI) | 60.9 (41.7, 74.9) | 44.2 (24.1, 64.1) |

[1] Two-sided exact (Clopper & Pearson); [2] In this analysis, patients who received subsequent cancer therapy prior to progression were censored at the last TA before the earliest start date of subsequent therapy.; [3] In this analysis, radiographic, photographic, or clinical evidence of progression before Week 12 made a patient PD. No truncation was performed.

**Figure 5. Overall Survival by treatment – ITT population**




## Main Clinical Study - Study MDX010-20

Only one of the studies included in the current submission (MDX010-20) was designated "pivotal" by the sponsor. However, the sponsor's *Clinical Overview* and the sponsor's *Study Protocol* for MDX010-20 (including *Protocol Amendment 06,* 15 January 2009) were inconsistent on this matter.

### *Sponsor comment*

*Study MDX010-20 was conducted between 2004 and 2009 with the aim to determine whether ipilimumab could offer a meaningful benefit to patients with pretreated advanced melanoma. The study underwent 6 amendments with an evolution of its core efficacy parameters including the change of the primary endpoint to OS. The sponsor acknowledged the change in language in describing the study as pivotal in January 2009. However, the unprecedented survival advantage demonstrated after completion of the study in November 2009, together with the robust design of MDX010-20, characterize the study as pivotal. The design and results of MDX010-20 are robust, based on the following:*

*1) The definitive primary endpoint of OS*
*2) Double blinding*
*3) The multicentre nature of the study (> 150 sites in 13 countries)*
*4) Two independent comparisons (ipilimumab +/- gp100 versus control)*
*5) Medically relevant results of 32% to 34% risk reduction for death from melanoma*
*6) Statistically persuasive results with hazard ratios of 0.68 (p=0.0004) and 0.66 (p=0.0026)*
*7) Internal consistency through statistically positive results on all efficacy endpoints and consistent clinical effects across all known prognostic patient subsets*

Table 12 below summarises this study.

**Table 12. Major study MDX010-20.**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects by arm: Treated (Completed *per* protocol) | Duration | Gender (Age): | Diagnosis and main inclusion criteria | Primary outcome variables |
|---|---|---|---|---|---|---|---|---|---|
| MDX010-20<br><br>(Sep 2004 - Oct 2009) | 125 sites in Europe, North America, South America, and Africa | Phase III, double-blind, parallel group, randomised. | (A) Yervoy + gp100[1] | Compare OS of patients administered Yervoy + gp100 melanoma peptide vaccine versus those administered vaccine alone.[4] | 381 (315) | Induction cycle 12 wks.<br>This could be repeated.<br><br>Patients off study treatment followed 3-monthly until 481 deaths in study. | 401M, 275F<br>(age 19-90, median 57)<br><br>(in the ITT population) | HLA-A2*0201-positive subjects with unresectable Stage III or Stage IV melanoma who, previously treated with designated regimen(s), had (1) relapsed following an objective response (PR/CR); (2) failed to demonstrate an objective response; or (3) could not tolerate such a regimen due to unacceptable toxicity. | OS[4] |
| | | | (B) Yervoy[2] | | 131 (106) | | | | |
| | | | (C) gp100[3] | | 131 (101) | | | | |

[1] Yervoy (3 mg/kg q3 weeks up to 4 doses) in combination with gp100 (2 mg Peptide A and 2 mg Peptide B q3 weeks up to 4 doses).

[2] Yervoy (3 mg/kg q3 weeks up to 4 doses) plus vaccine placebo (q3 weeks up to 4 doses).

[3] Yervoy placebo (q3 weeks up to 4 doses) plus gp100 (2 mg Peptide A and 2 mg Peptide B q3 weeks up to 4 doses).

[4] By protocol amendment dated 15 January 2009.

### *Study MDX010-20*

*Objectives*

"Primary objective: The primary objective of this study in patients with unresectable Stage III or IV melanoma who have been previously treated with other agents, is to compare overall survival of patients administered MDX-010 in combination with gp100 melanoma peptide vaccine versus those administered gp100 melanoma peptide vaccine alone."

"The secondary objectives of the study include:

- Comparison of overall survival of patients administered MDX-010 in combination with gp100 melanoma peptide vaccine versus. those administered MDX-010 monotherapy, and of patients administered vaccine monotherapy versus those administered MDX-010 monotherapy;
- Evaluation of safety; and
- Determination of best overall response rate (BORR), major durable response rate, duration of response, progression-free survival, time-to-progression, and health-related Quality of Life."

*Study Participants:*

Patients aged ≥ 18 with histological diagnosis of malignant melanoma with the following;

- Measurable unresectable Stage III or IV disease;
- Positive for HLA-A*0201[14];
- Must have demonstrated one of the following in response to ≥ 1 cycle of ≥ 1 regimens containing ≥ 1 of IL-2, DTIC, temozolamide, fotemustine or carboplatin:

  1) relapse following an objective response (PR/CR);

  2) failed to demonstrate an objective response; or

  3) inability to tolerate treatment due to unacceptable toxicity.
- At least 28 days since treatment such as chemotherapy, biochemotherapy, surgery and radiation.
- Life expectancy ≥ 4 months; ECOG performance status of 0 or 1;
- Required values for initial laboratory tests: WBC ≥ 2500/µL; neutrophils ≥ 1500/µL; platelets ≥ 100 x $10^3$/µL; haemoglobin ≥ 10 g/dL; haematocrit ≥ 30%; creatinine ≤ 2 x ULN; AST < 2 x ULN (except patients with AST ≤ 5 x ULN that was attributed to liver metastases); bilirubin < 2 x ULN (except patients with Gilbert's Syndrome, who must have a total bilirubin < 3.0 mg/dL).

[14] The Introduction explained:

"Use of gp100 in MDX010-20 required that the study population be restricted to HLA-A2*0201-positive individuals. Immune response to the 2 component epitopes of the gp100 vaccine was HLA-A2-restricted when originally identified in patient melanoma specimens. In subsequent vaccine design, HLA-A2-restriction of the 2 synthetic 9-amino acid epitopes of gp100 was accomplished using a common A2 subtype allele, A*0201. Therefore activity of the vaccine is limited to the A2*0201-positive population. Unlike the gp100 control, the direct mechanism of action for ipilimumab is not HLA-dependent (the CTLA-4 receptor-ligand interaction is HLA-independent)."

*Randomisation:* Patients enrolled into the study were stratified on the basis of baseline TNM status[15] (M0, M1a, or M1b versus M1c) and prior treatment with IL-2, then randomised 1:3:1 to receive melanoma peptide vaccine monotherapy, Yervoy in combination with melanoma peptide vaccine or Yervoy monotherapy.

*Blinding*: A double placebo technique was used.

*Prohibited therapy:* Subjects could not use any of the following therapies during the course of the study:

- IL-2, interferon or other non-study antimelanoma immunotherapy regimens;
- cytotoxic chemotherapy;
- immunosuppressive agents; other investigational therapies;
- or chronic use of systemic corticosteroids.

However, subjects with progressive disease who were not eligible for continued treatment or for re-induction were permitted to receive non-study antimelanoma medications at the discretion of the Investigator.

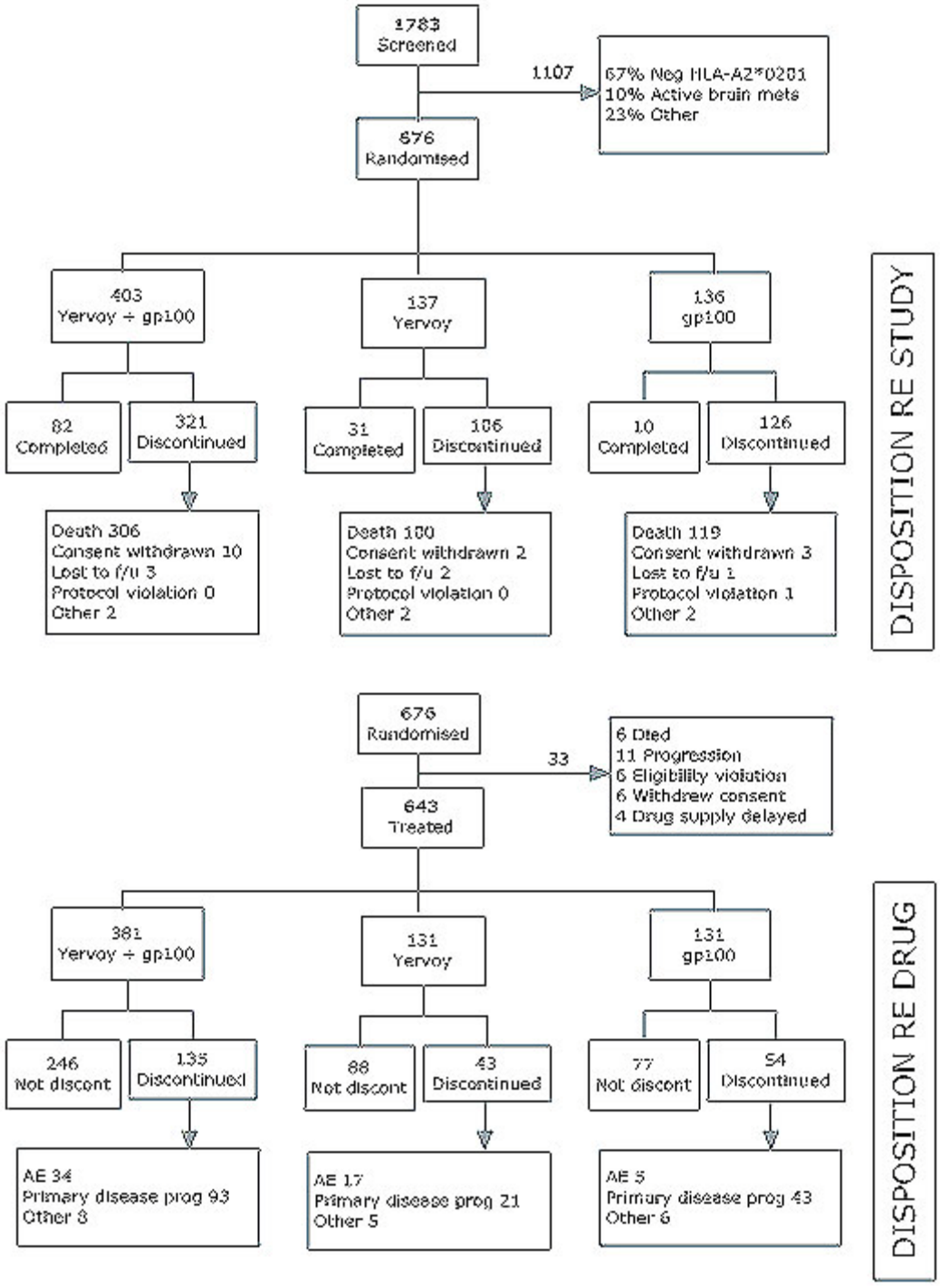
*Primary efficacy endpoint:* Comparison of overall survival of patients administered MDX-010 in combination with gp100 melanoma peptide vaccine versus those administered gp100 melanoma peptide vaccine alone.

*Statistical methods:* Planned analysis was as follows. Overall survival (time-to-death) difference between combination therapy and vaccine monotherapy, compared using stratified log-rank test along with the depiction of the Kaplan-Meier survival curve. If a patient has not died, the patient will be censored at the last known alive date. The median estimates with 95% confidence intervals to be computed using the Brookmeyer and Crowley method. The Cox proportional hazards model would be used to evaluate the effect of some prognostic factors and baseline disease status.

*Participant Flow:* Participant flow is shown in Figure 6

[15] The TNM Classification of Malignant Tumors (TNM) is a cancer staging system that describes the extent of cancer in a patient's body. **T** describes the size of the tumor and whether it has invaded nearby tissue, **N** describes regional lymph nodes that are involved, **M** describes distant metastasis (spread of cancer from one body part to another). The TNM staging system uses the size and extension of the primary tumor, its lymphatic involvement, and the presence of metastases to classify the progression of cancer

**Figure 6. Study MDX010-20.Participant flow.**




### *Outcomes*

Participants were well matched demographic characteristics; the mean age was 55.6-57.4 (range 19-90) years, 54-61% were males, 94.2-94.9 were White and 69.1-72.2% were in the <65 years of age group . Baseline characteristics and prior antineoplastic theraphies are tabulated in Tables 13 and 14. OS is shown in Table 15 and Figure 7.

**Table 13. Study MDX010-20. Base line characteristics**

| Characteristic | Yervoy + gp100 (n=403) | Yervoy (n=137) | gp100 (n=136) |
|---|---|---|---|
| Duration of melanoma (years) | | | |
| n | 401 | 137 | 136 |
| Mean (Min-Max) | 5.09 (0.2-38.9) | 4.34 (-0.0-35.9) | 5.65 (0.3-31.2) |
| Median | 3.14 | 2.93 | 3.67 |
| M stage | | | |
| M0 | 5 (1.2) | 1 (0.7) | 4 (2.9) |
| M1a | 37 (9.2) | 14 (10.2) | 11 (8.1) |
| M1b | 76 (18.9) | 22 (16.1) | 23 (16.9) |
| M1c | 285 (70.7) | 100 (73.0) | 98 (72.1) |
| Prior IL-2 | | | |
| No | 315 (78.2) | 105 (76.6) | 103 (75.7) |
| Yes | 88 (21.8) | 32 (23.4) | 33 (24.3) |
| LDH | | | |
| > ULN | 148 (36.7) | 53 (38.7) | 54 (39.7) |
| ≤ ULN | 255 (63.3) | 84 (61.3) | 82 (60.3) |

Some 99% of patients had received IL-2, DTIC, temozolomide, carboplatin or fotemustine. Prior antineoplastic therapies related to study indication are summarized below.

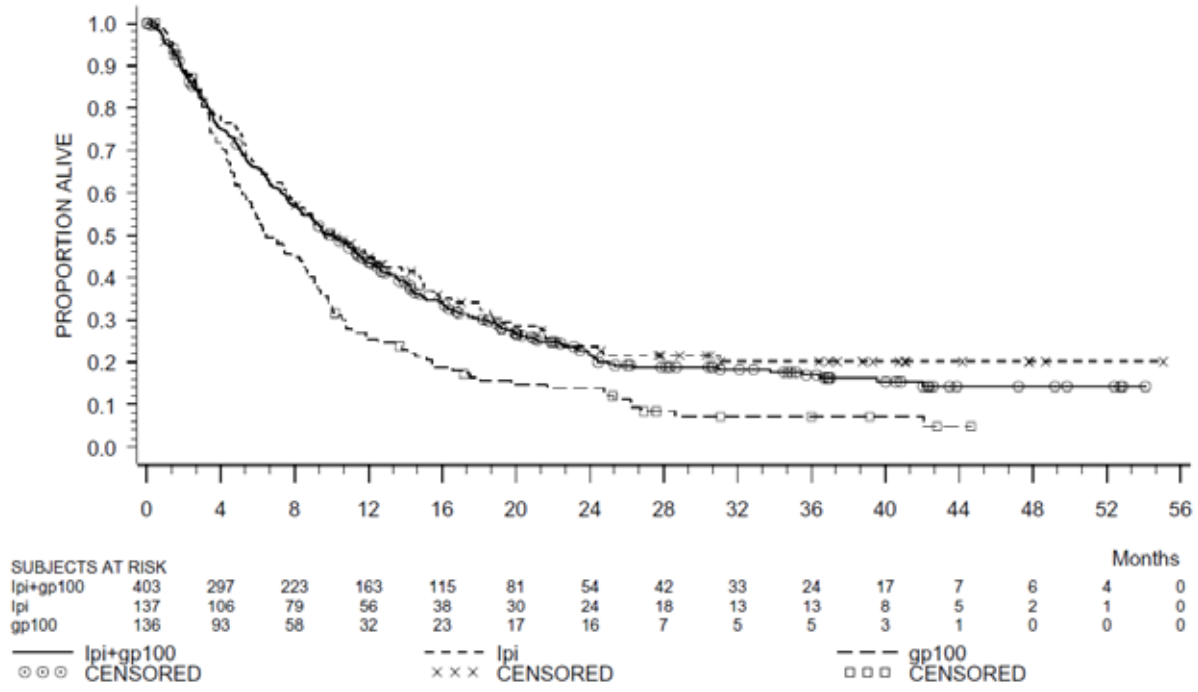
**Table 14. Study MDX010-20. Prior antineoplastic therapies.**

| Characteristic | Yervoy + gp100 (n=403) | Yervoy (n=137) | gp100 (n=136) |
|---|---|---|---|
| Surgery (n%) | 401 (99.5) | 137 (100.0) | 136 (100.0) |
| Radiotherapy (n%) | 154 (38.2) | 60 (43.8) | 52 (38.2) |
| Medication (n%) | 403 (100.0) | 137 (100.0) | 136 (100.0) |
| Number of prior medications | | | |
| Median (Min-Max) | 2.0 (1-10) | 2.0 (1-10) | 2.0 (1-9) |
| Therapy type (n%) | | | |
| Chemotherapy | 370 (91.8) | 124 (90.5) | 127 (93.4) |
| Immunotherapy | 203 (50.4) | 61 (44.5) | 80 (58.8) |
| Other | 34 (8.4) | 13 (9.5) | 13 (9.6) |
| Biologics | 30 (7.4) | 15 (10.9) | 7 (5.1) |

**Table 15. Overall Survival by treatment. ITT population.**

| | Yervoy + gp100 (n=403) | Yervoy (n=137) | gp100 (n=136) |
|---|---|---|---|
| Number of events | 306 | 100 | 119 |
| Median, months (95% CI) | 9.95 (8.48, 11.50) | 10.12 (8.02, 13.80) | 6.44 (5.49, 8.71) |
| Estimated 12-month survival, % (95% CI) | 43.6 (38.6, 48.5) | 45.6 (37.0, 54.1) | 25.3 (18.1, 32.9) |
| Estimated 24-month survival, % (95% CI) | 21.6 (17.2, 26.1) | 23.5 (16.0, 31.5) | 13.7 (8.0, 20.0) |
| HR versus gp100 (95% CI) | 0.68 (0.55, 0.85) | 0.66 (0.51, 0.87) | |
| Log-rank p value versus gp100 | 0.0004 | 0.0026 | |
| HR versus Yervoy (95% CI) | 1.04 (0.83, 1.30) | | |
| Log-rank p value versus Yervoy | 0.7575 | | |

**Figure 7. Overall Survival by treatment – ITT population**




Internal consistency was evident, with positive outcomes across relevant prognostic sub-populations and for secondary endpoints (BORR, DCR, and PFS). Data relating to these secondary endpoints are summarised in Table 16 for the ITT population.

| **Table 16. Secondary endpoints. ITT population.** | **Yervoy + gp100 (n=403)** | **Yervoy (n=137)** | **gp100 (n=136)** |
|---|---|---|---|
| **BORR, n (%)**[1] | 23 (5.7) | 15 (10.9) | 2 (1.5) |
| 95% CI | (3.7, 8.4) | (6.3, 17.4) | (0.2, 5.2) |
| P value versus gp100[2] | 0.0433 | 0.0012 | |
| P value versus Yervoy[2] | 0.0402 | | |
| **BOR, n (%)** | | | |
| CR | 1 (0.2) | 2 (1.5) | 0 |
| PR | 22 (5.5) | 13 (9.5) | 2 (1.5) |
| SD | 58 (14.4) | 24 (17.5) | 13 (9.6) |
| PD | 239 (59.3) | 70 (51.1) | 89 (65.4) |
| NE | 83 (20.6) | 28 (20.4) | 32 (23.5) |
| **DCR, n(%)**[3] | 81 (20.1) | 39 (28.5) | 15 (11.0) |
| 95% CI | (16.3, 24.3) | (21.1, 36.8) | (6.3, 17.5) |
| P value versus gp100[2] | 0.0179 | 0.0002 | |
| P value versus Yervoy[2] | 0.0429 | | |
| **PFS** (non-parametric analysis)[4] | | | |
| Number of events | 371 | 122 | 127 |
| Median (months) (95% CI) | 2.76 (2.73, 2.79) | 2.86 (2.76, 3.02) | 2.76 (2.73, 2.83) |
| HR versus gp100 (95% CI) | 0.81 (0.66, 1.00) | 0.64 (0.50, 0.83) | |
| HR versus Yer (95% CI) | 1.25 (1.01, 1.53) | | |
| | | | |
| PFS rate at Week 24 (95% CI) | 0.164 (0.129, 0.203) | 0.240 (0.171, 0.315) | 0.100 (0.056, 0.159) |

[1] Non-responder was defined as SD, PD, unknown or missing. Response was defined as a confirmed CR or PR.

[2] The comparison for P-values was performed between Yer + gp100 versus gp100, Yer versus gp100, and Yer + gp100 versus Yer. P-values were computed using CMH test stratified by baseline M-stage at randomisation (M0, M1a, M1b versus M1c) and prior IL-2 treatment (Yes versus No).

[3] Disease control rate (DCR) was defined as above.

[4] Cox model for HRs stratified by M-stage at randomisation and prior treatment with IL-2.

*Re-induction*

The Protocol provided for repetition of the treatment cycle. Eligibility criteria were as follows:

Efficacy: Subjects who in response to treatment Cycle 1 have evidence for:

- stable disease of ≥ 3 months duration (beginning Week 12) or an initial objective response (PR or CR) to the first cycle of therapy; and
- who have subsequent evidence for PD

Safety: subjects were excluded if they experienced

- a Grade 3 non-skin irAE except for endocrinopathies where clinical symptoms are controlled with appropriate hormone replacement therapy; or
- any related Grade 4 toxicity of any organ

Re-induction treatment was initiated in 40 patients, none of whom should have been excluded on the basis of the safety criteria but some of whom failed to meet the efficacy criteria. Of these 40, three were excluded on the basis that they had not met the criteria for inclusion in the Per Protocol (PP) population and five were excluded on the basis of a BOR of PD at Week 24. Among the remaining 32, no formal PD assessment was documented in 10, two had SD at Week 24 but for <3 months, and in one the BOR at Week 24 was unknown. However, these 32 were analysed for efficacy and the results are tabulated below in Table 17.

**Table 17. Re-induction. Efficacy results.**

| | **Yervoy + gp100 (N=23)** | **Yervoy (N=8)** | **gp100 (N=1)** |
|---|---|---|---|
| **BOR, n (%)[1]** | | | |
| CR | 0 | 1 (12.5) | 0 |
| PR | 3 (13.0) | 2 (25.0) | 0 |
| SD | 12 (52.2) | 3 (37.5) | 0 |
| PD | 8 (34.8) | 2 (25.0) | 1 (100.0) |

[1] BOR for the re-induction phase was determined from Cycle 2 on.

*Quality of life*

The following health-related quality of life (HRQoL) instruments were included in the protocol: European Organization for Research and Treatment of Cancer Quality of Life Questionnaire C-30 (EORTC QLQ C-30)[16], Short Form-36 (SF-36[17]) Health Survey, FACIT Fatigue scale[18], and

[16] The EORTC QLQ-C30 is a questionnaire developed to assess the quality of life of cancer patients. It is a copyrighted instrument, which has been translated and validated into 81 languages and is used in more than 3,000 studies worldwide. It is supplemented by disease specific modules for e.g. Breast, Lung, Head & Neck, Oesophageal, Ovarian, Gastric, Cervical cancer, Multiple Myeloma, Oesophago-Gastric, Prostate, Colorectal Liver Metastases, Colorectal and Brain cancer which are distributed from the EORTC Quality of Life Department.

[17] The SF-36 is a multi-purpose, short-form health survey with only 36 questions. It yields an 8-scale profile of functional health and well-being scores as well as psychometrically-based physical and mental health summary measures and a preference-based health utility index. It measures eight domains of health: physical functioning, role limitations due to physical health, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It yields scale scores for each of these eight health domains, and two summary measures of physical and

Symptom Distress Scale[19] (SDS). However, summary and analysis was carried out only for the EORTC QLQ-C30 instrument, which comprises 15 questions on functional scales, 13 questions on symptom scales and two questions on global health status scale. Higher scores for all functional scales and Global Health Status indicated better HRQoL; an increase from baseline for all functional scales and global health status indicated improvement in HRQoL compared to baseline. Lower scores for symptom scales indicated better status and a decline from baseline for symptom scales indicated improvement in symptoms compared to baseline.

Questionnaire completion rate at baseline was approximately 95% (362/381; 125/131; 125/131) for the Yervoy plus gp100, Yervoy monotherapy and gp100 monotherapy groups, respectively. On-study completion rates dropped in subsequent weeks to 236/381, 85/131 and 80/131 at Week 12, respectively, and the amount of missing HRQoL data further increased after Week 12. Changes in HRQoL scores from baseline to Week 12 by treatment group are summarized below.

mental health. It is a generic measure, as opposed to one that targets a specific age, disease, or treatment group. The SF-36 is available for two recall periods: standard (4-week recall) and acute (1-week recall).

[18] Functional Assessment of Chronic Illness Therapy (FACIT): The FACIT fatigue score has a range of 0 to 52, and in this case a higher total score is better. The questionnaire includes 13 questions regarding how fatigue affected the subject's activities over the previous 7 days. Each question is answered on a scale of 0 to 4, where 0 = not at all and 4 = very much.

[19] Developed as a cancer-specific tool for assessing symptoms. Subjects respond about how they have been feeling during the preceding week. Validation with chronic disease (primarily cancer) patients. Also used in breast disease and pregnancy.

**Table 18. HRQoL scores.**

| Measurement | LS Means (95% CI) | | |
|---|---|---|---|
| | Yervoy + gp100 (n=381) | Yervoy (n=131) | gp100 (n=131) |
| Global QoL[1]<br>n | -7.4 (-10.4, -4.3)<br>226 | -8.8 (-13.5, -4.1)<br>83 | -10.4 (-15.3, -5.5)<br>77 |
| Physical[2]<br>n | -6.2 ( -8.9, -3.4)<br>226 | -5.1 ( -9.4, -0.8)<br>83 | -10.1 (-14.5, -5.7)<br>78 |
| Role<br>n | -9.3 (-13.4, -5.3)<br>226 | -10.5 (-16.8, -4.1)<br>83 | -13.7 (-20.2, -7.2)<br>78 |
| Cognitive<br>n | -3.1 ( -5.8, -0.3)<br>227 | -4.3 ( -8.6, 0.0)<br>83 | -3.4 ( -7.8, 1.0)<br>78 |
| Emotional<br>n | -1.5 ( -4.2, 1.1)<br>227 | -3.6 ( -7.7, 0.6)<br>83 | -1.5 ( -5.8, 2.7)<br>78 |
| Social<br>n | -5.6 ( -9.2, -2.0)<br>227 | -7.5 (-13.2, -1.9)<br>83 | -4.2 (-10.1, 1.8)<br>76 |
| Fatigue[3]<br>n | 10.6 ( 7.0, 14.1)<br>226 | 12.5 ( 7.0, 18.1)<br>82 | 14.5 ( 8.8, 20.2)<br>78 |
| Nausea and vomiting<br>n | 4.6 ( 1.9, 7.3)<br>226 | 3.1 ( -1.0, 7.3)<br>83 | 4.4 ( 0.1, 8.7)<br>78 |
| Pain<br>n | 5.6 ( 2.0, 9.3)<br>227 | 7.9 ( 2.2, 13.6)<br>83 | 11.9 ( 6.0, 17.7)<br>78 |
| Dyspnoea<br>n | 3.5 ( 0.0, 6.9)<br>222 | 5.3 ( -0.1, 10.7)<br>81 | 9.1 ( 3.6, 14.6)<br>77 |
| Sleep disturbance<br>n | 6.5 ( 2.3, 10.7)<br>225 | 10.1 ( 3.6, 16.6)<br>83 | 11.0 ( 4.3, 17.8)<br>76 |
| Appetite loss<br>n | 8.5 ( 4.4, 12.5)<br>225 | 11.6 ( 5.3, 17.9)<br>83 | 10.3 ( 3.8, 16.8)<br>78 |
| Constipation<br>n | 5.2 ( 1.7, 8.7)<br>225 | 1.9 ( -3.5, 7.2)<br>83 | 11.8 ( 6.2, 17.4)<br>77 |
| Diarrhoea<br>n | 6.4 ( 2.8, 10.1)<br>223 | 9.1 ( 3.4, 14.7)<br>82 | 2.1 ( -3.7, 7.9)<br>78 |
| Financial impact<br>n | 0.0 ( -3.2, 3.2)<br>226 | 3.1 ( -1.9, 8.1)<br>83 | 1.7 ( -3.5, 6.9)<br>76 |

[1] Global QoL score is a transformation of the average raw scores of certain other scores, with 0 the worst and 100 the best.

[2] Functional scales: Physical (1 to 5), Role (6, 7), Cognitive (20, 25), Emotional (21 to 24), Social (26, 27). Each score is the transformation of the average raw scores with 0 the worst and 100 the best.

[3] Symptom scales or items include: Fatigue (10, 12, 18), Nausea and vomiting (14, 15), Pain (9, 19), Dyspnoea (8), Sleep disturbance (11), Appetite loss (13), Constipation (16), Diarrhoea (17), Financial impact (28). Each score is a transformation of the item score(s) with 0 as no symptom at all and 100 very severe.

## Supportive studies

Supportive studies are shown in Tables 19 and 20.

**Table 19. Supportive studies. (Table continued across four pages)**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects by arm: Treated (Completed per protocol) | Duration | Gender, age, weight | Diagnosis and main inclusion criteria | Primary outcome variables |
|---|---|---|---|---|---|---|---|---|---|
| CA184007<br><br>(Dec 2005 -Dec 2007) | 11 sites in Europe, North America, and South America | Phase II randomised, double-blind, placebo-controlled, comparison of safety of Yervoy administered with or without prophylactic oral budesonide. | **Induction period**[3,4]<br>(A) Y[1] at weeks 1, 4, 7, 10;<br>+ bud[2]<br>(B) Y at weeks 1, 4, 7, 10;<br>+ pbo<br>**Maintenance period**<br>Y at week 24 then every 12 weeks[5]. | Estimate the rate of Grade ≥ 2 diarrhoea in patients treated<br>with IV Yervoy at 10 mg/kg given with either prophylactic oral budesonide or placebo. | | Database lock for BORR determination: when last pt reached 24 wks[6].<br>Follow-up (3-monthly contact) continued indefinitely. | 115 randomised and treated with Yer: 81M, 34F; mean age 57.1 (sd 13); mean weight 80.6kg (sd 16).<br>Patients were randomised 1:1 to budesonide or pbo, stratified by use of prior immunotherapy for melanoma. | Measurable, stage III (unresectable) or IV melanoma; life expectancy ≥ 4 months; ECOG PS 0 or 1. | BORR.<br><br>Tumour assessments were performed every 4 weeks starting at Week 12 and continuing through Week 24[7]. |

[1] Y = Yervoy 10mg/kg IV over 90min. [2] Budesonide oral capsules 9mg daily weeks 1-12, 6mg daily weeks 13-14, 3mg daily weeks 15-16. [3] Subjects with Grade ≥ 2 diarrhoea or other irAEs were to be discontinued from blinded oral study medication. [4] Patients with PD at week 12 were discontinued and entered follow-up; others monitored for further 12 weeks then considered for entry to Maintenance period. Two categories of patient could continue in the maintenance period: (1) patients eligible for continued dosing; these were patients who had no documented disease progression throughout the induction period, including Wk 24, had an ECOG PS of 0-1 at Wk 24, and had no toxicity requiring discontinuation of study therapy; (2) patients who were not eligible for dosing and were only eligible for tumour assessments; these were patients who had no documented disease progression throughout the induction period to Wk 24, but experienced toxicity requiring discontinuation of study therapy.

**Table 19. Supportive studies**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects by arm: Treated (Completed) | Duration | Gender, age, weight | Diagnosis and main inclusion criteria | Primary outcome variable |
|---|---|---|---|---|---|---|---|---|---|
| CA184008<br><br>(Jun 2006-Dec 2007) | 50 in Europe and North America | Phase II, open, single-arm. | Yer 10mg/kg IV over 90min.<br><br>Induction period[4]: doses at weeks 1, 4, 7, 10.<br><br>Maintenance period: doses at week 24 then every 12 weeks[5]. | Assess efficacy and safety. | | Database lock for BORR determination: when last pt reached 24 wks[6].<br><br>Follow-up (3-monthly contact) continued indefinitely. | 155 enrolled and treated: 80M, 75F; mean age 57.5 (sd 13); mean weight 78.1kg (sd 16) | Patients with measurable, stage III (unresectable) or IV melanoma, who had progressed on previous chemotherapy. | BORR.<br><br>Primary determination of imaged-based endpoints was based on the IRC assessment[7]. |

[5] "Until progression, study drug-related toxicity leading to ipilimumab discontinuation, start of subsequent non-ipilimumab therapy, withdrawal of consent, or discontinuation due to database lock for BORR reporting."

[6] Patients who had not progressed at that time and all patients who had a response of stable disease (SD) or better at Week 12 and who subsequently progressed were offered, at investigator's discretion, entry in a separate protocol, CA184025. Note that at the time of database lock, the duration of treatment for patients who had entered the maintenance phase varied depending on the start of maintenance in relation to the last patient's first dose. If a patient started maintenance 24 wks before the last patient's first dose, (s)he could have been on maintenance for 48 wks.

[7] The assessment of tumour response was based on measurable index and non-index lesions, and the presence or absence of new lesions. See tables below.

**Table 19. continued.**

| Index lesion assessment | Non- Index lesion assessment | New lesions | Overall Response |
|---|---|---|---|
| CR | CR | No | CR |
| CR | IR/SD | No | PR |
| PR | CR or IR/SD | No | PR |
| SD | CR or IR/SD | No | SD |
| PD | Any | Yes or No | PD |
| Any | PD | Yes or No | PD |
| Any | Any | Yes | PD |

| Grade of response | Definition (for index lesions) |
|---|---|
| CR | Complete disappearance of all index lesions |
| PR | Decrease of ≥ 50% in the sum of the products of the 2 largest<br>perpendicular diameters of all index lesions relative to baseline |
| SD | Did not meet criteria for complete or partial response, in the<br>absence of progressive disease |
| PD | ≥ 25% increase in the sum of the products of all index lesions (taking as reference the smallest sum recorded at or following baseline) and/or the appearance of any new lesion(s) |

**Table 19. Supportive studies (continued.)**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects by arm: Treated (Completed) | Duration | Gender, age, weight | Diagnosis and main inclusion criteria | Primary outcome variable |
|---|---|---|---|---|---|---|---|---|---|
| MDX010-08<br><br>(Sep 2002-Aug 2005) | 12 in USA | Phase II, open, randomised, 2-arm. | (A) Yervoy 3mg/kg IV over 90 min every 28 days x4 doses. | Assess safety and efficacy of Yervoy. | 39 treated, including 2 who had not been randomised. (11 completed scheduled treatment) | 2 years | ITT pop: 76 enrolled and randomised: 50M, 26F; mean age 60.3 (sd 14); mean weight 83.4kg (sd 16) | Patients with unresectable or metastatic melanoma, who had not received previous chemotherapy or vaccine immunotherapy. | ORR as determined by RECIST and investigator assessment of target and non-target lesions throughout the study. |
| | | | (B) Yervoy as above + DTIC 250 mg/m$^2$ for 5 days every 28 days until intolerance or PD or for a maximum of 6 cycles. | | 35 treated.<br>(16 completed scheduled treatment.) | | | | |
| | | | (C) Crossover group[8] | | 13 crossed over from group (A).<br>(0 completed.) | | | | |

[8] Patients who had been randomised to Yervoy alone and in whom disease progression was observed were permitted the option of changing to combination therapy. This therapy was as for group (B). Crossover was to the beginning of the group B treatment schedule.

**Table 20. Supportive studies. Uncontrolled and other studies of minor relevance (table continued across three pages).**

| Study ID (Study period) | Centres | Design | Posology | Objective | Subjects treated | Duration | Diagnosis and main inclusion criteria |
|---|---|---|---|---|---|---|---|
| CA184042 (Jul 2008-Apr 2009[1]) | 8 in USA | Phase II, open, 2-arm. | Induction: Yervoy 3mg/kg IV over 90 min, wks 1, 4, 7, 10. Maintenance every 12 wks from wk 24. | Assess the disease control rate determined after Week 12 using modified WHO tumour assessment criteria. | Induction: 28 treated (11 received all 4 doses). Maintenance: 4. | Continuing[2] | Melanoma with brain metastases. ECOG PS 0-1. Off corticosteroid ≥ 10 days before starting Yer. |
| MDX010-19 (Mar 2004-Jan 2007) | 1 in USA | Phase II, open, 3-arm, dose escalation | Yer IV over 90 min q3wks. Doses 3, 5 or 9mg were given, increasing in each pt according to protocol. | Assess the clinical response of subjects with metastatic melanoma to intra subject escalating doses of Yer | 88 | Patients received up to 10 doses. Cumulative dose range 297-7095 mg. | Stage 4 melanoma |
| MDX010-13 (Mar 2003-Mar 2006) | 1 in USA | Phase I/2, open, 5-group, dose escalation by group. | Ipi given IV over 90 min q3wks x3. Doses (0.1, 0.3, 1, 2, 3 mg/kg) + IL-2 given to different groups, according to a sequential plan. | Assess activity of the maximum tolerated dose of ipi in combination with interleukin 2 | 36 (24 in the 3 mg/kg group; 3 in each other group) | | Stage 4 melanoma |
| MDX010-05 (Mar 2002-Mar 2006) | 1 in USA | Phase II, open | Yer 3 mg/kg + melanoma vaccine q3 wks or 3 mg/kg followed by 1 mg/kg + melanoma vaccine q3 wks | Assess the development of a clinical response to Yervoy administered with gp100 peptides | 56 | | Stage 4 melanoma that was HLA-A2 positive |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| MDXCTLA4-04<br><br>(Jul 2002-<br>Oct 2004) | 5 in Canada | Phase I, open. | Ipi 3 mg/kg q8 wks x 2 + Melacine +<br>cyclophosphamide | Evaluate safety and tolerability of CTLA4 blocked by ipi in combination with Melacine vaccination | 13 | | Unresectable melanoma |
| MDX010-03<br><br>(Aug 2001-<br>Jun 2005) | 1 in USA | Phase I, open, dose escalation by group | Ipi IV over 90 minutes at Months 0, 1, 2, 3, 4, 5, 8, and 11. Dosages 0.3, 1, or 3 mg/kg given to different groups, according to a sequential plan. | Establish a safety and AE profile for repeated doses of a combination of ipi with a peptide vaccine | 19 (7, 7 and 5 in the 0.3, 1, or 3 mg/kg groups) | | Resected Stage 3 or 4 melanoma |
| MDX010-07 | 11 in USA | Phase I/2, open, randomised. | 3 mg/kg IV q4 wks x 4 ± docetaxel | Determine safety and activity profile of ipi in 4 monthly doses, and of a single dose of cytotoxic chemo in combination with ipi | 44 | | Metastatic hormone-refractory<br>prostate cancer |
| MDX010-17<br><br>(Jun 2004-<br>Nov 2008) | 1 in Holland | Phase I, open,<br>dose escalation | Ipi q4 wks for 24 wks. Cohorts of 3; each assigned<br>escalating doses of 0.3, 1, 3<br>or 5 mg/kg IV. | Evaluate safety and determine MTD of ipi in combination with CG1940 and CG8711 | 28 | | Metastatic hormone-refractory<br>prostate cancer |
| MDX010-21[3] | | Phase I/2,<br>open, dose escalation | Dose escalation at 3, 5, and 10 mg/kg IV every 3<br>wks for 4 doses | Determine the safety profile of escalating doses of ipi with and without a single dose of focal radiotherapy | 70 | | Metastatic hormone-refractory<br>prostate cancer |
| MDX010-12<br>(Jul 2003- | 6 in USA | Phase II, open | 3 mg/kg IV q4 wks x 4 | Establish an initial anti tumour activity profile for ipi using RECIST | 31 | | Stage 4 breast adenocarcinoma that had progressed despite |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Feb 2006) | | | | | | | standard initial therapies |
| MDX010-11<br><br>(Mar 2003-<br>Jan 2006) | 1 in USA | Phase II, open | 3 mg/kg followed by 3 mg/kg or 1 mg/kg q3 wks IV | Determine whether monotherapy with ipi would induce clinically meaningful anti tumour responses | 61 | | Treatment refractory Stage 4 renal cancer |
| MDX010-23<br>(Jun 2005-<br>Apr 2007) | 1 in USA | Phase II, open | 3 mg/kg IV q3 wks x3 | Determine clinical response following treatment with ipi | 6 | | Advanced synovial sarcoma<br>Following treatment |
| MDX010-24<br>(Jul 2005-<br>Dec 2007) | 1 in USA | Phase II, open | Up to 2 courses of: 3 mg/kg IV q3 wks x4 | Assess the clinical response to ipi monotherapy | 27 | | Locally advanced and metastatic<br>pancreatic cancer |

[1] Last patient visit for the Interim Report: 19 Apr 2009.

[2] The Interim Report relates to the first 28 patients treated.

[3] A CSR was not provided for this study.

Q3wks= every 3 weeks

**Note:** Outlines of Studies MDX010-08, CA184042, MDX010-19, MDX010-13, MDX010-05, MDXCTLA4-04, MDX010-03, MDX010-07, MDX010-17, MDX010-21, MDX010-12, MDX010-11, MDX010-23 and MDX010-24 are included in this section for convenience, although the data from these studies relevant to the present application relate to safety rather than efficacy.

**Study CA184007**

This was primarily a study of the value of budesonide in reducing diarrhoea in patients treated with Yervoy. The main secondary objectives were to examine the BORR and OS for the two treatment groups (see Table 19).

***Prohibited Therapy***

Subjects could not use any of the following therapies during the course of the study:

- IL-2, interferon or other non-study anti-melanoma immunotherapy regimens
- Cytotoxic chemotherapy
- Immunosuppressive agents
- CTLA-4 agonists or antagonists
- Investigational therapies
- Chronic systemic steroids (except stable doses of hormone replacement therapy), including corticosteroids (unless for Grade 2-4 diarrhoea or Grade 3-4 other irAE, in which case treatment with blinded oral study medication was discontinued).

***Outcomes***

*Primary*

The rate of Grade ≥ 2 diarrhoea (the primary endpoint) was similar between the treatment groups (budesonide 19/58 patients; placebo 20/57 patients). Among patients with Grade ≥ 2 diarrhoea, 16 subjects in the budesonide group and 18 patients in the placebo group had one event of Grade ≥ 2 diarrhoea. No subject had more than two events. No patients reported gastrointestinal (GI) perforation or required colectomy.

*Secondary*

Response-evaluable subjects (budesonide 50 and placebo 46) included subjects who received any Yervoy dose and had measurable disease, histological diagnosis of malignant melanoma, and ≥1 screening and ≥1 on-study tumour assessment. BORR is shown in Table 21.

**Table 21. BORR. All randomised subjects**

| Response | IRC[4] Assessment | |
|---|---|---|
| | Yervoy+ Budesonide N=58 | Yervoy+ Placebo N=57 |
| BORR, n/N (%)[1] | 7/58 (12.1) | 9/57 (15.8) |
| 95% CI | (5.0, 23.3) | (7.5, 27.9) |
| | | |
| Best overall response, n (%) | | |
| CR | 1 (1.7) | 0 |
| PR | 6 (10.3) | 9 (15.8) |
| SD | 11 (19.0) | 11 (9.3) |
| PD | 34 (58.6) | 29 (50.9) |
| Unknown | 6 (10.3)[2] | 8 (14.0)[3] |

[1] Number of patients with CR or PR / N.

[2] Patients with only baseline measurements (n = 4), no Week 12 assessment (n = 2).

[3] Patients with only baseline measurements (n = 6), no Week 12 assessment (n = 2).

[4] IRC was instituted only after the study was in progress, by Protocol Amendment #5 (approved 12 March 2007) .

**Study CA184008**

This was primarily a study of BORR in subjects with previously treated Stage III (unresectable) or Stage IV melanoma receiving Yervoy 10 mg/kg. A secondary objective was to examine OS (see Table 19).

***Prohibited Therapy***

Subjects could not use any of the following therapies during the course of the study:

- IL-2, interferon or other non-study anti-melanoma immunotherapy regimens
- Cytotoxic chemotherapy
- Immunosuppressive agents
- CD137 agonist[20]
- CTLA-4 agonists or antagonists[21]
- Investigational therapies
- Vaccines (including those for common medical conditions), for up to 1 month pre and

[20] CD137 is a member of the tumour necrosis factor (TNF) receptor family

[21] **C**ytotoxic **T**-**L**ymphocyte **A**ntigen **4**), also known as **CD152** (Cluster of differentiation 152), is a protein that plays an important regulatory role in the immune system. It is a member of the immunoglobulin superfamily, which is expressed on the surface of Helper T cells and transmits an inhibitory signal to T cells. CTLA4 is similar to the T-cell co stimulatory protein CD28, and both molecules bind to CD80 and CD86 (also called B7) on antigen-presenting cells. CTLA4 transmits an inhibitory signal to T cells, whereas CD28 transmits a stimulatory signal.

- post dosing with ipilimumab
- Chronic systemic steroids
- Any systemic anticancer therapy prior to PD on or after Week 12.

### *Outcomes*

*All Treated Subjects* included 155 patients who received any Yervoy dose.

*All Response-evaluable Subjects* included 123 patients who received at least one dose of Yervoy, had measurable disease at baseline as determined by the IRC, had a histological diagnosis of malignant melanoma; received at least one prior therapy containing ≥ one of IL-2, DTIC, paclitaxel, carboplatin, fotemustine or temozolomide; and had ≥ 1 baseline and ≥ 1 post-baseline tumour assessment. BORR is shown in Table 22.

**Table 22. Primary endpoint: BORR. All treated subjects.**

| Response | IRC Assessment |
|---|---|
| BORR, n/N (%)[1] | 9/155 (5.8) |
| 95% CI | (2.7, 10.7) |
| | |
| Best overall response, n (%) | |
| CR | 0 |
| PR | 9 (5.8) |
| SD | 33 (21.3) |
| PD | 87 (56.1) |
| Unknown[2] | 26 (16.8) |

[1] Number of patients with CR or PR / N.

[2] Patients with only baseline measurements (n = 24), no Week 12 assessment (n = 1); early censoring therapy (n = 1).

### Study MDX010-08

This study compared Yervoy with and without DTIC, in patients with unresectable or metastatic melanoma who had not received previous chemotherapy or vaccine immunotherapy (see Table 19).

Objective response data for the ITT population are summarised in Table 23 below.

**Table 23. Response rates. ITT population.**

| | Yervoy N=40 | Yervoy + DTIC N=36 |
|---|---|---|
| **Best overall response (n %)** | | |
| CR | 0 | 2 (5.6) |
| CR ≥ 24 wks | 0 | 2 (5.6) |
| PR | 2 (5.0) | 3 (8.3) |
| PR ≥ 24 wks | 2 (5.0) | 0 |
| SD | 6 (15.0) | 8 (22.2) |
| SD ≥ 24 wks | 2 (5.0) | 0 |
| PD | 28 (70.0) | 20 (55.6) |
| Missing | 4 (10.0) | 3 (8.3) |
| **Best overall response rate (n %)** | | |
| Response (confirmed CR or PR) | 2 (5.0) | 5 (13.9) |
| 95% CI for % response | (0.6, 16.9) | (4.7, 29.5) |
| Non-response | 38 (95.0) | 31 (86.1) |
| Major durable response rate ( ≥ 24 wks) | 2 (5.0) | 2 (5.6) |
| **Disease control rate (CR+PR+SD)** | 8 (20.0) | 13 (36.1) |
| 95% CI for disease control rate | (9.1, 35.6) | (20.8, 53.8) |
| Major durable disease control rate ( ≥ 24 wks) | 4 (10.0) | 2 (5.6) |
| 95% CI for major durable disease control rate | (2.8, 23.7) | (0.7, 18.7) |

## Analyses performed across trials

### *Population pharmacokinetics and exposure-response analyses*

The sponsor submitted a set of analyses (*Ipilimumab Population Pharmacokinetics and Exposure-Response Analyses for Efficacy and Safety in Subjects with Advanced Melanoma*), based on mathematical modelling of data from the Phase II Studies CA184004, CA184007, CA184008 and CA184022.

The presentation of the analyses largely complies with that recommended in the relevant TGA-adopted EU guideline (EMEA 2007[22]).

### *Objectives*

- To characterize the population pharmacokinetics of ipilimumab in patients with advanced melanoma and to quantify the sources and correlates of variability in ipilimumab exposure in this population.
- To characterize the relationship between ipilimumab exposure and measures of efficacy (BOR, immune related clinical activity (irCA) and OS).
- To characterize the relationship between ipilimumab exposure and safety (irAEs).

[22] Guideline on reporting the results from population pharmacokinetic analyses. CHMP/EWP/185990/06.

### *Data sources*

The population pharmacokinetic analysis was conducted with 2089 ipilimumab serum concentration values from 498 subjects who were enrolled in the following four Phase II studies: CA184004, CA184007, CA184008, and CA184022. The PPK model was developed with 1761 observations from 419 subjects enrolled in three of the studies (CA184007, CA184008, and CA184022) and data from 79 subjects enrolled in the remaining study (Study CA184004) was used for external model validation.

Numbers of patients for whom sufficient data points were available for inclusion in the population pharmacokinetic analysis were as follows :

**Table 24. Population pharmacokinetics analysis.**

| Study | Patients | | |
|---|---|---|---|
| | Total | Excluded (%) | Included (%) |
| CA184004 | 82 | 3 (3.7) | 79 (96) |
| CA184007 | 116 | 4 (3.4) | 112 (97) |
| CA184008 | 155 | 7 (4.5) | 148 (95) |
| CA184022 | 196 | 37 (18.9) | 159 (81) |
| Total | 549 | 51 (9.3) | 498 (91) |

The exposure response (ER) analyses of efficacy characterizing tumour response (BOR and irCA) were conducted with data from patients in CA184007, CA184008 and CA184022 for whom measures of exposure were available (N=353 for BOR, and N=418 for irCA).

The ER analysis of efficacy characterizing OS was conducted with data from 497 subjects in CA184004, CA184007, CA184008 and CA184022 for whom summary measures of ipilimumab exposure were available. The ER analysis of safety (irAE) was also conducted with data from these 497 subjects.

### *Methods*

The methods used in the population analyses are described below:

**Population Pharmacokinetic (PPK) Analysis**

The PPK model was developed in three stages. First, a base model was developed to describe the pharmacokinetics of ipilimumab without consideration of covariate effects. Second, a full covariate model was developed by incorporating the effect of all pre-specified covariate parameter relationships, and lastly the final model was developed by retaining only the statistically significant and clinically important covariate parameter relationships.

Covariate parameter relationships were examined for the following baseline covariates: body weight, age, gender, estimated glomerular filtration rate (eGFR), ECOG status, baseline lactate dehydrogenase (LDH), albumin, concomitant budesonide, AST, ALT, alkaline phosphatase (AP), bilirubin, prior systemic anticancer therapy, metastatic stage, prior immunotherapy, prior IL-2, and HLA.A2*201 genotype status (HLA[23]). Furthermore,

[23] The human leukocyte antigen system (HLA) is the name of the major histocompatibility complex (MHC) in humans. The super locus contains a large number of genes related to immune system

the effect of immunogenicity on clearance was assessed as a time varying covariate to account for the possibility that human anti-human antibody response (HAHA) are not present at all times in immunogenic subjects.

Internal model evaluation was conducted by visual and quantitative predictive performance check methods. Furthermore, external model validation was performed with data from a Phase II study (CA184004) by visual and numeric predictive performance check methods.

The PPK model was applied to obtain estimates of steady state ipilimumab trough concentration ($C_{minss}$) that were used in the E-R analyses.

**Exposure Efficacy Response Analysis: BOR**

The ER of BOR was characterised by a logistic regression model relating $C_{minss}$ to the probability of achieving a BOR of CR or PR, as defined by the modified World Health Organization (WHO) criteria (mWHO). BOR was based on assessment by an IRC. Model development was conducted in 3 stages. First, a base model was developed to establish the existence and functional form of a relationship between ipilimumab exposure and probability of BOR. Second, the covariate effect that may potentially modulate the ER was examined. A covariate model incorporating all significant covariates was developed. Third, the final model was developed by backward elimination to only retain covariates that were significant at a 0.1% level. Covariate parameter relationships were examined for the following baseline covariates: body weight, age, gender, ECOG status, LDH, concomitant budesonide, prior systemic anticancer therapy, metastatic stage, prior immunotherapy, HLA, prior IL-2. Model evaluation was performed with predictive check.

**Exposure Efficacy Response Analysis: irCA**

The ER of immune related clinical activity (irCA) was characterised by a logistic regression model relating $C_{minss}$ to the probability of achieving irCA. irCA is a composite exploratory efficacy endpoint derived from the ir-Response criteria. The ir-Response criteria follow the tumour size over time of total tumour burden (the sum of the measurements of index lesions plus measurable new lesions, when present). The irCA is distinct from other subject subsets explored in the clinical program and was defined conservatively to include those subjects with the clearest evidence of anticancer activity (such as decline in total tumour burden ≥ 25% from baseline). irCA responders are subjects who achieved a best overall ir-Response of immune related complete response (irCR), immune related partial response (irPR), or late response (irCR or irPR or immune related stable disease (irSD) after tumour progression), or irSD with ≥ 25% tumour burden reduction from baseline. The base and final models were developed and evaluated by applying methods analogous to those for the ER analysis of BOR.

**Exposure Efficacy Response Analysis: OS**

The ER of OS was characterised by a CPH model relating $C_{minss}$ to the hazard of death. The CPH model was developed in 3 stages. First, a base model was developed to establish the existence and functional form of the ER relationship between OS and ipilimumab $C_{minss}$. Second, a full model was developed to assess the effect of all of the following potential covariates simultaneously: age, weight, gender, baseline absolute lymphocyte count (ALC), HLA, prior systemic anticancer therapy, LDH and prior immunotherapy, prior IL-2 therapy, ECOG status and metastatic stage at study entry. Third, the final model was developed by retaining the statistically significant predictors with appropriate functional forms of their relationships with OS. The CPH model was evaluated by comparing model predicted cumulative probability of OS versus time with that obtained by Kaplan-Meier analyses.

**Exposure Safety Response Analysis: irAE**

function in humans. The major HLA antigens are essential elements for immune function and different classes have different functions.

The ER of irAE was characterised by an ordinal logistic regression model relating $C_{minss}$ to the probability of experiencing Grade 1 or lower (Grade ≤ 1), Grade 2, and Grade 3 or higher (Grade ≥ 3) irAEs. The rationale for combining irAEs of Grade 0 and 1 into a single category (Grade ≤ 1) is that irAEs of Grade 1 are considered to be mild and generally do not require medical intervention. The irAEs of Grade 3 or greater (Grade ≥ 3) were combined into a single category as irAEs of Grade 3 or higher require medical treatment, and there were not many irAEs events of Grade 4 or 5.

The base and final model development as well as model evaluation, were conducted using methods analogous to ER analysis of BOR.

*Results. Population Pharmacokinetic Analysis*

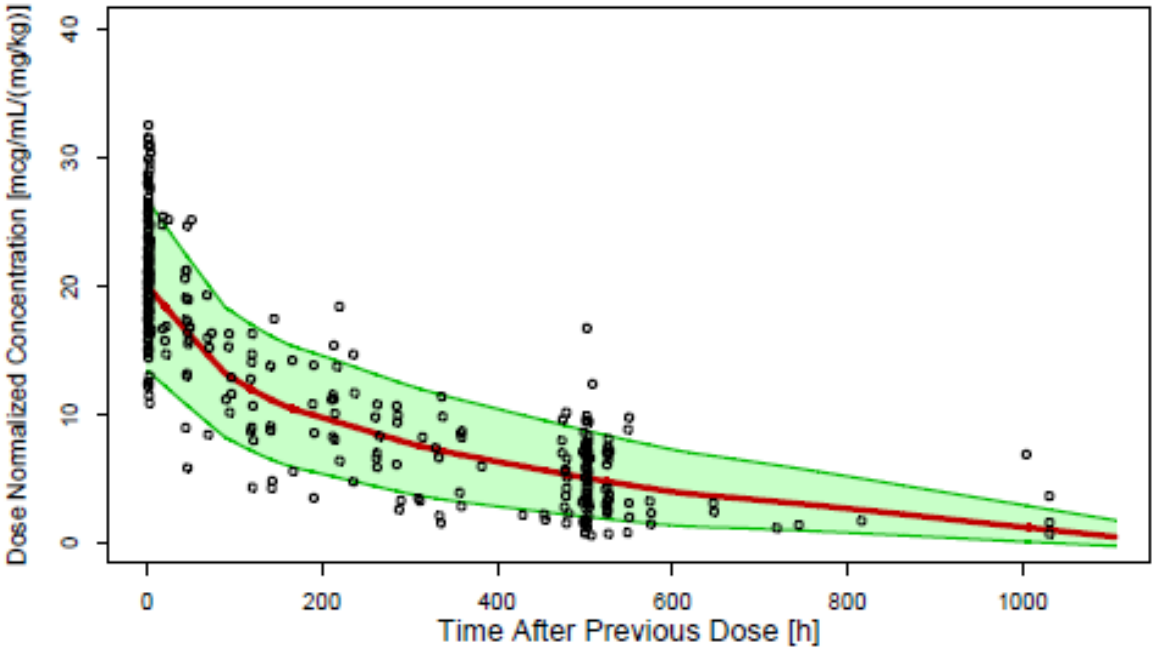
The PPK of ipilimumab was characterised by a two compartment model with zero order IV infusion and first order elimination. The model was parameterized in terms of clearance (CL), volume of central compartment (VC), inter-compartmental clearance (Q), and volume of peripheral compartment (VP). Inter individual variability in CL and VC were characterised by lognormal distributions and the residual error by a combined model (additive and proportional error). Analysis of covariate effects revealed that CL increased with increase in baseline body weight (BW) and LDH and VC increases with increase in BW. The effects of the other demographic and clinical covariates tested were not statistically significant or the magnitude of the effect was considered by the sponsor to be of minimal clinical relevance (less than 20% effect on the typical value of a model parameter relative to the reference value).

The sponsor considered that the comparison of predicted values with actually observed values from Study CA184004 provided external validation of the model. The comparison was presented graphically with actual observations of dose normalised concentrations at specific times after the previous dose marked on a graph showing "90% prediction intervals of simulated data from final PPK model". The relevant figure is shown below (Figure 8). Some odd features of the graph (such as the large number of observations plotted at time < 0, and the odd position of the shaded region) were noted by the clinical evaluator.

**Sponsor response:**

*Although this figure appears to have observations plotted at time < 0, this is an error. The x-axis (time) values of all observations in the figure are greater than zero (minimum value of 1.33 hours).*

**Figure 8. Observed Serum Concentrations from External Model Validation Dataset (CA184004) and 90% Prediction Intervals of Simulated Data from Final PPK Model**




Note: The solid line and shaded area represent median values of model prediction and 90% prediction interval (N=1000).

*Exposure Efficacy Response Analysis: BOR*

A linear logistic regression model with log ($C_{minss}$) as the predictor variable adequately represented the data. There was no external validation. Instead, 500 non-parametric bootstrapped datasets were used as a check of parameter estimates. (See FDA 1999[24]) $C_{minss}$ was found to be a statistically significant predictor of the probability of a BOR of CR or PR ($p < 0.001$) and the probability was found to increase with increase in log-transformed $C_{minss}$. However, none of the covariates examined was retained in the final model. The expected odds of a subject achieving BOR of CR or PR increased by 2.48-fold for a 2.7-fold increase in $C_{minss}$.

*Exposure Efficacy Response Analysis: irCA*

The irCA was qualitatively similar to that for BOR.

*Exposure Efficacy Response Analysis: OS*

The CPH model assumption of proportional hazards did not fit the data accurately. There was no external validation and the results were compared with those of Kaplan-Meier analysis.

*Exposure Safety Response Analysis: irAE*

Again, there was no external validation. The probability of Grade ≥ 2 and Grade ≥ 3 irAEs was found to increase with $C_{minss}$.

[24] FDA. 1999. Guidance for Industry. Population Pharmacokinetics.

*Absolute lymphocyte count (ALC) analyses*

Background

ALC is a composite measure of all circulating T and B lymphocytes. Baseline ALC has been reported to be positively associated with OS in a variety of haematologic and solid tumours. The sponsor's *ALC Integrated Summary* summarises the results of three types of ALC analyses from MDX010-20, CA184004, CA184007, CA184008 and CA184022:

- Since ipilimumab activates T cells, the first analysis explored whether ipilimumab modulated ALC levels during induction.
- Since high ALC at baseline has been reported to be associated with longer OS in a variety of tumours, the association between baseline ALC and OS was explored in the Phase III study MDX010-20.
- Associations were explored between OS and on-treatment ALC summary measures, including the rate of change in ALC during the induction dosing period and the ALC value at a fixed time point during induction.

Methods

In all these studies, ALC was measured routinely at screening or enrolment, before each dose during induction (at Weeks 1, 4, 7 and 10), and at the end of the induction-dosing period (at Week 13).

Four derived per-subject ALC measures were defined, each designed to capture a key feature of the pattern of ALC values during the induction dosing period for each subject. They were:

- **ALC1**: baseline ALC value.
- **ALC3**: ALC value half way through the induction dosing period.
- **Slope3**: the rate of change in ALC over the first half of the induction dosing period.
- **Slope5**: the rate of change in ALC over the entire induction dosing period.

The datasets were analysed using a range of statistical modelling techniques:

- Pharmacodynamic analyses examined the patterns of change in ALC over time, and how these patterns differed as a function of treatment group.
- Linear logistic regression was used to model the probability of clinical activity (CA) as an additive function of ipilimumab dose and ALC measure (ALC1, ALC3, Slope3, or Slope5).
- For Study MDX010-20, Cox proportional hazards (PH) models were used to assess the dependence of OS on ALC measures.

*Results*

In MDX010-20, ALC value at baseline was positively and significantly associated with longer OS for subjects with melanoma in all treatment groups.

In all 5 studies analysed, mean ALC increased after ipilimumab treatment throughout the 12 week induction dosing period in a dose dependent manner. For subjects treated with 3 or 10 mg/kg ipilimumab, mean ALC continued to increase throughout the induction dosing period. Neither gp100 vaccine alone (MDX010-20) nor 0.3 mg/kg ipilimumab (CA184022) appeared to modulate ALC levels.

*Sponsor's conclusions*

(1) On-treatment ALC is a pharmacodynamic biomarker for ipilimumab.
(2) High baseline ALC is a positive prognostic biomarker regardless of treatment assignment.

(3) An apparent association between change in ALC and OS benefit of ipilimumab was suggested but not definitively established. Therefore, based on currently available evidence the use of change in ALC to guide clinical management cannot be recommended.

**Study MDX010-28**

This was a study of long term outcome in patients who had participated in Studies MDXCTLA4-02, MDX010-08 and MDX010-15.

Data from a total 181 patients were included (ITT population) in this study, of which 169 had been treated with ipilimumab and were alive at the time of completion of the core studies (Eligible Subject Population) and 160 had survival data collected during the current study (Per-Protocol population). The ITT population included 181 (100%) subjects who were either assigned a randomisation number in MDX010-08 (n = 76) or who received at least one dose or any partial dose of ipilimumab in MDXCTLA4-02 (n = 17) or MDX010-15 (n = 88).

Overall, 79/181 (43.6%) patients survived ≥ 12 months. Survival of this duration was observed in patients with objective response, as well as in patients with SD or PD following ipilimumab treatment. Among the 181 patients included in the ITT population, 17 (14.4%) were alive at the last contact, with overall survival ranging from 45 to 93 months.

**Evaluator's overall conclusions on clinical efficacy**

***Introduction***

The trial evidence relating to efficacy was not extensive. There was a single Phase III study (MDX010-20) and supporting evidence from Studies CA184004 and CA184022 which provided some dose response data.

***A single Phase III study - discussion of relevant factors***

The TGA-adopted EU guideline which relates to this situation (EMEA 2001[25]) recommends the following:

In cases where the confirmatory evidence is provided by one pivotal study only, this study will have to be exceptionally compelling, and in the regulatory evaluation special attention will be paid to:

1. The internal validity. There should be no indications of a potential bias.
2. The external validity. The study population should be suitable for extrapolation to the population to be treated.
3. Clinical relevance. The estimated size of treatment benefit must be large enough to be clinically valuable.
4. The degree of statistical significance. Statistical evidence considerably stronger than $p<0.05$ is usually required, accompanied by precise estimates of treatment effects, that is, narrow confidence intervals. The required degree of significance will depend on factors such as the therapeutic indication, the primary endpoint, the amount of supportive data and whether the alternative analyses demonstrating consistency are pre-specified. When the aim is to demonstrate non-inferiority, one study is more likely to be accepted if the lower 95% confidence bound is well away from the non-inferiority margin.
5. Data quality.
6. Internal consistency. Similar effects demonstrated in different pre-specified sub-populations. All important endpoints showing similar findings.

[25] European Agency for Evaluation of Medical Products (EMEA). 2001. *Points to Consider on Application with 1. Meta-Analyses; 2. One Pivotal Study.* 31 May 2001. CPMP/EWP/2330/99.

7. Centre effects. None of the study centres should dominate the overall result, neither in terms of number of subjects nor in terms of magnitude of effect.
8. The plausibility of the hypothesis tested.

The study was carefully and competently planned and conducted and there was a plausible scientific basis for efficacy. The outcome studied (OS) was considered to be robust and there was no indication of bias. The statistical analysis yielded results of adequate significance. Thus, points numbered 1, 4, 5 and 8 are satisfied.

Regarding to point number 2, the population studied was generally broad within the defined disease group, raising the expectation of external validity. Two aspects deserve comment:

(1) The primary objective related to comparison of the "overall survival of patients administered MDX-010 in combination with gp100 melanoma peptide vaccine versus those administered gp100 melanoma peptide vaccine alone". However, the evaluator believed that the data in Table 15 above, supplemented by data from the Phase II studies, provide sufficient reassurance regarding the efficacy of Yervoy alone.

(2) In the major study, for reasons relating to the vaccine studied, the population was restricted to HLA-A2*0201-positive individuals. On the other hand, the direct mechanism of action for Yervoy (that is, the CTLA-4 receptor ligand interaction) is not HLA-dependent and the Phase II study CA184022, which provided some supporting data, did not use the gp100 vaccine and did not limit enrolment by HLAA2*0201 subtype.

Regarding point number 3, the study population comprised patients with a rapidly lethal condition who had failed previous therapy, so the evaluator believed the size of the benefit shown was clinically relevant.

Regarding point number 6, the following subgroups were pre-specified:

- M-stage (M0, M1a, M1b, M1c);
- prior IL-2 treatment (Yes, No);
- baseline LDH (≤ULN, >ULN);
- age (<65, ≥65);
- sex (male, female).

Results of the subgroup analyses are shown in Table 25 below. The results show that this criterion had been satisfied.

**Table 25. OS HR and 95% CIs – Subgroup analyses (Yervoy + gp100 *versus* gp100)**

| | Subgroup | #Death/ #Randomised | HR (95% CI) |
|---|---|---|---|
| | All subjects | 306/403 versus 119/136 | 0.69 (0.56, 0.85) |
| Gender | Male | 191/247 versus 66/73 | 0.66 (0.50, 0.87) |
| | Female | 115/156 versus 53/63 | 0.72 (0.52, 0.99) |
| Age | < 65 | 219/291 versus 81/94 | 0.70 (0.54, 0.90) |
| | ≥ 65 | 87/112 versus 38/42 | 0.69 (0.47, 1.01) |
| M-stage at Study Entry | M0, M1a, M1b | 78/118 versus 31/38 | 0.57 (0.38, 0.87) |
| | M1c | 228/285 versus 88/98 | 0.74 (0.58, 0.95) |
| Baseline LDH | ≤ ULN | 180/255 versus 67/82 | 0.70 (0.53, 0.93) |
| | > ULN | 126/148 versus 52/54 | 0.69 (0.50, 0.95) |
| Prior Use of IL-2 | Yes | 67/88 versus 25/33 | 0.77 (0.48, 1.22) |
| | No | 239/315 versus 94/103 | 0.67 (0.52, 0.85) |

Regarding point number 7, the multiplicity of centres (125) did not permit an efficacy analysis by centre. Almost half the patients were studied in the USA (801/1783 of those screened, and 328/676 of those randomised). The maximum number screened at any centre was 28.

***The dose selected***

The extent to which efficacy may increase at higher dosage was considered uncertain. Of the two Phase II studies which had dose response aspects, CA184004, which randomised only 82 patients, did not provide a clear outcome on this point. Study CA184022, which randomised 217 patients, was suggestive of an efficacy gain at dosage higher than that used in the Phase III study MDX010-20. This is discussed further below.

***Efficacy in re-induction***

In the one pivotal study, the 12 week treatment cycle could be repeated but the data were not convincing. See *Re-induction* above. The evaluator stressed that particularly with a drug where late response is at least a hypothetical possibility, rigorous testing is necessary to establish the extent to which repeated treatment is effective.

***Sponsor response:***

*It is unlikely that objective responses achieved in re-induction can be ascribed to late response for the reasons outlined below. Progression followed by spontaneous response has been ascribed to drug induced tumour inflammation. This effect has not been reported in patients more than ~4 months after the first dose of ipilimumab.*

*The majority of patients who were eligible for re-induction received re-induction (32/40 patients). Of these, 65% to 75% in the ipilimumab containing treatment groups achieved disease control (Table 26). Among the re-induced patients who achieved disease control, 50% to 65.2% were alive for at least 2 years from randomization.*

**Table 26. Efficacy following re-induction. Study MDX010-20.**

| | Ipilimumab (N = 8) | Ipilimumab+gp100 (N = 23) | gp100 (N = 1) |
|---|---|---|---|
| Best overall response,[a] n (%) | | | |
| Complete response (CR) | 1 (12.5) | 0 | 0 |
| Partial response (PR) | 2 (25.0) | 3 (13.0) | 0 |
| Stable disease (SD) | 3 (37.5) | 12 (52.2) | 0 |
| Progressive disease (PD) | 2 (25.0) | 8 (34.8) | 1 (100.0) |
| Unknown | 0 | 0 | 0 |
| Disease control rate (DCR) | 6 (75.0) | 15 (65.2) | 0 |
| Number alive for > 2 years, n (%) | 4 (50.0) | 15 (65.2) | 1 (100.0) |
| Survival range (months) | 24.7-55.06+ | 26.02-54.08+ | 25.3+ |

[a] Best overall response was based on response after a single or multiple re-induction(s)

*Among ipilimumab treated patients, the median time to the first re-induction dose, relative to the first induction dose, was 10.4 months (range: 6.0 to 48.8 months) in the ipilimumab+gp100 group and was 9.1 months (range: 6.4 to 29.0 months) in the ipilimumab alone group. Across the ipilimumab containing treatment groups, the 5 patients who achieved PR during re-induction were first re-induced 6.4, 8.4, 11.9, 14.6 and 21.4 months, respectively, after their first induction dose. The 1 patient who achieved CR during re-induction was first re-induced 9.9 months after their first induction dose.*

*Therefore, the option of re-induction with ipilimumab should be offered to patients with progressive metastatic melanoma who have responded to ipilimumab in the past. Spontaneous remission in such patients is unlikely and no alternative treatment options exist. Re-induction is associated with disease control and/or prolonged clinical benefit, which is likely attributable to the re-induction dosing due to the timing of re-induction relative to the previous ipilimumab dosing period. This represents a clinically important option for melanoma patients with no other treatment options. The sponsor believed that this information should be provided in the Australian PI.*

### *Comments on the PPK and exposure-response analyses*

*Population pharmacokinetic analysis*

The maximum number of pharmacokinetic samples per patient was 12, but the majority of patients had ≤ 6. This introduces a possible bias, in that samples may have been missing systematically in particular categories of patient.

There are some problems with the validation of the PPK described:

- Precise details on how the "simulated data" were produced from the model are lacking.
- The nature of the comparison was not very convincing. Merely noting where observed values lie on the 90% prediction interval surrounding a predicted median, in a situation in which most of the observations used in the comparison have been made either immediately post-infusion, or about three weeks post-infusion. Use of more detailed pharmacokinetic data from Study CA194004 might have enabled a useful comparison with individually predicted values.

Thus, it appears that the model presented was of a preliminary nature, has not been thoroughly validated, and is unsuitable for producing estimates of $C_{minss}$ for use in the ER analyses.

*Exposure efficacy response analyses: BOR and irCA*

The problem with estimates of $C_{minss}$ has been noted above. The lack of external validation further diminishes the weight of conclusions drawn from the model. Certainly, the outcome of the model is of interest and the relationship between efficacy and $C_{minss}$ is an important matter for further investigation. However, mathematical modelling cannot convert a Phase II trial into Phase III and the results cannot be regarded as definitive.

*Comments on the ALC analyses*

Sponsor's conclusion (2): While interesting to the basic scientist, this cannot be the basis of practical guidance for prescribers as to the value of Yervoy in a particular case.

Sponsor's conclusion (1): The text "ALC is a pharmacodynamic biomarker for ipilimumab" seems to be an inappropriately grand statement of the rather routine observation that the drug tends to increase ALC.

**Sponsor response:**

*The sponsor agreed with the interpretations that, based in the submitted data, change in ALC cannot be used for clinical management.*

*Quality of life data*

No convincing QoL data were presented. The results obtained in the pivotal study demonstrated statistically significant differences between groups in mean baseline to 12 week changes in Constipation scores for the ipilimumab plus gp100 versus gp100 monotherapy group (5.2 versus 11.8, p=0.043) and the ipilimumab monotherapy versus the gp100 monotherapy group (1.9 versus 11.8, p=0.010). No other statistically significant differences were seen between the three treatment groups.

**Conclusion on efficacy**

In summary, it was considered that there was sufficient evidence of efficacy, in a defined population, of the 12 week course used in the pivotal study.

## Safety

### Introduction

The safety evidence presented comprises:

- Routine safety data from the clinical studies MDXCTLA4-01, MDXCTLA4-02, MDX010-15, CA184004, CA184007, CA184008, CA184022, MDX010-20 and MDX010-08.
- Routine safety data from the ancillary studies listed in Table 20. In general, for studies in this group, the sponsor states: "No analyses were performed on an integrated level for these studies as they represented various tumour types and ipilimumab doses, schedules, and regimens, including in combination with other therapies." Note that for one of these, no report of the study was included in the current Australian submission: For Study MDX010-21, an interim report of some electrocardiogram (ECG) findings was included and some AE data were summarised only. Where appropriate, safety data from these studies are discussed in sections headed "Ancillary studies", below.
- Data from ongoing studies. The "ongoing studies" mentioned included Study CA184025 and Study CA184045, which was described by the sponsor as "an

ongoing open label protocol for the expanded access use of ipilimumab in the US". Some safety data from ongoing studies are contained in the sponsor's *Summary of Clinical Safety* but the information was generally not subject to convenient synopsis (for example *Safety in Ongoing Studies* comprises over 10000 pages of detailed tables). The focus of this evaluation was therefore on Studies CA184025 and CA184045 (see *Ongoing studies* below).

*Note*

- "On-study" or "Treatment-emergent" events are events reported between first dose and 70 days after last dose of study therapy.
- "Drug related" events are events with a relationship to study drug reported as "Certain", "Probable", "Possible" or "Missing".

**Patient exposure**

The number of patients exposed to ipilimumab in the sponsor's studies was as summarised below (numbers for ongoing studies (in italics) as at 6 January 2010).

Phase I melanoma: 307

Phase I other tumours: 140

Phase II melanoma monotherapy (CA184004 82, CA184008 155, CA184022 214, *CA184025[1] 171, CA184045 870, CA184042 72*, MDX010-28[26] 181): 1393

Phase II melanoma combination therapy (MDX010-05 56, MDX010-08 74, *MDX010-16 76,* MDX010-19 88, CA184007 115[27]): 409

Phase II other tumours (MDX010-11 61, MDX010-12 31, MDX010-24 27, *CA184041 331*): 450

Phase III melanoma (MDX010-20 643, *CA184024 497, CA184029 198*): 1338

Phase III prostate (*CA184043 27*): 27

Details of exposure to Yervoy in the main study and the more important supportive studies are shown in Tables 27-31 below.

[26] Numbers in these studies are not included in the total, as participants had all been treated in other studies.

[27] This study included a monotherapy group (N=57) and a combination therapy group (N=58)

**Table 27. MDX010-20**

| Number of doses per patient, first cycle | Number of patients (%) | |
|---|---|---|
| | **Yervoy + gp100 N=380** | **Yervoy N=131** |
| 1 | 30 (7.9) | 10 (7.6) |
| 2 | 56 (14.7) | 16 (12.2) |
| 3 | 52 (13.7) | 17 (13.0) |
| 4 | 242 (63.7) | 88 (67.2) |
| *Mean no. of doses (SD)* | *3.33 (1.0)* | *3.40 (0.97)* |

Some 40 patients commenced a second cycle of treatment (re-induction), seven a third cycle and one a fourth cycle. Of these 40, 29 were in the Yervoy + gp100 group, nine were in the Yervoy group, and two were in the gp100 group.

**Table 28. CA184007**

| Number of doses per patient | Number of patients (%) | |
|---|---|---|
| | **Yervoy + budesonide N=58** | **Yervoy N=57** |
| Induction Period (n=115) | | |
| 1 | 3 (5.2) | 4 (7.0) |
| 2 | 10 (17.2) | 7 (12.3) |
| 3 | 13 (22.4) | 11 (19.3) |
| 4 | 32 (55.2) | 35 (61.4) |
| *Mean no. of doses (SD)* | *3.3 (0.93)* | *3.4 (0.95)* |
| | | |
| Maintenance Period (n=13) | | |
| 1 | 4 (57.1) | 4 (66.7) |
| 2 | 1 (14.3) | 1 (16.7) |
| 3 | 1 (14.3) | 1 (16.7) |
| 5 | 1 (14.3) | |
| *Mean no. of doses (SD)* | *2.0 (1.5)* | *1.5 (0.8)* |

**Table 29. CA184008**

| Number of doses per patient | Number of patients (%) N=155 |
|---|---|
| Induction Period (n=155) | |
| 1 | 15 (9.7) |
| 2 | 21 (13.5) |
| 3 | 28 (18.1) |
| 4 | 91 (58.7) |
| *Mean no. of doses (SD) 3.3 (1.02)* | |
| | |
| Maintenance Period (n=19) | |
| 1 | 15 (78.9) |
| 2 | 3 (15.8) |
| 3 | 1 (5.3) |
| *Mean no. of doses (SD) 1.3 (0.56)* | |

**Table 30. CA184004, CA184022, CA184007, CA184008, CA184042 – Treated patients, induction period.**

| Number of doses per patient | Number of patients (%) | | |
|---|---|---|---|
| | CA184/022 Pooled 3mg/kg N=111 | CA184004/ 007/008/022 Pooled 10mg/kg N=325 | CA184042 10mg/kg N=28 |
| 1 | 6 (5.4) | 26 (8.0) | 5 (17.9) |
| 2 | 11 (9.9) | 49 (15.1) | 7 (25.0) |
| 3 | 16 (14.4) | 61 (18.8) | 5 (17 9) |
| 4 | 78 (70.3) | 189 (58.2) | 11 (39.3) |
| *Mean no. of doses (SD)* | *3.5 (0.88)* | *3.3 (0.99)* | *2.8 (1.2)* |

**Table 31. MDX010-08.**

| Number of Yervoy doses per patient | Number of patients (%) | |
|---|---|---|
| | Yervoy N=39 | Yervoy + DTIC N=35 |
| Initial Cycle | | |
| 1 | 7 | 3 |
| 2 | 9 | 5 |
| 3 | 9 | 7 |
| 4 | 14 | 20 |
| *Mean no. of doses (SD)* | *2.8 (1.1)* | *3.3 (1.0)* |
| | | |
| Crossover Cycle (n=13)[1] | | |
| 1 | 2 | |
| 2 | 5 | |
| 3 | 2 | |
| 4 | 4 | |
| *Mean no. of doses (SD)* | *2.6 (1.1)* | |
| | | |
| Total doses received by the 13 patients who crossed over (Initial Cycle + Crossover Cycle) | | |
| 2 | 2 | |
| 3 | 1 | |
| 4 | 2 | |
| 5 | 3 | |
| 6 | 2 | |
| 7 | 1 | |
| 8 | 2 | |
| *Mean no. of doses (SD)* | *5.0 (2.0)* | |

[1] In addition to doses received in the Initial Cycle

## Adverse events

### *Note on "Immune related Adverse Events (irAEs)"*

The sponsor's Protocol for Study MDX010-20 stated that :

> "Blocking CTLA-4 function may permit the emergence of immune mediated adverse events that result in clinical syndromes resembling autoimmunity. Rash/vitiligo, diarrhoea/colitis, uveitis/episcleritis, hepatitis and hypopituitarism were drug related, presumptive immune mediated events, now termed irAEs, noted in previous MDX-010 studies.
>
> For the purposes of this study, an irAE is defined as an adverse event of unknown aetiology, associated with drug exposure and is consistent with an immune phenomenon.

Efforts should be made to rule out neoplastic, infectious, metabolic, toxin or other aetiologic causes prior to labelling an adverse event an irAE. Serological, immunological and histological (biopsy) data should be used to support the diagnosis of an immune-mediated toxicity."

### *Pharmacokinetic and pharmacodynamic studies*

The fact that the Phase I studies were done in patients with serious disease and the small numbers in cohorts, rendered meaningful interpretation of routine AE results unlikely. Thus, only serious AEs are considered for this group of studies.

### *Clinical efficacy and safety studies*

*Major efficacy studies and major safety studies*

A summary of the severity of adverse events reported in Study MDX010-20 is presented in Table 32 with individual adverse effects, sorted by System Organ Class (SOC) shown in Table 33 and irAEs are presented in Table 34.

**Table 32. MDX010-20. Severity of treatment-emergent AEs. Safety population.**

| | **Number (%) of patients** | | | |
|---|---|---|---|---|
| | **Yervoy + gp100 N=380** | **Yervoy N=131** | **gp100 N=132** | **Total N=643** |
| Any grade | 374 (98.4) | 127 (96.9) | 128 (97.0) | 629 (97.8) |
| Grade 3-4 | 173 (45.5) | 60 (45.8) | 62 (47.0) | 295 (45.9) |
| Grade 5 | 21 (5.5) | 13 (9.9) | 7 (5.3) | 41 (6.4) |

**Table 33. MDX010-20. Treatment emergent AEs classified as at least possibly related to study drug. Safety population. (Table continued over three pages).**

| SOC<br>Preferred Term[1] | Yervoy + gp100<br>N=380 | Yervoy<br>N=131 | gp100<br>N=132 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Number of patients with ≥ 1 such AE | 339 (89.2) | 106 (80.9) | 104 (78.8) |
| | | | |
| **Blood and lymphatic system disorders** | 24 (6.3) | 6 (4.6) | 6 (4.5) |
| Anaemia | 18 (4.7) | 2 (1.5) | 2 (1.5) |
| Lymphopenia | | | 3 (2.3) |
| **Cardiac disorders** | 1 (0.3) | 1 (0.8) | 1 (0.8) |
| **Ear and labyrinth disorders** | 2 (0.5) | | 1 (0.8) |
| **Endocrine disorders** | 14 (3.7) | 8 (6.1) | 2 (1.5) |
| Hypothyroidism | 6 (1.6) | 3 (2.3) | 2 (1.5) |
| Hypopituitasism | 3 (0.8) | 3 (2.3) | |
| **Eye disorders** | 23 (6.1) | 8 (6.1) | 8 (6.1) |
| Vision blurred | 6 (1.6) | 3 (2.3) | 2 (1.5) |
| **Gastrointestinal disorders** | 182 (47.9) | 63 (48.1) | 49 (37.1) |
| Abdominal discomfort | 4 (1.1) | 3 (2.3) | 1 (0.8) |
| Abdominal distension | 4 (1.1) | | 4 (3.0) |
| Abdominal pain | 31 (8.2) | 8 (6.1) | 6 (4.5) |
| Abdominal pain lower | 1 (0.3) | 3 (2.3) | |
| Abdominal pain upper | 6 (1.6) | 1 (0.8) | 3 (2.3) |
| Colitis | 20 (5.3) | 10 (7.6) | 1 (0.8) |
| Constipation | 19 (5.0) | 4 (3.1) | 2 (1.5) |
| Diarrhoea | 115 (30.3) | 36 (27.5) | 18 (13.6) |
| Dyspepsia | 4 (1.1) | 0 | 3 (2.3) |
| Flatulence | 6 (1.6) | 2 (1.5) | 5 (3.8) |
| Nausea | 73 (19.2) | 31 (23.7) | 23 (17.4) |
| Vomiting | 36 (9.5) | 16 (12.2) | 9 (6.8) |
| **General disorders and admin site** | 265 (69.7) | 52 (39.7) | 76 (57.6) |
| Asthenia | 15 (3.9) | 6 (4.6) | 5 (3.8) |
| Chills | 14 (3.7) | 7 (5.3) | 6 (4.5) |
| Fatigue | 91 (23.9) | 32 (24.4) | 26 (19.7) |
| Flu-like illness | 16 (4.2) | 4 (3.1) | 2 (1.5) |
| Injection site erythema | 27 (7.1) | 1 (0.8) | 5 (3.8) |

| | | | |
|---|---|---|---|
| Injection site induration | 27 (7.1) | | 3 (2.3) |
| Injection site inflammation | 4 (1.1) | | 3 (2.3) |
| Injection site pain | 26 (6.8) | 2 (1.5) | 14 (10.6) |
| Injection site pruritus | 18 (4.7) | | 2 (1.5) |
| Injection site reaction | 109 (28.7) | 2 (1.5) | 26 (19.7) |
| Injection site swelling | 16 (4.2) | | 3 (2.3) |
| Oedema peripheral | 10 (2.6) | 3 (2.3) | 1 (0.8) |
| Pain | 7 (1.8) | 1 (0.8) | 4 (3.0) |
| Pyrexia | 43 (11.3) | 10 (7.6) | 8 (6.1) |
| Vaccination site erythema | 10 (2.6) | | 2 (1.5) |
| Vaccination site pain | 4 (1.1) | 1 (0.8) | 3 (2.3) |
| **Hepatobiliary disorders** | 3 (0.8) | 3 (2.3) | |
| **Immune system disorders** | 3 (0.8) | | 1 (0.8) |
| **Infections and infestations** | 29 (7.6) | 6 (4.6) | 3 (2.3) |
| **Injury, poisoning and procedural** | 4 (1.1) | | 2 (1.5) |
| **Investigations** | 35 (9.2) | 16 (12.2) | 11 (8.3) |
| AP ↑ | 2 (0.5) | 2 (1.5) | 4 (3.0) |
| ALT ↑ | 3 (0.8) | 2 (1.5) | 3 (2.3) |
| Weight ↓ | 12 (3.2) | 4 (3.1) | 2 (1.5) |
| **Metabolism and nutrition** | 51 (13.4) | 17 (13.0) | 11 (8.3) |
| Anorexia | 27 (7.1) | 8 (6.1) | 7 (5.3) |
| Appetite ↓ | 14 (3.7) | 7 (5.3) | 1 (0.8) |
| Dehydration | 7 (1.8) | 2 (1.5) | 1 (0.8) |
| **Musculoskeletal and connective tissue** | 68 (17.9) | 14 (10.7) | 20 (15.2) |
| Arthralgia | 14 (3.7) | 6 (4.6) | 4 (3.0) |
| Muscle spasms | 5 (1.3) | 3 (2.3) | 4 (3.0) |
| Myalgia | 24 (6.3) | 5 (3.8) | 3 (2.3) |
| Pain in extremity | 24 (6.3) | 1 (0.8) | 7 (5.3) |
| **Neoplasms** | 7 (1.8) | 2 (1.5) | 2 (1.5) |
| **Nervous system disorders** | 57 (15.0) | 11 (8.4) | 17 (12.9) |
| Dizziness | 7 (1.8) | 1 (0.8) | 5 (3.8) |
| Headache | 31 (8.2) | 5 (3.8) | 8 (6.1) |
| **Psychiatric disorders** | 9 (2.4) | 3 (2.3) | 5 (3.8) |
| Insomnia | 2 (0.5) | 1 (0.8) | 3 (2.3) |
| **Renal and urinary disorders** | 2 (0.5) | 3 (2.3) | 3 (2.3) |
| **Reproductive system and breast** | 1 (0.3) | 2 (1.5) | |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic and mediastinal** | 29 (7.6) | 7 (5.3) | 6 (4.5) |
| Cough | 11 (2.9) | 4 (3.1) | 2 (1.5) |
| Dyspnoea | 6 (1.6) | 2 (1.5) | 3 (2.3) |
| **Skin and subcutaneous tissue** | 171 (45.0) | 58 (44.3) | 28 (21.2) |
| Dry skin | 8 (2.1) | 1 (0.8) | 2 (1.5) |
| Erythema | 15 (3.9) | 6 (4.6) | 4 (3.0) |
| Pruritus | 67 (17.6) | 32 (24.4) | 15 (11.4) |
| Pruritus generalised | 8 (2.1) | 5 (3.8) | 0 |
| Rash | 68 (17.9) | 25 (19.1) | 5 (3.8) |
| Rash pruritic | 7 (1.8) | 6 (4.6) | 1 (0.8) |
| Urticaria | 9 (2.4) | 1 (0.8) | 1 (0.8) |
| Vitiligo | 17 (4.5) | 5 (3.8) | 2 (1.5) |
| **Uncoded** | | 1 (0.8) | |
| **Vascular disorders** | 21 (5.5) | 14 (10.7) | 6 (4.5) |
| Flushing | 8 (2.1) | 6 (4.6) | 0 |
| Hot flush | 4 (1.1) | 1 (0.8) | 4 (3.0) |
| Hypotension | 6 (1.6) | 4 (3.1) | 1 (0.8) |
| Lymphoedema | 4 (1.1) | | |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 2% in any group.

**Table 34. MDX010-20. Immune-related Adverse Events occurring in ≥ 2% patients in any group. Safety Population.**

| irAE | Yervoy + gp100 N=380 | Yervoy N=131 | gp100 N=132 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Diarrhoea | 115 (30.3) | 36 (27.5) | 18 (13.6) |
| Pruritus | 67 (17.6) | 32 (24.4) | 15 (11.4) |
| Rash | 68 (17.9) | 25 (19.1) | 5 (3.8) |
| Colitis | 20 (5.3) | 10 (7.6) | 1 (0.8) |
| Erythema | 15 (3.9) | 6 (4.6) | 4 (3.0) |
| Vitiligo | 17 (4.5) | 5 (3.8) | 2 (1.5) |
| Rash pruritic | 7 (1.8) | 6 (4.6) | 1 (0.8) |
| Pruritus generalised | 8 (2.1) | 5 (3.8) | 0 |
| Urticaria | 9 (2.4) | 1 (0.8) | 1 (0.8) |
| Hypothyroidism | 6 (1.6) | 3 (2.3) | 2 (1.5) |
| ALT↑ | 3 (0.8) | 2 (1.5) | 3 (2.3) |
| Hypopituitarism | 3 (0.8) | 3 (2.3) | 0 |
| Rash generalised | 1 (0.3) | 4 (3.1) | 1 (0.8) |
| GGT↑ | 0 | 1 (0.8) | 4 (3.0) |

GTT=Gamma Glutamyl transferase

A summary of the severity of adverse events reported in Study CA18004 is presented in Table 35 with individual adverse effects, sorted by System Organ Class (SOC) shown in Table 36.

**Table 35. CA184004. Severity of treatment-emergent AEs. Safety population.**

| | Number (%) of patients | | |
|---|---|---|---|
| | Yervoy 3mg/kg N=40 | Yervoy 10mg/kg N=42 | Total N=82 |
| Any grade | 33 (82.5) | 32 (76.2) | 65 (79.3) |
| Grade 3-4 | 6 (15.0) | 13 (31.0) | 19 (23.2) |
| Grade 5 | 1 (2.5) | 0 | 1 (1.2) |

**Table 36. CA184004. On-study AEs. Safety Population. (Table continued over three pages).**

| SOC<br>Preferred Term[1] | Yervoy<br>3 mg/kg<br>N=40 | Yervoy<br>10 mg/kg<br>N=42 |
|---|---|---|
| | n (%) | n (%) |
| Number of patients with any such AE | 39 (97.5) | 38 (90.5) |
| | | |
| **Blood and lymphatic system disorders** | 1 (2.5) | 2 (4.8) |
| Anaemia | 1 (2.5) | 2 (4.8) |
| **Cardiac disorders** | | 2 (4.8) |
| **Ear and labyrinth disorders** | | 2 (4.8) |
| **Endocrine disorders** | 2 (5.0) | 2 (4.8) |
| Hypopituitarism | 2 (5.0) | 1 (2.4) |
| **Eye disorders** | 8 (20.0) | |
| Lacrimation increased | 2 (5.0) | |
| **Gastrointestinal disorders** | 21 (52.5) | 30 (71.4) |
| Abdominal pain | 4 (10.0) | 3 (7.1) |
| Abdominal pain upper | 2 (5.0) | 3 (7.1) |
| Ascites | 1 (2.5) | 2 (4.8) |
| Colitis | 2 (5.0) | 4 (9.5) |
| Constipation | 5 (12.5) | 4 (9.5) |
| Diarrhoea | 12 (30.0) | 21 (50.0) |
| Dyspepsia | 3 (7.5) | 1 (2.4) |
| Flatulence | 2 (5.0) | |
| Nausea | 10 (25.0) | 16 (38.1) |
| Vomiting | 6 (15.0) | 8 (19.0) |
| **General disorders and admin site** | 30 (75.0) | 27 (64.3) |
| Chest pain | | 2 (4.8) |
| Chills | 2 (5.0) | 1 (2.4) |
| Disease progression | 6 (15.0) | 5 (11.9) |
| Fatigue | 19 (47.5) | 16 (38.1) |
| Oedema | 2 (5.0) | |
| Oedema localised | | 2 (4.8) |
| Oedema peripheral | 4 (10.0) | 2 (4.8) |
| Pain | 5 (12.5) | 3 (7.1) |

| | | |
|---|---|---|
| Pyrexia | 11 (27.5) | 10 (23.8) |
| **Hepatobiliary disorders** | 2 (5.0) | 2 (4.8) |
| Bile duct obstruction | 2 (5.0) | |
| **Immune system disorders** | 1 (2.5) | 2 (4.8) |
| **Infections and infestations** | 5 (12.5) | 10 (23.8) |
| Cystitis | | 2 (4.8) |
| UTI | | 2 (4.8) |
| **Injury, poisoning and procedural** | 8 (20.0) | 3 (7.1) |
| Humerus fracture | 2 (5.0) | |
| **Investigations** | 4 (10.0) | 4 (9.5) |
| Haemoglobin decreased | 3 (7.5) | |
| Weight increased | 3 (7.5) | 2 (4.8) |
| **Metabolism and nutrition disorders** | 9 (22.5) | 13 (31.0) |
| Anorexia | 7 (17.5) | 12 (28.6) |
| Dehydration | 1 (2.5) | 3 (7.1) |
| Hypokalaemia | 2 (5.0) | |
| **Musculoskeletal and connective tissue** | 11 (27.5) | 9 (21.4) |
| Arthralgia | 2 (5.0) | |
| Back pain | 3 (7.5) | |
| Musculoskeletal pain | 3 (7.5) | 1 (2.4) |
| Myalgia | 3 (7.5) | 1 (2.4) |
| **Neoplasms** | 3 (7.5) | 5 (11.9) |
| Tumour pain | 1 (2.5) | 3 (7.1) |
| **Nervous system disorders** | 12 (30.0) | 9 (21.4) |
| Convulsion | 2 (5.0) | |
| Dizziness | 2 (5.0) | 1 (2.4) |
| Headache | 6 (15.0) | 4 (9.5) |
| Oedema brain | | 2 (4.8) |
| Speech disorder | 2 (5.0) | |
| **Psychiatric disorders** | 8 (20.0) | 2 (4.8) |
| Insomnia | 4 (10.0) | |
| **Renal and urinary disorders** | 1 (2.5) | 1 (2.4) |
| **Reproductive system and breast** | 1 (2.5) | |
| **Respiratory, thoracic and mediastinal** | 9 (22.5) | 17 (40.5) |
| Cough | 5 (12.5) | 5 (11.9) |

| | | |
|---|---|---|
| Dyspnoea | 4 (10.0) | 9 (21.4) |
| Rhinitis allergic | 1 (2.5) | 3 (7.1) |
| **Skin and subcutaneous tissue** | 22 (55.0) | 25 (59.5) |
| Dry skin | 4 (10.0) | 4 (9.5) |
| Hyperhidrosis | 2 (5.0) | 1 (2.4) |
| Pruritus | 11 (27.5) | 13 (31.0) |
| Rash | 13 (32.5) | 17 (40.5) |
| **Vascular disorders** | 4 (10.0) | 5 (11.9) |
| Flushing | 2 (5.0) | 1 (2.4) |
| Hypertension | | 2 (4.8) |
| Lymphoedema | | 2 (4.8) |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 2 patients in any group.

A summary of the severity of adverse events reported in Study CA184022 is presented in Table 37 with individual adverse effects, sorted by System Organ Class (SOC) shown in Table 38.

**Table 37. CA184022. Severity of treatment-emergent AEs. Safety population.**

| | Number (%) of patients | | | |
|---|---|---|---|---|
| | **Yervoy 0.3mg/kg N=72** | **Yervoy 3mg/kg N=71** | **Yervoy 10mg/kg N=71** | **Total N=214** |
| Any grade | 68 (94.4) | 69 (97.2) | 71 (100.0) | 208 (97.2) |
| Grade 3-4 | 21 (29.2) | 21 (29.6) | 29 (40.8) | 71 (33.2) |
| Grade 5 | 15 (20.8) | 14 (19.7 | 15 (21.1) | 44 (20.6) |

**Table 38. CA184022. Treatment emergent AEs classified as at least possibly related to study drug. (Table continued over four pages.)**

| SOC<br>Preferred Term[1] | Yervoy<br>0.3mg/kg<br>N=72<br>n (%) | Yervoy<br>3mg/kg<br>N=71<br>n (%) | Yervoy<br>10mg/kg<br>N=71<br>n (%) |
|---|---|---|---|
| Number of patients with ≥ 1 such AE | 46 (63.9) | 55 (77.5) | 71 (100.0) |
| **Blood and lymphatic system disorders** | 2 (2.8) | 4 (5.6) | 8 (11.3) |
| Anaemia | 2 (2.8) | | 6 (8.5) |
| Lymphadenopathy | | | 2 (2.8) |
| Lymphopenia | | 2 (2.8) | |
| **Cardiac disorders** | | 1 (1.4) | 7 (9.9) |
| Tachycardia | | | 3 (4.2) |
| Sinus tachycardia | | | 2 (2.8) |
| **Ear and labyrinth disorders** | | 1 (1.4) | 4 (5.6) |
| **Endocrine disorders** | | 4 (5.6) | 3 (4.2) |
| Adrenal insufficiency | | | 2 (2.8) |
| Hypophysitis | | 2 (2.8) | 2 (2.8) |
| **Eye disorders** | 3 (4.2) | 4 (5.6) | 10 (14.1) |
| Conjunctivitis | | | 2 (2.8) |
| Eye pain | | | 2 (2.8) |
| Keratoconjunctivitis sicca | | | 2 (2.8) |
| Vision blurred | | 2 (2.8) | 2 (2.8) |
| **Gastrointestinal disorders** | 24 (33.3) | 33 (46.5) | 48 (67.6) |
| Abdominal distension | 2 (2.8) | | |
| Abdominal pain | 7 (9.7) | 5 (7.0) | 11 (15.5) |
| Abdominal pain upper | | 2 (2.8) | |
| Blood in stool | | | 2 (2.8) |
| Colitis | | 4 (5.6) | 5 (7.0) |
| Constipation | 4 (5.6) | 5 (7.0) | 13 (18.3) |
| Diarrhoea | 12 (16.7) | 18 (25.4) | 31 (43.7) |
| Enterocolitis | | | 2 (2.8) |
| Flatulence | | | 2 (2.8) |
| Gastritis | | 2 (2.8) | |
| GORD | | | 2 (2.8) |

| | | | |
|---|---|---|---|
| Nausea | 11 (15.3) | 13 (18.3) | 24 (33.8) |
| Vomiting | 6 (8.3) | 5 (7.0) | 16 (22.5) |
| **General disorders and admin site** | 25 (34.7) | 19 (26.8) | 53 (74.6) |
| Asthenia | 5 (6.9) | 5 (7.0) | 8 (11.3) |
| Chest pain | 3 (4.2) | | 4 (5.6) |
| Chills | | 3 (4.2) | 2 (2.8) |
| Death | | | 2 (2.8) |
| Disease progression | | | 10 (14.1) |
| Fatigue | 16 (22.2) | 12 (16.9) | 22 (31.0) |
| Flu-like illness | | 2 (2.8) | |
| General physical health deterioration | | | 2 (2.8) |
| Mucosal inflammation | 2 (2.8) | | |
| Non-cardiac chest pain | | | 2 (2.8) |
| Oedema | | | 2 (2.8) |
| Oedema peripheral | | | 11 (15.5) |
| Pain | | | 3 (4.2) |
| Pyrexia | 2 (2.8) | 6 (8.5) | 15 (21.1) |
| **Hepatobiliary disorders** | | | 3 (4.2) |
| **Immune system disorders** | 1 (1.4) | | 2 (2.8) |
| Hypersensitivity | | | 2 (2.8) |
| **Infections and infestations** | 2 (2.8) | 5 (7.0) | 26 (36.6) |
| Bronchitis | | | 3 (4.2) |
| Cellulitis | | | 2 (2.8) |
| Cystitis | | | 2 (2.8) |
| Nasopharyngitis | | | 3 (4.2) |
| Sinusitis | | | 3 (4.2) |
| URTI | | | 3 (4.2) |
| **Injury, poisoning and procedural** | | | 1 (1.4) |
| **Investigations** | 2 (2.8) | 3 (4.2) | 24 (33.8) |
| ALT ↑ | | | 3 (4.2) |
| Creatinine ↑ | | | 4 (5.6) |
| Haemoglobin ↓ | | | 5 (7.0) |
| Weight ↓ | | | 7 (9.9) |
| **Metabolism and nutrition** | 8 (11.1) | 6 (8.5) | 18 (25.4) |
| Anorexia | 6 (8.3) | 5 (7.0) | 7 (9.9) |
| Dehydration | | 3 (4.2) | 4 (5.6) |

| | | | |
|---|---|---|---|
| Fluid retention | | | 2 (2.8) |
| Hypokalaemia | | | 4 (5.6) |
| Hyponatraemia | | | 2 (2.8) |
| **Musculoskeletal and connective tissue** | 10 (13.9) | 9 (12.7) | 31 (43.7) |
| Arthralgia | 4 (5.6) | | 8 (11.3) |
| Back pain | | 2 (2.8) | 12 (16.9) |
| Bone pain | 2 (2.8) | | 2 (2.8) |
| Muscle spasms | | | 3 (4.2) |
| Musculoskeletal chest pain | | | 3 (4.2) |
| Musculoskeletal pain | | 3 (4.2) | 4 (5.6) |
| Myalgia | 2 (2.8) | 3 (4.2) | 5 (7.0) |
| Pain in extremity | | | 4 (5.6) |
| **Neoplasms** | 3 (4.2) | 2 (2.8) | 13 (18.3) |
| Tumour pain | | | 5 (7.0) |
| Malignant melanoma | | | 2 (2.8) |
| Tumour haemorrhage | | | 2 (2.8) |
| **Nervous system disorders** | 5 (6.9) | 5 (7.0) | 26 (36.6) |
| Dizziness | | | 3 (4.2) |
| Dysgeusia | | | 2 (2.8) |
| Facial palsy | | | 2 (2.8) |
| Headache | 3 (4.2) | 3 (4.2) | 12 (16.9) |
| Paraesthesia | | | 3 (4.2) |
| Somnolence | | | 3 (4.2) |
| Tremor | | | 2 (2.8) |
| **Psychiatric disorders** | 1 (1.4) | 3 (4.2) | 20 (28.2) |
| Agitation | | | 2 (2.8) |
| Anxiety | | | 3 (4.2) |
| Confusional state | | | 4 (5.6) |
| Depression | | | 3 (4.2) |
| Insomnia | | 2 (2.8) | 7 (9.9) |
| **Renal and urinary disorders** | | | 7 (9.9) |
| Dysuria | | | 2 (2.8) |
| Renal failure | | | 2 (2.8) |
| **Reproductive system and breast** | 1 (1.4) | | 6 (8.5) |
| Dysmenorrhoea | | | 2 (2.8) |
| Erectile dysfunction | | | 2 (2.8) |

| | | | |
|---|---|---|---|
| **Respiratory, thoracic & mediastinal** | 3 (4.2) | 3 (4.2) | 29 (40.8) |
| Cough | | | 14 (19.7) |
| Dyspnoea | 3 (4.2) | 2 (2.8) | 10 (14.1) |
| Dyspnoea exertional | | | 2 (2.8) |
| Epistaxis | | | 2 (2.8) |
| Productive cough | | | 2 (2.8) |
| Rhinorrhoea | | | 3 (4.2) |
| **Skin and subcutaneous tissue** | 12 (16.7) | 32 (45.1) | 40 (56.3) |
| Alopecia | | 3 (4.2) | |
| Dry skin | | | 2 (2.8) |
| Dermatitis acneiform | | | 2 (2.8) |
| Erythema | | 2 (2.8) | 3 (4.2) |
| Hyperhidrosis | | | 3 (4.2) |
| Pruritus | 2 (2.8) | 15 (21.1) | 23 (32.4) |
| Rash | 3 (4.2) | 17 (23.9) | 18 (25.4) |
| Rash erythematous | 2 (2.8) | | |
| Rash papular | | 2 (2.8) | |
| Rash pruritic | | 3 (4.2) | 2 (2.8) |
| Subcutaneous nodule | | | 2 (2.8) |
| Urticaria | | | 3 (4.2) |
| Vitiligo | | 2 (2.8) | |
| **Vascular disorders** | 2 (2.8) | 1 (1.4) | 12 (16.9) |
| Flushing | | | 2 (2.8) |
| Hot flush | | | 2 (2.8) |
| Hypertension | | | 3 (4.2) |
| Hypotension | | | 3 (4.2) |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 2 patients in any group.

## Serious adverse events (SAEs) and deaths

### *Pharmacokinetic and pharmacodynamic studies*

All patients with SAEs at least possibly related to a study drug are counted in the total, but only SAEs occurring in ≥ 5% patients in any group are listed in the last column of Table 39 below.

**Table 39. SAEs occurring in ≥ 5% patients in any group.**

| Study | On-study deaths (cause) | No. of patients with such SAE /N | SAEs occurring in ≥ 5% treated patients, with frequencies |
|---|---|---|---|
| MDXCTLA4-01 | 2 (PD) | 1/14 | Rash |
| MDXCTLA4-02 | 2 (spinal cord compression; PD) | 1/17 | Fever |
| MDX010-15[1] | 2 (arteriosclerotic cardiovascular disease; DP) | 9/88 | |

[1] This was designed in such a way that increased dosage was administered to new patients only after satisfactory experience with patients on lower dosage.

Numbers of on-study deaths are listed in the second column.

***The main study and the important supportive studies***

Deaths in Study CA184004 are shown in Table 40 with SAEs in Table 41.

**Table 40. Deaths within 70 days following exposure. Number (%) of patients, by cause.**

| Cause | 0-30 days after last dose of study therapy | | 0-70 days after last dose of study therapy | |
|---|---|---|---|---|
| | 3 mg/kg N=40 | 10 mg/kg N=42 | 3 mg/kg N=40 | 10 mg/kg N=42 |
| Total | 3 (7.5) | 4 (9.5) | 8 (20.0) | 8 (19.0) |
| | | | | |
| Progressive disease | 3 (7.5) | 2 (4.8) | 7 (17.5) | 6 (14.3) |
| Other[1] | 0 | 2 (4.8) | 1 (2.5) | 2 (4.8) |

[1] One was classified as drug-related: The death in the 3mg/kg group was due to large intestine perforation, considered probably related to Yervoy.

**Table 41. SAEs classified as at least possibly related to study drug, occurring in ≥ 5% patients in any group.**

| **SOC**<br>Preferred Term[1] | **3 mg/kg N=40** | **10 mg/kg N=42** |
|---|---|---|
| | **n (%)** | **n (%)** |
| Number of patients with ≥ 1 such SAE | 7 (17.5) | 8 (19.0) |
| | | |
| **Endocrine disorders** | 2 (5.0) | 2 (4.8) |
| Hypopituitarism | 2 | 1 (2.4) |
| **Gastrointestinal disorders** | 4 (10.0) | 2 |
| Colitis | 2 | 2 |
| Diarrhoea | 2 | 2 |

*CA184007*

Deaths in Study CA184007 are shown in Table 42 with SAEs in Table 43.

**Table 42. Deaths within 70 days following exposure. Number (%) of patients, by cause.**

| **Cause** | **0-30 days after last dose of study therapy** | | **0-70 days after last dose of study therapy** | |
|---|---|---|---|---|
| | **Yer + Bud N=58** | **Yer + Pbo N=57** | **Yer + Bud N=58** | **Yer + Pbo N=57** |
| Total | 4 (6.9) | 7 (12.3) | 7 (12.1) | 11 (19.3) |
| | | | | |
| Progressive disease | 3 (5.2) | 5 (8.8) | 5 (8.6) | 9 (15.8) |
| Other[1] | 1 (1.7) | 2 (3.5) | 2 (3.4) | 2 (3.5) |

[1] None of these was classified as drug-related.

**Table 43. On-study SAEs occurring in ≥ 5% patients in any group.**

| SOC<br>Preferred Term[1] | Yer + Bud<br>N=58<br>n (%) | Yer + Pbo<br>N=57<br>n (%) |
|---|---|---|
| Number of patients with ≥ 1 such SAE | 34 (58.6) | 31 (54.4) |
| **Endocrine disorders** | 3 (5.2) | 4 (7.0) |
| Hypopituitarism | 3 (5.2) | 2 (3.5) |
| **Gastrointestinal disorders** | 19 (32.8) | 14 (24.6) |
| Abdominal pain | 1 (1.7) | 4 (7.0) |
| Colitis | 6 (10.3) | 7 (12.3) |
| Diarrhoea | 7 (12.1) | 7 (12.3) |
| **General disorders and admin site** | 6 (10.3) | 7 (12.3) |
| Disease progression | 5 (8.6) | 6 (10.5) |
| **Hepatobiliary disorders** | 4 (6.9) | 7 (12.3) |
| Autoimmune hepatitis | 4 (6.9) | 3 (5.3) |
| **Investigations** | 2 (3.4) | 3 (5.3) |
| ALT ↑ | 1 (1.7) | 3 (5.3) |
| AST ↑ | 1 (1.7) | 3 (5.3) |
| **Metabolism and nutrition** | 3 (5.2) | 5 (8.8) |
| Dehydration | 1 (1.7) | 3 (5.3) |

### *CA184008*

Deaths (among all treated subjects) considered by investigators to be at least possibly related to study drug in Study CA184008 are shown in Table 44.

**Table 44. Deaths. Possibly related to treatment.**

| Study day of last dose/ Study day of death | Stated cause of death | Relevant AE |
|---|---|---|
| **≤ 70 days after last dose** | | |
| 1/7 | Progressive disease | Multi-organ failure (possibly related) |
| 22/40 | Study drug toxicity (glomerulonephritis) | Glomerulonephriris acute (possibly related) |
| 64/87 | Study drug toxicity (liver dysfunction) | Hepatic function abnormal (possibly related) |
| **> 70 days after last dose** | | |
| 1/127 | Study drug toxicity (acute myeloid leukaemia) | Acute myeloid leukaemia (possibly related) |
| 43/115 | Hypovolaemic shock | Hypovolaemic shock (possibly related) |

SAEs (any grade) occurring between the first dose and up to 70 days (5 half-lives) after the last dose of study therapy were reported for 83 (53.5%) subjects and were reported as Grade 3-4 for 37 (23.9%) subjects. SAEs reported for ≥ 5% of patients during the same period ("on study") are tabulated below in Table 45.

**Table 45. SAE reported for ≥ 5% of patients. On study.**

| Body System Preferred Term | No. of patients (%) with worst SAE grade | | |
|---|---|---|---|
| | Any grade | Severe (Grade 3-4) | Fatal (Grade 5) |
| Any SAE | 83 (53.5) | 37 (23.9) | 32 (20.6) |
| GI disorders | 29 (18.7) | 20 (12.9) | 0 |
| Diarrhoea | 17 (11.0) | 10 (6.5) | 0 |
| Colitis | 13 (8.4) | 5 (3.2) | 0 |
| General disorders and admin site conditions | 26 (16.8) | 4 (2.6) | 15 (9.7) |
| Disease progression | 14 (9.0) | 0 | 14 (9.0) |
| | | | |
| Any drug-related SAE | 49 (31.6) | 30 (19.4) | 4 (2.6) |
| GI disorders | 23 (14.8) | 13 (8.4) | 0 |
| Diarrhoea | 17 (11.0) | 9 (5.8) | 0 |
| Colitis | 13 (8.4) | 5 (3.2) | 0 |

*MDX010-20*

Deaths considered by investigators to be at least possibly related to study drug were as shown below in Table 46.

**Table 46. Deaths possibly related to treatment. (Table continued across two pages.)**

| Demographics | Study day of death/ Death within 70 days of last dose? | Stated cause of death | Drug-related AEs with outcome death |
|---|---|---|---|
| **Yervoy + gp100** | | | |
| 70/M | 108/Y | Malignant disease | Grade 4 hyponatraemia<br>Grade 3 colitis<br>Grade 2 bilateral leg swelling<br>Grade 1 rash<br>Grade 1 anaemia<br>Grade 1 leucocytosis |
| 46/M | 22/Y | Sepsis with other condition of metastatic melanoma on death<br>certificate | Grade 5 sepsis |
| 58/F | 91/Y | Bowel perforation<br>due to ischemic colitis | Grade 1 injection site reaction - arms<br>Grade 5 inflammatory colitis<br>Grade 5 GI perforation<br>Grade 5 infection-septic shock |
| 53/M | 489/N | Myelofibrosis | Grade 5 myelofibrosis |
| 59/M | 25/Y | Malignant disease | Grade 5 bowel perforation |
| 42/M | 18/Y | Acute respiratory distress syndrome | Grade 5 acute respiratory distress syndrome |
| 69/M | 66/Y | Toxicity | Grade 5 multi-organ failure<br>Grade 5 peritonitis<br>Grade 3 diarrhoea |
| 62/M | 102/Y | Toxicity | Grade 5 Guillain-Barre Syndrome |
| **Yervoy monotherapy** | | | |
| 62/M | 25/Y | Liver failure | Grade 5 liver failure<br>Grade 3 possible sepsis<br>Grade 4 possible tumour lysis syndrome<br>Grade 4 renal insufficiency<br>Grade 4 respiratory failure<br>Grade 4 hypotension |

| | | | |
|---|---|---|---|
| 77/F | 193/N | Bowel perforation | Grade 5 bowel perforation |
| 60/F | 123/N | Toxicity | Grade 5 severe infection<br>Grade 5 renal failure<br>Grade 5 septic shock |
| 55/M | 20/Y | Vascular leak syndrome | Grade 5 vascular leak |
| **gp100 monotherapy** | | | |
| 67/F | 85/Y | Malignant disease | Grade 1 Loss of appetite |
| 43/M | 37/Y | Septic shock | Grade 5 septic shock |

Treatment emergent SAEs classified as at least possibly related to study drug are tabulated below in Table 47.

**Table 47. TEAEs possibly related to treatment.**

| SOC<br>Preferred Term[1] | Yervoy + gp100<br>N=380<br>n (%) | Yervoy<br>N=131<br>n (%) | gp100<br>N=132<br>n (%) |
|---|---|---|---|
| Number of patients with ≥ 1 SAE | 54 (14.2%) | 24 (18.3%) | 5 (3.8%) |
| **Blood and lymphatic system disorders** | 3 (0.8%) | 1 (0.8%) | 0 |
| **Endocrine disorders** | 4 (1.1%) | 5 (3.8%) | 0 |
| Hypophysitis | 1 (0.3%) | 2 (1.5%) | 0 |
| Hypopituitarism | 3 (0.8%) | 2 (1.5%) | 0 |
| **Eye disorders** | 1 (0.3%) | 0 | 0 |
| **Gastrointestinal disorders** | 27 (7.1%) | 11 (8.4%) | 2 (1.5%) |
| Colitis | 14 (3.7%) | 7 5.3%) | 0 |
| Diarrhoea | 15 (3.9%) | 5 (3.8%) | 0 |
| **General disorders and administration site conditions** | 8 (2.1%) | 3 (2.3%) | 0 |
| Pyrexia | 4 (1.1%) | 0 | 0 |
| **Hepatobiliary disorders** | 1 (0.3%) | 1 (0.8%) | 0 |
| **Immune system disorders** | 1 (0.3%) | 0 | 0 |
| **Infections and infestations** | 7 (1.8%) | 4 (3.1%) | 1 (0.8%) |
| **Investigations** | 0 | 1 (0.8%) | 1 (0.8%) |
| **Metabolism and nutrition disorders** | 2 (0.5%) | 1 (0.8%) | 1 (0.8%) |
| **Musculoskeletal and connective tissue disorders** | 3 (0.8%) | 0 | 1 (0.8%) |
| **Neoplasms** | 1 (0.3%) | 0 | 0 |
| **Nervous system disorders** | 3 (0.8%) | 0 | 1 (0.8%) |
| **Psychiatric disorders** | 0 | 0 | 1 (0.8%) |
| **Renal and urinary disorders** | 0 | 3 (2.3%) | 0 |
| Renal failure | 0 | 2 (1.5%) | 0 |
| **Respiratory, thoracic and mediastinal disorders** | 3 (0.8%) | 1 (0.8%) | 0 |
| **Skin and subcutaneous tissue** | 6 (1.6%) | 0 | 0 |
| **Vascular disorders** | 0 | 4 (3.1%) | 1 (0.8%) |
| Hypotension | 0 | 2 (1.5%) | 0 |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 1% in any group.

*MDX010-08*

Deaths (among all treated subjects) considered by investigators as having a suspected relationship[1] to study drug were as shown below in Table 48. None of these patients was in the crossover group.

**Table 48. Deaths suspected to be related to treatment.**

| Age/Sex | Days from first dose to death | Stated cause of death |
|---|---|---|
| **Yervoy** | | |
| 68/M | 108 | Pulmonary embolus and sepsis |
| **Yervoy + DTIC** | | |
| 70/M | 86 | Disease progression |
| 60/M | 59 | Multi-organ failure |

[1] Or no assessment of relationship reported.

SAEs classified as at least possibly related to study drug are tabulated below in Table 49. None of these occurred in the crossover group.

**Table 49. SAEs possibly related to treatment.**

| **SOC**<br>Preferred Term[1] | **Yervoy**<br>**N=39**<br>**n (%)** | **Yervoy + DTIC**<br>**N=35**<br>**n (%)** |
|---|---|---|
| Number of patients with ≥ 1 such SAE | 5 (12.8) | 6 (17.1) |
| | | |
| **Blood and lymphatic system disorders** | 0 | 1 (2.9) |
| **Eye disorders** | 1 (2.6) | 0 |
| **Gastrointestinal disorders** | 4 (10.3) | 2 (5.7) |
| Colitis | 3 (7.7) | 1 (2.9) |
| Diarrhoea | 2 (5.1) | 2 (5.7) |
| **General disorders and administration site conditions** | 1 (2.6) | 2 (5.7) |
| **Psychiatric disorders** | 1 (2.6) | 0 |
| **Skin and subcutaneous tissue** | 0 | 1 (2.9) |
| **Vascular disorders** | 0 | 1 (2.9) |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 2 patients in any group.

*CA184022*

Deaths are shown in Table 50 with SAEs in Table 51.

**Table 50. Deaths within 70 days following exposure. Number (%) of patients, by cause.**

| Cause | 0-30 days after last dose of study therapy | | | 0-70 days after last dose of study therapy | | |
|---|---|---|---|---|---|---|
| | 0.3 mg/kg N=72 | 3 mg/kg N=71 | 10 mg/kg N=71 | 0.3 mg/kg N=72 | 3 mg/kg N=71 | 10 mg/kg N=71 |
| Total | 9 (12.5) | 6 (8.5) | 10 (14.1) | 18 (25.0) | 18 (25.4) | 18 (25.4) |
| | | | | | | |
| Progressive disease | 8 (11.1) | 4 (5.6) | 10 (14.1) | 16 (22.2) | 15 (21.1) | 17 (23.9) |
| Other | | | | | | |
| Pulmonary embolus | 1 (1.4) | 0 | 0 | 0 | 0 | 0 |
| Myocardial infarct | | 1 (1.4) | | | | |
| Respiratory infection | | 1 (1.4) | | | | |
| Multi-organ failure | | | | | | 1 (1.4) |
| Unknown or not specified | 0 | 0 | 0 | 1 (1.4) | 1 (1.4) | 0 |

**Table 51. SAEs classified as at least possibly related to study drug.**

| SOC<br>Preferred Term[1] | 0.3 mg/kg<br>N=72<br>n (%) | 3 mg/kg<br>N=71<br>n (%) | 10 mg/kg<br>N=71<br>n (%) |
|---|---|---|---|
| Number of patients with ≥ 1 such SAE | 6 (8.3) | 13 (18.3) | 19 (26.8) |
| | | | |
| **Blood and lymphatic system disorders** | 2 (2.8) | | 1 (1.4) |
| Anaemia | 2 (2.8) | | 1 (1.4) |
| **Endocrine disorders** | | 2 (2.8) | 2 (2.8) |
| Hypophysitis | | 2 (2.8) | 2 (2.8) |
| **Eye disorders** | 1 (1.4) | | 1 (1.4) |
| **Gastrointestinal disorders** | | 7 (9.9) | 12 (16.9) |
| Colitis | | 3 (4.2) | 3 (4.2) |
| Diarrhoea | | 3 (4.2) | 11 (15.5) |
| Enterocolitis | | | 2 (2.8) |
| Vomiting | | | 2 (2.8) |
| **General disorders and admin site** | 2 (2.8) | 3 (4.2) | |
| Pyrexia | 1 (1.4) | 2 (2.8) | |
| **Immune system disorders** | | | 1 (1.4) |
| **Infections and infestations** | | 3 (4.2) | 1 (1.4) |
| **Investigations** | 1 (1.4) | | 3 (4.2) |
| ALT increased | | | 2 (2.8) |
| **Metabolism and nutrition** | 1 (1.4) | 1 (1.4) | 2 (2.8) |
| **Musculoskeletal and connective tissue** | 1 (1.4) | 1 (1.4) | |
| **Neoplasms** | 1 (1.4) | | |
| **Nervous system disorders** | | 1 (1.4) | 2 (2.8) |
| **Psychiatric disorders** | | 1 (1.4) | |
| **Respiratory, thoracic and mediastinal** | | | 1 (1.4) |

[1] The SOC counts are comprehensive; Preferred Terms are included only when reported in ≥ 2 patients in any group.

### *Ancillary studies*

All patients with SAEs at least possibly related to a study drug (Table 52) are counted in the total but only SAEs occurring in ≥ 5% patients in any group are listed in the last column of the table below. Numbers of on-study deaths are listed in the second column.

**Table 52. Number of SAEs and deaths.**

| Study | On-study deaths (cause) | No. of patients with such SAE /N | SAEs occurring in ≥ 5% treated patients, with frequencies |
|---|---|---|---|
| CA184042 | 14 (PD) | 7/28 | 3 colitis, 3 diarrhoea, 2 dehydration |
| MDX010-19 | 3 (PD) | 29/88 | 12 colitis, 10 diarrhoea, 6 hypophysitis |
| MDX010-13 | 0 | 13/24 | 2 abdominal pain, 2 diarrhoea, 3 hypokalaemia, 2 hypophosphataemia, |
| MDX010-05 | 1 (PD) | 19/56 | 4 abdominal pain, 9 colitis, 8 diarrhoea, 3 rash |
| MDXCTLA4-04 | 0 | 0/13 | |
| MDX010-03 | 0 | 4/19 | 4 diarrhoea |
| MDX010-07 | 1 (PD) | 7 /44 | |
| MDX010-17 | 12 (PD) | 7/28 | Data not presented |
| MDX010-12 | 0 | 3/31 | 2 colitis |
| MDX010-11 | 1 (bowel perforation) | 20/61 | 16 colitis, 16 diarrhoea |
| MDX010-23 | 0 | 1/6 | 1 diarrhoea, 1 vomiting |
| MDX010-24 | 9 (PD) | 4/27 | |

### *Ongoing studies*

*CA184045*

As of 6 January 2010, a total of 870 subjects were enrolled and treated with 10 mg/kg of Yervoy (four induction doses every three weeks and maintenance every 12 weeks starting at Week 24). On-study SAEs were reported for 62.1% (540/870) of the subjects, of which 26.1% (227/870) were drug related. The most common treatment related SAEs included diarrhoea (9.3%), colitis (7.5%), dehydration (4.1%), vomiting (3.4%), nausea (3.1%), fatigue (2.6%), elevated ALT (1.6%), elevated AST (1.5%), abdominal pain (1.5%), hypophysitis (1.5%), pyrexia (1.3%) and hypopituitarism (1.1%). AEs leading to study drug discontinuation were reported in 33.7% of subjects with the most common being disease progression (13.8%), colitis (4.6%) and diarrhoea (3.6%). There were four deaths reported as possibly related to Yervoy, which included multiorgan failure, sepsis, acute respiratory distress syndrome (ARDS) with extensive disease in the lung and melanoma infiltration in the alveolar space, and large intestine perforation. No new types of SAEs were observed in this expanded access study and the SAE profile was considered consistent with that observed at the same dose of 10 mg/kg in the Phase II program.

*CA184025*

No deaths were reported. Two GI perforations were reported.

### *Studies of specific effects relating to safety*

*ECG*

An *Interim Report of ECG Findings* from Study MDX010-21 was presented. The only general information about Study MDX010-21 included in the current Australian submission is that shown at Table 20 above but apparently the study included routine ECG monitoring.

Two ECG 2 reports were included; the first, dated 22 August 2008, related to ECGs from 14 patients, and the second, dated 26 February 2010, related to 28 patients. These 28 included at least some of the original 14. The first report included the following findings:

> "... seven ECGs were considered Abnormal, Clinically Significant (ACS).
>
> The seven ECGs labelled ACS represent four patients. One patient had two ECGs labelled as ACS after the screening ECG labelled as ACI. Both of these were because of a long QTcB (Bazett's corrected QT-interval).
>
> Another patient had a V6 ECG as ACS due to a prolonged QTcB.
>
> A third patient had three ACS ECGs due to atrial fibrillation. These were during unscheduled ECGs. The final ECG for this patient demonstrated sinus rhythm.
>
> A fourth had an ACS ECG at Visit 6. This was due to the presence of atrial fibrillation."

The second report included the following:

> "After the screening ECGs, there was a trend towards higher heart rates. There were only three patients with APCS ECGs after screening, one of which was from a patient who presented with APCS.
>
> There were no trends indicating increasing QRS duration. Two patients had QRS durations greater than 110 ms and an increase of greater than 10%. No QRS duration exceeded 120 ms.
>
> There were no QTcF measurements greater than 500 ms. Two ECG had QTcF measurements greater than 470 ms. These were both seen in the same patient (492 ms and 479 ms. Both in the presence of a high heart rate (93 beats per minute (bpm) and 101 bpm, respectively). The investigators interpreted these ECGs as APCS."

The sponsor's Medical Monitor wrote an assessment which included the following:

> **"Sponsor's Conclusions Regarding QT Prolongation:**
>
> Overall, given the fluctuating nature of the modest QTcB changes over a short period of time, the lack of clinically significant QTcF findings, their temporal association to adverse events with significant physiological stress, and the long time span from last dose of study drug, it is difficult to attribute any relatedness (or significance) to ipilimumab."
>
> and
>
> **"Sponsor's Conclusions Regarding Atrial Fibrillation**
>
> In this population, atrial fibrillation is fairly common. In both cases the events ultimately resolved without specific intervention by management of the other concomitant medical issues. Therefore, these probably do not represent a clinically significant finding."

The sponsor's *Clinical Overview* does not include any comment on this study.

*Laboratory findings in clinical efficacy and safety studies*

The evaluator found it difficult to derive useful information about the drug from routine blood monitoring in advanced disease.

*CA184007*

Routine haematology monitoring was unremarkable. Increased ALT was reported as Grade 3-4 for 7 (12.5%) subjects in the budesonide group and 7 (12.7%) subjects in the placebo group; increased AST was reported as Grade 3-4 for 5 (8.9%) subjects in the budesonide group and 8 (14.5%) subjects in the placebo group. Grade 4 ALT was reported for 7 subjects (3 budesonide, 4 placebo); and Grade 4 AST was reported for 7 subjects (2 budesonide, 5 placebo). All but one of these subjects had Grade 4 ALT and Grade 4 AST reported concurrently; two subjects had Grade 4 ALT and Grade 4 AST reported as SAEs both of which were assessed as probably related to study therapy; one subject with Grade 4 ALT and Grade 4 AST had an SAE of autoimmune hepatitis which the investigator assessed as certainly related to study therapy.

Elevated liver function tests (LFTs) at baseline were not associated with development of drug-related elevated LFTs. Nine subjects across both groups had elevated (Grade 1-2) LFTs at baseline or before treatment; of these, only one subject developed Grade 3-4 elevated LFTs on treatment, and this was attributed to PD from a pre-existing liver metastasis.

Two of 115 subjects developed a positive HAHA; these were positive only at the 1:10 dilution (considered borderline positive) and directed to the Ig portion of ipilimumab. Neither subject had any infusion related, peri-infusional hypersensitivity or anaphylactic reactions.

*CA184008*

Routine haematology and biochemical laboratory monitoring did not reveal any notable abnormality which could be related to the test drug, as would be expected in an uncontrolled trial in a seriously ill population.

Of the four subjects who developed a positive anti-ipilimumab antibody response, none had any infusion related, peri-infusional hypersensitivity or anaphylactic reactions.

*MDX010-20*

As well as standard haematology and biochemistry, an autoimmune panel (including rheumatoid factor, antinuclear antibody (ANA), erythrocyte sedimentation rate (ESR)) and thyroid function tests were routinely performed.

On-study abnormalities in WBC, ANC and platelets were primarily Grade 1-2 in severity. Grade 3-4 abnormalities in ANC were reported in < 1% of subjects in each group. No Grade 3-4 abnormalities in WBC or platelets were reported in any group. On-study haemoglobin abnormalities were common (~ 50% of subjects) and almost entirely of Grade 1-2 in severity. Grade 3-4 haemoglobin abnormalities were reported in 1.7%, 0.8% and 4.0% of subjects in the ipilimumab + gp100, ipilimumab monotherapy and gp100 monotherapy groups, respectively.

For most parameters, there was no notable difference between the groups.

***MDX010-08***

In this trial against the combination with DTIC, there were no consistent patterns in clinical laboratory values over time that would indicate that treatment with ipilimumab resulted in clinically meaningful abnormalities.

***CA184004***

No systematic changes were noted in routine monitoring of haematology or biochemical parameters. A total of four out of 82 subjects developed a positive HAHA; these were

positive at the 1:10 dilution (and therefore considered borderline positive) and directed to the Ig portion of ipilimumab.

***CA184022***

No systematic changes were noted in routine monitoring of haematology parameters. Minor changes in LFTs were noted.

Sixteen subjects developed a positive HAHA; however, 13 of these 16 subjects were positive only in the 1:10 dilution sample and it was directed to the Ig portion of ipilimumab.

**Discontinuation due to adverse events**

Table 53 summarises the results from the Phase I studies.

**Table 53. Summary of Phase I studies.**

| Study | Number discontinuing (AE) |
|---|---|
| MDXCTLA4-01 | 0 |
| MDXCTLA4-02 | 0 |
| MDX010-15 | 5 (2 colitis; 2 CNS metastases; 1 facial palsy) |

***Studies beyond Phase I***

***CA184004***

A summary of on study AEs classified as drug related and leading to discontinuation of study therapy in treated subjects is provided in Table 54.

**Table 54. AEs leading to study discontinuation and considered treatment related.**

| SOC<br>Preferred Term | Yervoy<br>3 mg/kg<br>N=40<br>n (%) | Yervoy<br>10 mg/kg<br>N=42<br>n (%) |
|---|---|---|
| Number of patients with any such AE | 5 (12.5) | 11 (26.2) |
| **Cardiac disorders** | | 1 (2.4) |
| Cardiomyopathy | | 1 (2.4) |
| Myocarditis | | 1 (2.4) |
| **Endocrine disorders** | 2 (5.0) | 2 (4.8) |
| Hypopituitarism | 2 (5.0) | 1 (2.4) |
| Hypophysitis | | 1 (2.4) |
| **Gastrointestinal disorders** | 1 (2.5) | 3 (7.1) |
| Colitis | 1 (2.5) | 3 (7.1) |
| Diarrhoea | | 2 (4.8) |
| **Hepatobiliary disorders** | | 1 (2.4) |
| Hepatitis | | 1 (2.4) |
| **Metabolism and nutrition disorders** | 2 (5.0) | 2 (4.8) |
| Anorexia | 2 (5.0) | 2 (4.8) |
| Dehydration | | 1 (2.4) |
| **Nervous system disorders** | 2 (5.0) | 2 (4.8) |
| Convulsion | 1 (2.5) | |
| Headache | 1 (2.5) | |
| Oedema brain | | 1 (2.4) |
| Cognitive disorder | | 1 (2.4) |
| **Psychiatric disorders** | 1 (2.5) | |
| Depression | 1 (2.5) | |
| **Respiratory, thoracic and mediastinal** | | 3 (7.1) |
| Dyspnoea | | 1 (2.4) |
| Pleural effusion | | 1 (2.4) |
| Pneumonitis | | 1 (2.4) |
| **Skin and subcutaneous tissue** | | 1 (2.4) |
| Rash | | 1 (2.4) |

### *CA184008*

A summary of on study AEs classified as drug related and leading to discontinuation of study therapy in treated subjects is provided in Table 55 below.

**Table 55. AEs classified as drug-related and leading to discontinuation of study therapy. (Table continued across two pages.)**

| **Body System** | **No. of patients (%) with worst AE grade** | | |
|---|---|---|---|
| Preferred Term | **Any grade** | **Severe (Grade 3-4)** | **Fatal (grade 5)** |
| Any drug-related AE leading to discontinuation | 28 (18.1) | 20 (12.9) | 3 (1.9) |
| GI disorders | 13 (8.4) | 9 (5.8) | 0 |
| Colitis | 9 (5.8) | 3 (1.9) | 0 |
| Diarrhoea | 8 (5.2) | 7 (4.5) | 0 |
| Vomiting | 2 (1.3) | 1 (0.6) | 0 |
| Gastritis erosive | 1 (0.6) | 0 | 0 |
| Pancreatitis | 1 (0.6) | 0 | 0 |
| Investigations | 5 (3.2) | 5 (3.2) | 0 |
| AST↑ | 4 (2.6) | 4 (2.6) | 0 |
| ALT↑ | 2 (1.3) | 1 (0.6) | 0 |
| GGT↑ | 1 (0.6) | 1 (0.6) | 0 |
| Transaminases↑ | 1 (0.6) | 1 (0.6) | 0 |
| General disorders and admin site | 3 (1.9) | 1 (0.6) | 1 (0.6) |
| Asthenia | 1 (0.6) | 1 (0.6) | 0 |
| Multi-organ failure | 1 (0.6) | 0 | 1 (0.6) |
| Pyrexia | 1 (0.6) | 0 | 0 |
| Hepatobiliary disorders | 3 (1.9) | 2 (1.3) | 1 (0.6) |
| Autoimmune hepatitis | 2 | 2 | 0 |
| Hepatic function abnormal | 1 | 0 | 1 |
| Endocrine disorders | 2 | 1 | 0 |
| Hypophysitis | 1 | 1 | 0 |
| Thyroiditis | 1 | 0 | 0 |
| Renal and urinary disorders | 2 | 1 | 0 |
| Glomerulonephritis acute | 1 | 0 | 0 |
| Haematuria | 1 | 0 | 0 |
| Proteinuria | 1 | 1 | 0 |
| Blood and lymphatic system | 1 | 0 | 0 |
| Anaemia | 1 | 0 | 0 |

| | | | |
|---|---|---|---|
| Metabolism and nutrition | 1 | 1 | 0 |
| Hypoalbuminaemia | 1 | 0 | 0 |
| Malnutrition | 1 | 0 | 0 |
| Metabolic acidosis | 1 | 1 | 0 |
| Musculoskeletal and connective | 1 | 1 | 0 |
| Arthritis | 1 | 1 | 0 |
| Neoplasms | 1 | 0 | 1 |
| Acute myeloid leukaemia | 1 | 0 | 1 |
| Nervous system disorders | 1 | 1 | 0 |
| Headache | 1 | 1 | 0 |
| Skin and subcutaneous tissue | 1 | 1 | 0 |
| Rash generalised | 1 | 1 | 0 |
| Vascular disorders | 1 | 0 | 0 |
| Temporal arteritis | 1 | 0 | 0 |

***MDX010-20***

A summary of TEAEs leading to discontinuation of study therapy are provided below in Table 56.

**Table 56. TAEs leading to discontinuation of study therapy. Safety population. (Table continued over two pages.)**

| **SOC**<br>Preferred Term | **Yervoy + gp100**<br>**N=380** | **Yervoy**<br>**N=131** | **gp100**<br>**N=132** |
|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** |
| Any such AE leading to discontinuation | 35 (9.2) | 17 (13.0) | 5 (3.8) |
| **Blood and lymphatic system disorders** | 2 (0.5) | 0 | 0 |
| Anaemia | 1 (0.3) | 0 | 0 |
| Haemolytic anaemia | 1 (0.3) | 0 | 0 |
| **Cardiac disorders** | 1 (0.3) | 0 | 0 |
| Cardiac failure | 1 (0.3) | 0 | 0 |
| **Endocrine disorders** | 0 | 1 (0.8) | 0 |
| Hypopituitarism | 0 | 1 (0.8) | 0 |
| **Eye disorders** | 0 | 2 (1.5) | 0 |
| Uveitis | 0 | 2 (1.5) | 0 |
| **Gastrointestinal disorders** | 19 (5.0) | 5 (3.8) | 1 (0.8) |
| Colitis | 10 (2.6) | 3 (2.3) | 0 |
| Diarrhoea | 10 (2.6) | 2 (1.5) | 0 |
| Intestinal perforation | 1 (0.3) | 0 | 0 |
| Vomiting | 0 | 0 | 1 (0.8) |
| **General disorders and administration site conditions** | 1 (0.3) | 0 | 1 (0.8) |
| Asthenia | 0 | 0 | 1 (0.8) |
| General physical health deterioration | 1 (0.3) | 0 | 0 |
| **Hepatobiliary disorders** | 1 (0.3) | 2 (1.5) | 0 |
| Cholecystitis | 0 | 1 (0.8) | 0 |
| Hepatic failure | 0 | 1 (0.8) | 0 |
| Hepatitis | 1 (0.3) | 0 | 0 |
| **Infections and infestations** | 1 (0.3) | 3 (2.3) | 1 (0.8) |
| Sepsis | 1 (0.3) | 2 (1.5) | 0 |
| Hepatitis B | 0 | 1 (0.8) | 0 |
| Septic shock | 0 | 0 | 1 (0.8) |
| **Injury, poisoning, procedural comp** | 2 (0.5) | 0 | 0 |

| | | | |
|---|---|---|---|
| Cervical vertebral fracture | 1 (0.3) | 0 | 0 |
| Procedural complication | 1 (0.3) | 0 | 0 |
| **Investigations** | 1 (0.3) | 2 (1.5) | 1 (0.8) |
| Blood creatinine ↑ | 1 (0.3) | 1 (0.8) | 0 |
| GGT ↑ | 0 | 0 | 1 (0.8) |
| Weight ↑ | 0 | 1 (0.8) | 0 |
| **Metabolism and nutrition disorders** | 1 (0.3) | 1 (0.8) | 0 |
| Malnutrition | 1 (0.3) | 0 | 0 |
| Tumour lysis syndrome | 0 | 1 (0.8) | 0 |
| **Musculoskeletal & connective tissue** | 1 (0.3) | 0 | 1 (0.8) |
| Pain in extremity | 0 | 0 | 1 (0.8) |
| Polymyalgia rheumatica | 1 (0.3) | 0 | 0 |
| **Neoplasms** | 1 (0.3) | 0 | 0 |
| Metastatic malignant melanoma | 1 (0.3) | 0 | 0 |
| **Nervous system disorders** | 2 (0.5) | 1 (0.8) | 0 |
| Haemorrhage intracranial | 1 (0.3) | 0 | 0 |
| Headache | 0 | 1 (0.8) | 0 |
| Meningeal disorder | 1 (0.3) | 0 | 0 |
| **Renal and urinary disorders** | 0 | 2 (1.5) | 0 |
| Glomerulonephritis | 0 | 1 (0.8) | 0 |
| Renal failure | 0 | 1 (0.8) | 0 |
| **Respiratory, thoracic and mediastinal** | 2 (0.5) | 2 (1.5) | 1 (0.8) |
| Dyspnoea | 0 | 1 (0.8) | 1 (0.8) |
| Pleural effusion | 1 (0.3) | 0 | 0 |
| Pneumonitis | 1 (0.3) | 0 | 0 |
| Respiratory failure | 0 | 1 (0.8) | 0 |
| **Skin and subcutaneous tissue** | 0 | 2 (1.5) | 0 |
| Decubitus ulcer | 0 | 1 (0.8) | 0 |
| Rash erythematous | 0 | 1 (0.8) | 0 |
| **Vascular disorders** | 1 (0.3) | 0 | 0 |
| Lymphoedema | 1 (0.3) | 0 | 0 |

### *MDX010-08*

A summary of patients who discontinued study therapy due to AE is given below in Table 57. None of these was in the crossover group.

**Table 57. Summary of patients who discontinued study therapy due to AE.**

| AE | Study day of AE onset | Relationship |
|---|---|---|
| **Yervoy** | | |
| Uveitis &<br>colitis | 67<br>85 | Suspected<br>Suspected |
| Colitis | 73 | Suspected |
| Disease progression | 52 | Not suspected |
| **Yervoy + DTIC** | | |
| Pneumonia | 54 | Not suspected |
| Pruritic rash | 19 | Suspected |
| Multi-organ failure | 58 | Suspected |
| AST ↑ and ALT ↑ | 57 | Suspected |
| Rash | 57 | Suspected |

### *CA184022*

A summary of treatment-emergent AEs leading to discontinuation of study therapy is provided below (Table 58).

**Table 58. Summary of treatment-emergent AEs leading to discontinuation of study therapy. (Table continued across two pages.)**

| **SOC** Preferred Term **n (%)** | **0.3 mg/kg N=72** | **3 mg/kg N=71** | **10 mg/kg N=71** |
|---|---|---|---|
| Any such AE leading to discontinuation | 9 (12.5) | 7 (9.9) | 19 (26.8) |
| **Endocrine disorders** | | 1 (1.4) | 1 (1.4) |
| Hypophysitis | | | 1 (1.4) |
| Hypopituitarism | | 1 (1.4) | |
| **Eye disorders** | | | 1 (1.4) |
| Vision blurred | | | 1 (1.4) |
| **Gastrointestinal disorders** | 1 (1.4) | 2 (2.8) | 7 (9.9) |
| Blood in stool | | | 1 (1.4) |
| Colitis | | 1 (1.4) | |
| Diarrhoea | | 1 (1.4) | 6 (8.5) |
| Enteritis | | 1 (1.4) | |
| Enterocolitis | | | 1 (1.4) |
| Nausea | 1 (1.4) | | |
| Vomiting | | | 1 (1.4) |
| **General disorders & Admin site cond** | 8 (11.1) | 1 (1.4) | 6 (8.5) |
| Asthenia | 1 (1.4) | | 1 (1.4) |
| Death | 2 (2.8) | | |
| Disease progression | 5 (6.9) | 1 (1.4) | 3 (4.2) |
| Fatigue | 2 (2.8) | | 1 (1.4) |
| General physical health deterioration | 1 (1.4) | | 1 (1.4) |
| Pyrexia | | | 1 (1.4) |
| **Hepatobiliary disorders** | | | 1 (1.4) |
| Hepatic failure | | | 1 (1.4) |
| **Infections and infestations** | | 2 (2.8) | |
| Respiratory tract infection | | 1 (1.4) | |
| Sepsis | | 1 (1.4) | |
| **Investigations** | 1 (1.4) | | 3 (4.2) |
| ALT ↑ | | | 2 (2.8) |
| AST ↑ | | | 1 (1.4) |
| Haemoglobin ↓ | | | 1 (1.4) |
| Weight ↓ | 1 (1.4) | | |
| **Metabolism and nutrition disorders** | 2 (2.8) | 1 (1.4) | 1 (1.4) |
| Anorexia | 1 (1.4) | | |

| | | | |
|---|---|---|---|
| Dehydration | 1 (1.4) | | |
| Hyperglycaemia | | 1 (1.4) | |
| Metabolic acidosis | | | 1 (1.4) |
| **Musculoskeletal & connective tissue** | 2 (2.8) | | |
| Back pain | 1 (1.4) | | |
| Bone pain | 1 (1.4) | | |
| Musculoskeletal pain | 1 (1.4) | | |
| Pain in extremity | 1 (1.4) | | |
| **Neoplasms** | | | 5 (7.0) |
| Melanoma | | | 1 (1.4) |
| Metastases to bone | | | 1 (1.4) |
| Metastases to meninges | | | 1 (1.4) |
| Metastatic malignant melanoma | | | 1 (1.4) |
| Tumour pain | | | 1 (1.4) |
| **Nervous system disorders** | | 1 (1.4) | 2 (2.8) |
| Aphasia | | | 1 (1.4) |
| Convulsion | | | 1 (1.4) |
| Facial palsy | | | 1 (1.4) |
| Hydrocephalus | | 1 (1.4) | |
| Somnolence | | | 1 (1.4) |
| **Psychiatric disorders** | | 1 (1.4) | 1 (1.4) |
| Agitation | | | 1 (1.4) |
| Confusional state | | 1 (1.4) | |
| **Renal and urinary disorders** | | | 1 (1.4) |
| Renal failure | | | 1 (1.4) |
| **Respiratory, thoracic and mediastinal** | 1 (1.4) | | 2 (2.8) |
| COPD | | | 1 (1.4) |
| Respiratory alkalosis | | | 1 (1.4) |
| Pulmonary embolism | 1 (1.4) | | |
| **Skin and subcutaneous tissue** | | | 1 (1.4) |
| Rash papular | | | 1 (1.4) |

Admin site cond=administration site condition.

*CA184007*

A summary of drug related AEs leading to discontinuation of study therapy is provided below (Table 59).

**Table 59. Summary of on study AEs classified as drug-related and leading to discontinuation of study therapy in treated subjects.**

| **SOC** Preferred Term | **Yer + Bud N=58** | **Yer + Pbo N=57** |
|---|---|---|
| | **n (%)** | **n (%)** |
| Number of patients with any such AE | 15 (25.9) | 17 (29.8) |
| **Endocrine disorders** | 1 (1.7) | 1 (1.8) |
| Hypopituitarism | 1 (1.7) | 1 (1.8) |
| **Gastrointestinal disorders** | 10 (17.2) | 7 (12.3) |
| Diarrhoea | 7 (12.1) | 5 (8.8) |
| Colitis | 2 (3.4) | 3 (5.3) |
| Diarrhoea, haemorrhagic | 1 (1.7) | |
| Enterocolitis, haemorrhagic | 1 (1.7) | |
| Ileus | 1 (1.7) | |
| Vomiting | | 1 (1.8) |
| **General disorders & admin site cond** | | 1 (1.8) |
| Pyrexia | | 1 (1.8) |
| **Hepatobiliary disorders** | 2 (3.4) | 6 (10.5) |
| Autoimmune hepatitis | 2 (3.4) | 3 (5.3) |
| Jaundice | | 2 (3.5) |
| Hepatitis | | 1 (1.8) |
| Hyperbilirubinaemia | | 1 (1.8) |
| **Infections and infestations** | 1 (1.7) | |
| Enterocolitis infectious | 1 (1.7) | |
| **Investigations** | 1 (1.7) | 2 (3.5) |
| ALT ↑ | 1 (1.7) | 2 (3.5) |
| AST ↑ | 1 (1.7) | 2 (3.5) |
| Bilirubin ↑ | | 1 (1.8) |
| **Metabolism and nutrition disorders** | 1 (1.7) | 1 (1.8) |
| Dehydration | 1 (1.7) | 1 (1.8) |
| **Skin and subcutaneous tissue** | 1 (1.7) | 1 (1.8) |
| Alopecia | | 1 (1.8) |
| Rash | 1 (1.7) | |

## Other safety issues

### *Safety in re-induction*

Adverse effects occurring with repeated treatment in various regimens are included in the data presented above. For the pivotal study, AE data for the patient population which received re-induction treatment were included among the general data but were also extracted and presented separately, as summarised in Table 60 below.

**Table 60. Study MDX010-20. Number of subjects experiencing AEs during re-induction cycles.**

| | **Yervoy + gp100 N=29** | **Yervoy N=9** | **gp100 N=2** |
|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** |
| Any AE | 27 (93.1) | 9 (100.0) | 2 (100.0) |
| Any drug related AE | 25 (86.2) | 7 (77.8) | 2 (100.0) |
| Any Grade 3-4 drug related AE | 6 (20.7) | 3 (33.3) | 0 |
| Any irAE | 15 (51.7) | 7 (77.8) | 1 (50.0) |
| Any Grade 3-4 irAE | 2 (6.9) | 2 (22.2) | 0 |
| Any drug related SAE | 4 (13.8) | 1 (11.1) | 0 |
| Any drug related AE leading to discontinuation | 1 (3.4) | 0 | 0 |
| Deaths | 1 (3.4) | 0 | 0 |
| Malignant disease | 1 (3.4) | 0 | 0 |

Table 61 describes treatment related AEs reported in ≥ 2 patients in any group during the re-induction cycles.

**Table 61. Study MDX010-20.Treatment-related AEs reported in ≥ 2 patients in any group during re-induction cycles.**

| SOC<br>Preferred Term | Yervoy + gp100<br>N=29 | Yervoy<br>N=9 | gp100<br>N=2 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Any drug-related AE | 25 (86.2) | 7 (77.8) | 2 (100.0) |
| **Eye disorders** | 2 (6.9) | 1 (11.1) | 0 |
| Vision blurred | 2 (6.9) | 0 | 0 |
| **Gastrointestinal disorders** | 10 (34.5) | 3 (33.3) | 0 |
| Diarrhoea | 5 (17.2) | 3 (33.3) | 0 |
| Constipation | 2 (6.9) | 1 (11.1) | 0 |
| Nausea | 3 (10.3) | 1 (11.1) | 0 |
| Abdominal pain | 2 (6.9) | 0 | 0 |
| Vomiting | 2 (6.9) | 0 | 0 |
| **General disorders & admin site cond** | 20 (69.0) | 2 (22.2) | 0 |
| Fatigue | 5 (17.2) | 1 (11.1) | 0 |
| Pyrexia | 3 (10.3) | 1 (11.1) | 0 |
| Chills | 2 (6.9) | 0 | 0 |
| Influenza like illness | 3 (10.3) | 0 | 0 |
| Injection site induration | 3 (10.3) | 0 | 0 |
| Injection site reaction | 12 (41.4) | 0 | 0 |
| **Investigations** | 2 (6.9) | 2 (22.2) | 1 (50.0) |
| Lipase ↑ | 2 (6.9) | 0 | 0 |
| **Metabolism and nutrition disorders** | 2 (6.9) | 1 (11.1) | 0 |
| Appetite↓ | 2 (6.9) | 0 | 0 |
| **Musculoskeletal and connective tissue** | 4 (13.8) | 0 | 1 (50.0) |
| Arthralgia | 3 (10.3) | 0 | 0 |
| **Nervous system disorders** | 3 (10.3) | 1 (11.1) | 0 |
| Headache | 2 (6.9) | 0 | 0 |
| **Skin and subcutaneous tissue** | 12 (41.4) | 6 (66.7) | 0 |
| Pruritus | 7 (24.1) | 4 (44.4) | 0 |
| Rash | 7 (24.1) | 3 (33.3) | 0 |
| Alopecia | 2 (6.9) | 0 | 0 |
| Rash pruritic | 2 (6.9) | 0 | 0 |

No Grade 3-5 hepatic or endocrine irAEs or neurologic irAEs of any grade were reported during re-induction cycles.

Data on AE experience in patients given maintenance treatment in the Phase II studies CA184004, CA184007, CA184008 and CA184042 are also relevant to the question of the safety of repeated treatment. Pooled data are given in Table 62 below**.** Treatment related AEs reported in ≥ 2 patients in any group during re-induction cycles are tabulated in table 63.

**Table 62. Number of subjects experiencing AEs during maintenance phase.**

| | **CA184004/022 Pooled Yer 3mg/kg N=13** | **CA184004/ 007/008/022 Pooled Yer 10mg/kg N=39** | **CA184042 Yer 10mg/kg N=4** |
|---|---|---|---|
| | **n (%)** | **n (%)** | **n (%)** |
| Any AE | 8 (61.5) | 25 (64.1) | 3 (75.0) |
| Any drug related AE | 6 (46.2) | 17 (43.6) | 1 (25.0) |
| Any Grade 3-4 drug related AE | 0 | 6 (15.4) | 0 |
| Any irAE | 6 (46.2) | 14 (35.9) | 1 (25.0) |
| Any Grade 3-4 irAE | 0 | 5 (12.8) | 0 |
| Any drug related SAE | 0 | 4 (10.3) | 0 |
| Any drug related AE leading to discontinuation | 0 | 1 (2.6) | 0 |
| Deaths | 0 | 0 | 0 |

**Table 63. Treatment-related AEs reported in ≥ 2 patients in any group during re-induction cycles.**

| SOC<br>Preferred Term | CA184004/022<br>Pooled<br>Yer 3mg/kg<br>N=13 | CA184004/<br>007/008/022<br>Pooled<br>Yer 10mg/kg<br>N=39 | CA184042<br>Yer 10mg/kg<br>N=4 |
|---|---|---|---|
| | n (%) | n (%) | n (%) |
| Any drug-related AE | 6 (46.2) | 17 (43.6) | 1 (25.0) |
| **Gastrointestinal disorders** | 1 (7.7) | 8 (20.5) | 0 |
| Diarrhoea | 1 (7.7) | 5 (12.8) | 0 |
| Colitis | 0 | 2 (5.1) | 0 |
| **General disorders and administration site conditions** | 0 | 3 (7.7) | 0 |
| Fatigue | 0 | 2 (5.1) | 0 |
| **Skin and subcutaneous tissue** | 5 (38.5) | 7 (17.9) | 1 (25.0) |
| Pruritus | 3 (23.1) | 2 (5.1) | 0 |
| Rash | 2 (15.4) | 3 (7.7) | 1 (25.0) |

### Evaluator's overall conclusions on clinical safety

Adverse effects of Yervoy were particularly seen in the following SOCs (in decreasing order of combined frequency in the two groups on Yervoy in the Phase III study:

*General disorders and Administrative Site Conditions* (62.0%); *Gastrointestinal Disorders* (47.9%); *Skin and Subcutaneous Tissue Disorders* (44.8%); *Musculoskeletal and Connective Tissue Disorders* (16.0%); *Metabolism and Nutrition Disorders* (13.3%); *Nervous System Disorders* (13.3%); *Investigations* (10.0%); *Respiratory, Thoracic and Mediastinal Disorders* (7.0%); *Infections and Infestations* (6.8%); *Vascular Disorders* (6.8%); *Eye Disorders* (6.1%); *Blood and Lymphatic System Disorders* (5.9%); and *Endocrine Disorders* (4.3%).

Many of the AEs fitted the definition of "immune-mediated". On the evidence available, the more common irAEs (in particular, those relating to the gastrointestinal tract) appeared to be dose dependent. The irAEs were generally manageable. An indication of this was the information on gastrointestinal adverse effects in the Phase III study (see Table 64 below).

**Table 64. Gastrointestinal AEs.**

| | Yervoy + gp100 N=380 n (%) | Yervoy N=131 n (%) | gp100 N=132 n (%) |
|---|---|---|---|
| AEs (drug-related) | 182 (47.9) | 63 (48.1) | 49 (37.1) |
| SAEs (drug-related) | 27 (7.1) | 11 (8.4) | 2 (1.5) |
| Discontinuation due to AE | 19 (5.0) | 5 (3.8) | 1 (0.8) |

No particular pattern of AEs emerged from the data relating to re-induction treatment. However, the number of subjects studied was small.

## List of Questions

During 2010, the TGA began to change the way applications were evaluated. As part of this change, after an initial evaluation, a List of Questions to the sponsor is generated.

### 1. Efficacy

The sponsor was asked to explain the inconsistencies in their submission regarding whether Study MDX010-20 was regarded as a pivotal study. In particular, the sponsor was asked to explain why on 15 January 2009 it no longer considered Study MDX010-20 to be pivotal. The sponsor's response is presented in the *Introduction* to the Clinical section.

Following review of the clinical evaluation report (CER), the sponsor also provided other responses to comments made by the clinical evaluator. Most of these have been inserted as *Sponsor comment* above in this AusPAR.

A response was also submitted by the sponsor regarding:

- Potential Bias in PK Parameter Estimates (comment made by clinical evaluator in the section on *Population Pharmacokinetic analysis* above):

The sponsor did not agree that the PK parameter estimates determined by PPK analysis are biased. The PPK analysis was performed using nonlinear mixed effects maximum likelihood methodology, which has the property of producing unbiased estimates, even in the presence of missing and unbalanced data.[28]

The Phase II study protocols specified a sparse PK sampling design for most of the enrolled patients (97%) and an intensive PK sampling design for a small (3%) subset of patients. This sparse/intensive PK sampling design was selected to enable collection of PK data in all patients without excessively burdensome sample collection, while at the same time to enable identification of the structural component of the PK model and determination of non-compartmental PK parameters with data from the subset of intensively sampled patients. Although logistical considerations precluded random selection of patients for intensive PK sampling (for example, patients could opt to not

[28] Davidian M and Giltinan DM. Monographs on Statistics and Applied Probability 62: Nonlinear Models for Repeated Measurement Data. Chapman & Hall, New York, 1995.
Sheiner LB, Beal SL. (1983). Evaluation of methods for estimating population pharmacokinetic parameters: III. Monoexponential model: routine clinical pharmacokinetic data. *J Pharmacokinet Biopharm* 11:303-319.

have intensive PK sampling), the pattern of missing data was not informative[29] and was therefore not expected to bias the parameter estimates. This is a widely accepted approach to characterizing PK in large patient clinical trials.

*Detailed Description of Simulation Methods Used for Model Evaluation*:

Standard simulation based methods were used for internal and external model evaluation, as described in the PPK/ER Report.

Internal and external model evaluation was conducted using visual and quantitative predictive performance checks. These checks provide an evaluation of model assumptions and population parameter estimates by comparing model predictions and observations. Both visual and quantitative predictive checks were performed with 500 simulated datasets obtained by Monte Carlo simulation with the Final Model. Each simulated dataset was identical to the model development dataset, except that simulated values were substituted for actual observations. To elaborate, each simulated dataset contained a model simulated ipilimumab serum concentration value corresponding to each observed serum concentration value in the model development dataset. Overall therefore, 500 simulated concentration values were obtained for each observed concentration value.

*PPK Model Evaluation*: Rigorous internal and external model evaluations were performed to establish the accuracy of PPK parameter estimates. Both internal and external model evaluations were conducted by standard visual and quantitative predictive check comparisons of simulated and observed data.[30] The purpose of the visual performance check was to assess the consistency of model predicted concentration time profiles with the observed data, whereas the purpose of quantitative predictive check was to assess the consistency of selected summary measures of exposure determined from observed and simulated data. It should be noted that the comparison of individual observed and predicted concentration time data as a means of model evaluation (as suggested by the evaluator) is less rigorous than the simulation based evaluation presented in the PPK/ER report, because the former utilizes data from the individual to adjust the model PK parameters, thus enabling a better fit to the individual data, whereas the latter is based solely on the model and is more representative of model predictions for the general patient population.

The results of the internal visual performance check were presented in the PPK/ER report and the external visual performance check was presented in figures which demonstrated that the model predicted concentration time profile is indeed consistent with the observed data for the 0.3, 3, and 10 mg/kg dose groups.

Furthermore, numerical summaries of the percentage of values above and below the 90% prediction interval in the external visual predictive check were provided and demonstrated the consistency of the observed and model simulated 5th, 25th, 50th, 75th and 95th percentiles of concentration values.

The purpose of the quantitative predictive check was to complement the visual predictive check by focus on summary measures of exposure that are of special interest, namely, peak and trough concentration ($C_{min}$ and $C_{max}$, respectively). The results of the quantitative predictive check for $C_{maxss}$ and $C_{minss}$ datasets were presented and summarized in the report. These figures showed that the observed statistics of $C_{min}$

[29] Rubin DB. (1976). Inference and missing data. *Biometrika*. 63(3): 581-592.
[30] Committee for Medicinal Products for Human Use (CHMP). Guideline on Reporting The Results of Population Pharmacokinetic Analyses. London, 2007. Adopted by TGA June 2009.

and $C_{max}$ are consistent with corresponding model simulated statistics, demonstrating the consistency of model predictions with observed values for these summary measures of exposure.

In conclusion, the PPK model adequately describes the overall concentration time profile of ipilimumab, as well as the $C_{min}$ and $C_{max}$ summary measures of exposure. Given the consistency of the observed and model predicted $C_{min}$ values, it is appropriate to use model predicted exposures to characterize ipilimumab exposure response of efficacy (BOR and irCA), as well as safety (irAE).

### Clinical Summary and Conclusions

The evidence from the Phase III study (MDX010-20) of some benefit on survival was convincing.

The data indicate that there may be an increased efficacy at a higher dosage than that used in the Phase III study. The studies of different dosages show that there would be some trade off in AEs. Further studies are necessary to elucidate the optimal dosage in the various patient groups.

**Sponsor Response**

*To date, the results from MDX010-20 represent the best characterised evidence to support an increase in OS in previously treated patients with metastatic melanoma, treated with ipilimumab at a dose of 3 mg/kg. The sponsor acknowledged the clinical evaluator's comments that the benefit risk relationship was advantageous at the dosage used in MDX010-20 and recommends approval of the product.*
*A further Phase III clinical trial (CA184024) in patients with untreated advanced melanoma, examining the effects of ipilimumab when administered at a dose of 10 mg/kg to a similar but distinct patient population, will provide further evidence on the benefits and risks of therapy with ipilimumab when used at this dose.*

#### Benefit-risk assessment and conclusion

In the population enrolled in Study MDX010-20, the benefit-risk relationship was advantageous at the dosage used. The clinical evaluator recommended approval of the product. The indications proposed were however considered to be a little too broad, in that "advanced" may be subject to misinterpretation. The clinical evaluator proposed the word "metastatic" as a substitute.

**Sponsor response:**

*The sponsor agreed to change the wording to reflect the exact patient population included in the Phase II Study MDX010-20: "unresectable or metastatic melanoma".*

# V. Pharmacovigilance Findings

## Risk Management Plan

The sponsor submitted a Risk Management Plan (RMP) which was reviewed by the TGA's Office of Product Review (OPR).

A summary of the Ongoing Safety Concerns as specified by the sponsor are tabulated below (Table 65).

**Table 65: Ongoing safety concerns.**

| | |
|---|---|
| Important identified risks | • GI irAEs<br>• Hepatic irAEs<br>• Skin irAEs<br>• Neurologic irAEs<br>• Endocrine irAEs<br>• Other irAEs |
| Important potential risks | • Infusion reactions<br>• Immunogenicity |
| Important missing information | • Reproductive data<br>• Pediatric data<br>• Data in ethnic groups |

The above summary of the Ongoing Safety Concerns, as specified by the sponsor, was considered acceptable by the RMP evaluator.

The RMP evaluator provided these recommendations in the context that the submitted RMP is supportive to the application. The implementation of a RMP satisfactory to the TGA was imposed as a condition of registration.

It was recommended to the Delegate that:

1. The sponsor update the nonclinical safety specification of the RMP.

**Sponsor Response**

*A revised RMP was submitted by the sponsor.*

2. The sponsor provide copies of the structured questionnaires and the full protocol of the planned postmarketing observational study to the OPR for review, or provide a date by which these will be provided to the OPR. In addition, inform the TGA which international regulatory body will be providing the sponsor with the final approval for the study.

**Sponsor Response**

*The sponsor provided the draft protocol for the postmarketing observational study to the TGA for review. The sponsor also committed to share any subsequent revision to the protocol with the TGA.*

*The sponsor was in the process of developing a postmarketing observational study to support the Risk Management Plan. The study is to be implemented as a global, prospective, observational cohort study and is being designed, in large part, to understand the safety profile of ipilimumab (Yervoy) in routine clinical practice.*

*The first two objectives of the study, which are directly related to safety assessment, have been refined and will be incorporated into the revised RMP. These objectives are as follows:*

*1) Estimate the incidence and severity of adverse events in patients treated with ipilimumab in the post-marketing setting*

*2) Assess management of adverse reactions of special interest (such as diarrhoea, colitis, hepatitis, elevated liver enzymes, hypopituitarism, hypophysitis, rash,*

*neurologic syndromes) and their outcome in ipilimumab treated patients in the post-marketing setting.*

*The development of the protocol for this observational cohort study is a global effort that will incorporate input from Health Authorities to ensure that the design, scope, objectives, processes, and outcomes accommodate the interests and standards of the different regions. In particular, the European Medicines Agency will be contributing to the development of the protocol.*

3. The sponsor was asked to confirm if the educational campaign will be implemented in Australia.

**Sponsor Response**

*The sponsor confirmed that an educational campaign will be implemented in Australia in a modified form to that initially described in the RMP (see response to Question 5).*

4. The sponsor was asked to confirm that the detailed irAE treatment guidelines have been developed by an appropriately qualified person and that the sponsor is committed to updating these guidelines as new information arises.

**Sponsor Response**

*The detailed irAE treatment guidelines were developed in response to safety data obtained from >4000 study patients treated with ipilimumab. They were developed in cooperation with external experts and have been implemented in all ipilimumab clinical trials and the ipilimumab Expanded Access Program globally. The irAE treatment guidelines were first presented at the European Society of Medical Oncology Congress (ESMO) in 2008[31].*

*Subsequent to the first presentation at ESMO, these guidelines have been regularly updated with new information. The sponsor committed to continuing to update these guidelines as required with new information to ensure ongoing safe and effective use of ipilimumab.*

5. The sponsor was asked to confirm if the materials provided at Annex 12 of the RMP will be included in the Tool Kit for the Ipilimumab Educational Program or if they are merely examples. The sponsor was asked to provide a full set of the copies of the actual materials to the TGA for review. If these materials are not available the sponsor should provide a date by which they will be provided;

**Sponsor Response**

*Annex 12 includes early draft examples of educational materials the sponsor intends to develop as part of its routine educational program to support the quality use of this medicine which will not be part of the RMP.*

[31] Chin, K (BMS), Ibrahim R (BMS), Berman D (BMS), Yolling M, Lowy I, Lin H, Hoos A. Treatment Guidelines for the Management of Immune-Related Adverse Events in Patients Treated with Ipilimumab, an Anti-CTLA-4 Therapy. *Ann Oncol* 19 (Suppl 8), Abstract 787P.

*The sponsor has reconsidered the appropriateness of the patient materials outlined in the original RMP in the context of the management of patients with metastatic melanoma and wishes to take a more consultative approach in the development of patient education materials with Australian hospitals and centres of excellence who care for patients with metastatic melanoma.*
*The sponsor has amended its position, principally because the development of these materials require careful consideration for sensitivities associated with the care of terminally ill patients, which are beyond the sponsor's current expertise.*
*With this in mind, the sponsor proposed to form partnerships with major Australian centres with experience in caring for patients with metastatic melanoma and patient advocacy groups to determine the most appropriate means of developing and disseminating patient materials whilst being careful not to diminish any established evidence-based processes, protocols, or materials currently in use by hospitals and centres in this field.*
*For example, it would be improper and naive of the sponsor to suggest to the TGA that a patient discharge letter or patient alert card would be widely adopted and accepted without extensive modification by an Australian hospital pharmacy or oncology department.*
*As a consequence the sponsor proposed to amend the table titled "Tool Kit for Ipilimumab Education Program" in the RMP to include the following items:*

- *Product Information*
- *Consumer Medicines Information*
- *Detailed irAE Treatment Guidelines for Health-Care Providers*
- *Diarrhoea*
- *Hepatotoxicity*
- *Endocrinopathies*
- *Neurologic*
- *General irAEs (including skin irAEs)*
- *BMS Medical information for Health care Providers*
- *Contact Information for Health-Care Professionals on how to contact the sponsor (BMS).*

*The sponsor's approach to the development of patient educational materials means that the Patient Education Brochure, Patient FAQ, Patient Diary (see Question 6) and Wallet Card will not be included as part of the RMP. In order for the sponsor to establish compliance of the website with Medicines Australia requirements it has also been removed from the RMP tool kit at this stage but will be considered as part of its routine educational program following consultation with external groups with expertise in the care of patients with metastatic melanoma.*

6. The sponsor was asked to provide information on the role of the patient diary and how it would function as part of the risk minimisation plan to reduce the risks associated with ipilimumab as it is not clear from the information the sponsor has provided what the role of the patient diary is as a risk minimisation tool.

**Sponsor Response**

*The sponsor elected to delete the patient diary from the RMP following feedback that the diary was not helpful as a risk minimisation tool.*

*The sponsor confirmed that the patient diary will not be used as part of the RMP.*

# VI. Overall Conclusion and Risk/Benefit Assessment

The submission was summarised in the following Delegate's overview and recommendations:

## Quality

There were no objections to registration on chemistry, manufacturing and quality control grounds. The application was considered by the March 2011 meeting of the Pharmaceutical Subcommittee and no objections to registration were raised.

## Nonclinical

There were no nonclinical objections to registration. Repeat dose toxicity was studied in monkeys and the drug was generally well tolerated. However, as ipilimumab has a 2-5 fold lower binding affinity for monkey CTLA-4 than human CTLA-4, the full toxicological profile of the drug may not have been established. Isolated cases of colitis and dermatitis were observed, consistent with the toxicity profile observed in humans.

## Clinical

The clinical evaluator recommended approval of the application. The sponsor provided a response to the clinical evaluation.

The TGA has adopted an EMA guideline on clinical data requirements for anticancer agents which is to be considered with this application[32].

### Pharmacokinetics (PK)

Two early Phase I PK studies (MDXCTLA4-01 and -02) were conducted using a form of ipilimumab produced in a hybridoma cell line. Results of these studies are summarised in the clinical evaluation report (CER) above. The PK of ipilimumab were consistent with those of an IgG molecule with a small volume of distribution (4.0 – 5.0 L), slow clearance (10 mL/hr) and an elimination half-life of approximately 14 days.

Another Phase I study (MDX010-15) used ipilimumab produced in the CHO cell line for most cohorts. PK were again consistent with those of an IgG molecule. PK were non-linear with less than proportional increases in $C_{max}$ and AUC with increasing dose. There was moderate accumulation after repeated dosing.

Limited PK data were collected in some Phase II studies in melanoma patients conducted with ipilimumab produced in the CHO cell line. Results for two of these studies (CA184-007 and -008) showed that the PK parameters were again consistent with those of an IgG molecule. There was some modest accumulation with repeated dosing.

The current Australian submission also included a population PK analysis based on 498 subjects with melanoma enrolled in four Phase II studies. PK parameters obtained were consistent with those obtained in the above Phase I and II studies. Both clearance and volume of distribution increased with body weight. Other covariates (including measures of renal and hepatic function) did not have a clinically significant effect on the PK of the drug.

[32] The European Agency for Evaluation of Medical Products (EMEA). 2005. *Guideline on the Evaluation of Anticancer Medicinal Products in Man.* 14 December 2005. CPMP/EWP/205/95/Rev.3/Corr.

**Efficacy**

***Pivotal study***

The main evidence for efficacy comes from a single pivotal randomised, double-blind, controlled trial (**Study MDX010-20**). This trial has been published[33].

Subjects enrolled in the trial had unresectable Stage III or IV melanoma and had to have failed at least one previous regimen containing interleukin-2, dacarbazine, temozolomide, fotemustine or carboplatin. Subjects were randomised (3:1:1) to receive one of the following three investigational regimens:

- Ipilimumab plus an investigational gp100 vaccine;
- Ipilimumab alone;
- the investigational gp100 vaccine alone.

Glycoprotein 100 (gp100) is an antigen expressed in melanocytes and melanoma cells. Vaccines against this antigen had previously demonstrated some evidence of efficacy in the treatment of melanoma. The particular vaccine used in this study consisted of two separately administered peptides - gp100: 209-217(210M) and gp100:280-288(288V), which are epitopes of the gp100 protein. These epitopes are only recognised by individuals who are HLA-A2*0201 positive and hence enrolment in the study was restricted to these subjects.

Subjects received ipilimumab (3 mg/kg IV over 90 minutes) once every three weeks for a total of four doses. Vaccine was administered subcutaneously according to the same schedule.

The primary efficacy endpoint was overall survival (OS). Both ipilimumab treatment arms were associated with a statistically significant improvement in overall survival compared to monotherapy with the vaccine. For the ipilimumab monotherapy arm, the hazard ratio was 0.66 (95% CI: 0.51 – 0.87; p = 0.0026). Median survival was improved by 3.68 months (10.12 versus 6.44 months). Survival at 12 months was increased from 25.3% in the gp100 group to 45.6% in the ipilimumab arm. Ipilimumab treatment was also associated with improvements in the secondary endpoints of overall response rate, disease control rate and progression free survival. Quality of life was not notably different between groups.

Patients who responded or had stable disease following the first round of treatment, could be treated with a further round following disease progression. A total of 32 patients underwent such 're-induction' and a proportion of these patients responded again.

***Other studies***

The submission contained details of two Phase II dose ranging studies of ipilimumab monotherapy (**CA184-022** and **CA184-004**). Ipilimumab treatment was associated with objective responses in a small proportion of patients. There was a suggestion in one of the studies (CA184-022) that a higher dose (10 mg/kg) may be associated with greater efficacy.

**Safety**

In the submitted studies approximately 3,450 subjects were treated with ipilimumab. In the pivotal study, 521 subjects received the drug and approximately 65% of these received the full schedule of four doses. Much of the observed toxicity of the drug in the clinical trial

[33] Hodi FS *et al* (2010). Improved Survival with Ipilimumab in Patients with Metastatic Melanoma. NEJM 36:711-723.

program was considered to be due to excess activity of the immune system with resulting autoimmune effects. Such adverse events have been termed 'immunerelated adverse events' (irAEs).

The overall toxicity of the drug in the pivotal study is summarised in Table 66. In all three treatment groups there was a high incidence of adverse events, with events ≥Grade 3 occurring in more than 50% of patients. There was an excess of patients discontinuing treatment due to adverse events in the ipilimumab arms (9.2 and 13.0 % versus 3.8%). As shown in Table 66 below, there was a clear excess of irAEs in the ipilimumab groups, including ≥ Grade 3 irAEs, serious irAEs and deaths due to irAEs.

**Table 66. Summary of Safety. (Safety population).**

| | Ipi+gp100 (n=380) | Ipi (n=131) | gp100 (n=132) | Total (n=643) |
|---|---|---|---|---|
| Subject with any AE (n %) | 374 (98.4) | 128 (97.7) | 128 (97.0) | 630 (98.0) |
| Subjects with any on-study AE[a] (n %) | 374 (98.4) | 127 (96.9) | 128 (97.0) | 629 (97.8) |
| Severe (≥ Grade 3) | 194 (51.1) | 73 (55.7) | 69 (52.3) | 336 (52.3) |
| Serious | 156 (41.1) | 56 (42.7) | 52 (39.4) | 264 (41.1) |
| Related | 339 (89.2) | 106 (80.9) | 104 (78.8) | 549 (85.4) |
| AEs leading to study drug discontinuation | 35 (9.2) | 17 (13.0) | 5 (3.8) | 57 (8.9) |
| AE with outcome of death (n%) | 23 (6.1) | 13 (9.9) | 8 (6.1) | 44 (6.8) |
| Related AE with outcome of death | 8 (2.1) | 4 (3.1) | 2 (1.6) | 14 (2.2) |
| **Immune Related Adverse Events (irAE)[b]** | | | | |
| Subjects with any irAE (n %) | 220 (57.7) | 81 (61.8) | 42 (32.1) | 343 (53.3) |
| Severe irAE | 44 (11.5) | 21 (16.0) | 4 (3.0) | 69 (10.7) |
| Serious irAE | 41 (10.8) | 18 (13.7) | 1 (0.8) | 60 (9.3) |
| irAE leading to study drug discontinuation | 22 (5.8) | 11 (8.4) | 1 (0.8) | 34 (5.3) |
| Death due to irAE (n %) | 4 (1.0) | 2 (1.5) | 0 | 6 (0.9) |
| Gastrointestinal irAEs (any grade) | 122 (32.1) | 39 (29.8) | 19 (14.4) | 180 (28.0) |
| Severe (≥ Grade 3) | 25 (6.6) | 11 (8.4) | 1 (0.8) | 37 (5.8) |
| Hepatic irAEs (any grade) | 8 (2.1) | 5 (3.8) | 6 (4.5) | 19 (3.0) |
| Severe (≥ Grade 3) | 4 (1.1) | 1 (0.8) | 3 (2.3) | 8 (1.2) |
| Endocrine irAEs (any grade) | 16 (4.2) | 10 (7.6) | 2 (1.5) | 28 (4.4) |
| Severe (≥ Grade 3) | 4 (1.1) | 5 (3.8) | 0 | 9 (1.4) |
| Skin irAEs (any grade) | 152 (40.0) | 56 (42.7) | 25 (18.9) | 233 (36.2) |
| Severe (≥ Grade 3) | 9 (2.4) | 2 (1.5) | 0 | 11 (1.7) |
| Other irAEs (any grade) | 15 (3.9) | 6 (4.6) | 3 (2.3) | 24 (3.7) |
| Severe (≥ Grade 3) | 8 (2.1) | 3 (2.3) | 1 (0.8) | 12 (1.9) |

Source: Supplemental Tables 7.1.1, 7.13.1, 7.14.1, and 7.15.1

Key: AE = adverse event; irAE = immune-related AE

a On-study adverse events include all AEs after the first dose and occurring within 70 days of the last dose or any AE related to the study drug.

b irAEs are adverse events of unknown etiology associated with study drug exposure and consistent with an immune phenomenon that were reported by the Investigator to be possibly, probably, or definitely related to study drug or with unknown causality

Specific adverse events in the pivotal study were discussed by the clinical evaluator. Compared to the gp100 vaccine alone arm, ipilimumab was associated with increased incidences of:

- Gastrointestinal tract (GIT) toxicity – colitis, diarrhoea, abdominal pain, anorexia, nausea and vomiting;
- skin toxicity – rash, pruritus;
- hepatotoxicity;
- endocrine disorders – hypothyroidism and hypopituitarism;

- blurred vision;
- fatigue.

The pattern of toxicity was similar on examination of serious adverse events and discontinuations due to adverse events. The incidence of deaths possibly related to treatment was slightly higher in the ipilimumab arms (2.1% and 3.1% versus 1.6%)

The toxicity profile of the drug in Phase I and II studies was comparable to that seen in the pivotal trial. The Phase II dose ranging studies suggested that the incidence of adverse events increased with increasing dose.

## Risk Management Plan

An acceptable RMP has been negotiated between the sponsor and the TGA's Office of Product Review.

## Risk-Benefit Analysis

### Delegate Considerations

The pivotal study has demonstrated a statistically and clinically significant improvement in overall survival for subjects in the ipilimumab monotherapy arm, compared to those in the gp100 vaccine arm. The improvement in median survival was approximately 3.7 months. Patients with advanced melanoma who have already failed one line of treatment have a poor prognosis, as evidenced by the median survival of only 6.4 months for patients in the vaccine only arm. Prolongation of life by an additional 3.7 months is therefore considered clinically significant.

The drug causes significant toxicity, including fatalities, although the overall effect of the drug on mortality was favourable. In general, the toxicities appear manageable as the incidence of discontinuation due to adverse events in the ipilimumab monotherapy arm was only 10% higher than that in the vaccine arm (13.0% versus 3.8%).

There are currently no approved therapies for the second line treatment of advanced melanoma. Given the poor prognosis of these patients and the lack of alternative therapies the Delegate considered that the risk benefit balance for the drug in this setting was favourable and proposed to approve the application.

#### *Restriction to HLA-A2*0201 positive subjects*

The pivotal study restricted enrolment to HLA-A2*0201 positive patients, as the vaccine component would only be effective in these subjects. As noted by the clinical evaluator, the mechanism of action of ipilimumab is not dependent on HLA type and patients studied in the supportive Phase II studies were not required to be HLA-A2*0201 positive. The Delegate therefore considered it would be reasonable to include HLA-A2*0201 negative patients in the approved indication.

#### *Indication*

Ipilimumab is being developed for use in combination with other agents (such as dacarbazine). Data evaluated to date only support use of the drug as monotherapy. In addition, the pivotal study was restricted to patients in whom prior therapy had failed. The Delegate therefore proposed to approve the following indication:

> *"Yervoy, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma ~~in patients who have received~~ after failure of prior therapy."*

### *Re-induction*

The sponsor proposed that for patients who initially respond/stabilise and then progress, a further course of four doses may be prescribed. The clinical evaluator recommended that such "re-induction" should not be approved. Only 31 patients in the pivotal study received such re-treatment with an ipilimumab containing regimen. Six patients developed a partial or complete response and the toxicity profile of the re-induction regimen was consistent with that observed previously.

The Delegate agreed with the clinical evaluator and rejected the re-induction component of the application, as the data were very limited and there were no evidence of any additional survival benefit.

### *Use in the first-line setting (for information)*

The sponsor has recently completed another Phase III study (CA184024) in the setting of the *first line* treatment of advanced melanoma. The study compared the combination of ipilimumab and dacarbazine with dacarbazine alone, and showed a significant benefit in terms of overall survival.

The Delegate proposed to approve the application, with the amended indication outlined above. The Delegate proposed to reject the "re-induction" regimen. The advice of the Advisory Committee for Prescription Medicines (ACPM) was requested.

## Response from Sponsor

The sponsor accepted the Delegate's recommendation to amend the indication, however, the sponsor provided a further refinement to:

> *Yervoy, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.*

Justification for this proposal was provided. In regard to a formal evaluation of "re-induction" in a controlled setting, the sponsor acknowledges that this has not been conducted. In the sponsor's opinion, however, among 32 patients in the Phase III study evaluable for efficacy after re-induction, 65% to 75% in the ipilimumab containing treatment groups achieved disease control. The sponsor stated that given the limited number of treatments for patients with progressive metastatic melanoma who initially respond or display stable disease on ipilimumab, re-induction may need to be considered in their clinical management. The sponsor proposed an amendment to the "re-induction section" of the *Dosage and Administration* section of the PI to accurately describe the body of evidence with a view that it may be of assistance to oncologists considering future management options for patients in this clinical situation.

### *Discussion on Clinical Evidence*

The main clinical evidence for efficacy submitted with this application was based on a single Phase III study (MDX010-20) supported by two late Phase II studies (CA184004 and CA184022) for the 3 mg/kg monotherapy dose administered intravenously over 90 minutes every 3 weeks in patients with unresectable or metastatic melanoma who had failed or were intolerant to prior therapy. These data were supplemented by the results from three Phase II studies (CA184007, and CA184008 and MDX010-08).

The sponsor acknowledged the clinical evaluator's comments on the quality of study - 020 in relation to the criteria set by the TGA adopted EU guideline[34] and reiterated these comments.

The study was carefully and competently planned and conducted and there was a plausible scientific basis for efficacy. The outcome studied (overall survival) is robust and the statistical analysis yielded results of adequate significance. The study population comprised of patients with a rapidly lethal condition who had failed previous therapy and the size of the benefit shown was clinically relevant and consistent across pre-specified and prognostically important sub-groups. The clinical evaluator noted that internal consistency was evident with positive outcomes across relevant prognostic subpopulations for the primary endpoint and for all secondary endpoints (best overall response rate [BORR], disease control rate [DCR], and progression free survival [PFS]) for the intent to treat (ITT) population. The clinical evaluator stated that there is sufficient evidence of efficacy based on the results from Study -020 and that the benefit risk relationship was advantageous at the dose used. This opinion was also endorsed by the Delegate.

During evaluation of the current application, top line preliminary results from a second major Phase III study (CA184024) in 502 randomized patients, which investigated the effects of a combination of ipilimumab (10 mg/kg) + dacarbazine compared with dacarbazine alone as first line therapy in the treatment of advanced melanoma, became available. This information was shared with the TGA and other Health Authorities, including the FDA, prior to their decision to approve the application to register ipilimumab in the USA. The results demonstrated a statistically significant and clinically meaningful benefit in overall survival in favour of ipilimumab combination therapy compared with dacarbazine alone and provides confirmatory evidence that immunomodulation via CTLA-4 blockade with ipilimumab in subjects with metastatic melanoma translates clinically to an overall survival benefit.

The study demonstrated a 28% reduction in the risk of death (hazard ratio: 0.72, p-value: 0.0009) in favour of the ipilimumab+dacarbazine over dacarbazine alone and the survival benefit was consistent across prognostic subgroups. Twenty nine percent of patients in the ipilimumab arm survived more than 2 years, compared with 18% in the control arm. The study has similar features of robustness as the pivotal trial MDX010-20. A summary of the clinical data were provided to the ACPM for review by the Delegate and were publicly announced in June 2011 at the annual meeting of the American Society of Clinical Oncology (ASCO). It is anticipated that the results will subsequently be published and will be the subject of a future application by the sponsor.

The sequelae of blocking CTLA-4 function is the emergence of immune related adverse events (irAEs). The most common treatment related adverse events were irAEs affecting the GIT and skin, and less frequently, the liver, endocrine glands, and nervous system. These events have been characterized in the clinical trial program and described in the proposed Australian Product Information and included in teh final Aus.

The proposed Australian Product Information and the sponsor's routine pharmacovigilance activities (monitoring, evaluation and reporting of individual adverse events and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team and timely safety updates to the Product Information) are

[34] CPMP/EWP/2330/99. Points to consider on application with 1. Meta-Analysis; 2. One Pivotal Study (adopted by the TGA 27 March 2002).
http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003657.pdf

the primary sources and means to adequately communicate and monitor risks, respectively.

The sponsor also plans to implement a postmarketing education program as part of the risk minimization activities to mitigate risks and maximize benefits. The goal and objectives of this postmarketing education program are to minimize the risk of serious irAEs in patients prescribed ipilimumab and to ensure that Health Care Providers (HCPs) are made aware of signs, symptoms and risks associated with irAEs and have immediate access to treatment and management recommendations.

The sponsor has committed to implement the Risk Management Plan (RMP) submitted with this application. The RMP has been assessed by the Office of Product Review and found to be acceptable by the TGA.

### *Response to TGA Recommendation to Amend the Indication*

In considering the amendment to the indication proposed by the TGA, the sponsor believed that the population reflected in the indication should also include patients with intolerance to prior therapy.

The pivotal Study MDX010-20 was conducted in patients who had received at least one cycle of one or more regimens containing one or more of the following: IL-2, dacarbazine, temozolamide, fotemustine, and/or carboplatin and demonstrated either:

1) Relapse following an objective response (partial response [PR]/complete response [CR])
2) Failed to demonstrate an objective response (PR/CR), or
3) Inability to tolerate treatment due to unacceptable toxicity

The sponsor proposed to refine the proposed indication to also include patients who are intolerant to prior therapy so that they are not denied access to a possibly life prolonging therapy. The following indication was submitted by the sponsor for consideration by the Delegate and the ACPM:

> *"Yervoy, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy."*

### *Response to Re-Induction*

The sponsor acknowledged that a formal evaluation of re-induction in a controlled setting has not been performed. However, among 32 patients in the Phase III study evaluable for efficacy after re-induction, 65% to 75% in the ipilimumab containing treatment groups achieved disease control. Given the limited number of treatments for patients with progressive metastatic melanoma who initially respond or display stable disease on ipilimumab, re-induction may need to be considered in their clinical management.

The sponsor acknowledged the TGA's comments in relation to the limited body of evidence supporting re-induction and welcomed the careful consideration of ACPM on the usefulness of this information in clinical practice and its appropriateness for inclusion in the Product Information. The sponsor proposed an amendment to the re-induction section of the *Dosage and Administration* section of the Product Information to accurately describe the body of evidence with a view that it may be of assistance to oncologists considering future management options for patients in this clinical situation.

### *Conclusion*

Pretreated unresectable and metastatic melanoma is a disease with no treatment options that can improve patient survival and represents a high unmet medical need. The sponsor

believed that the clinical evidence from the robust pivotal Phase III study MDX010-20 and four supporting Phase II trials demonstrates a statistically significant and clinically meaningful Overall Survival Benefit with a manageable safety profile in patients with this disease. The results of the pivotal Phase III study are consistent across patient subgroups and endpoints and meet the robustness criteria set by the TGA-adopted EU guideline (CPMP/EWP/2330/99[27]) for a single pivotal study. The results of a second Phase III trial in untreated, unresectable, and metastatic melanoma have recently become available and confirm the overall survival result of the pivotal study in the application. The US FDA approved Yervoy on the basis of the data from the pivotal Study MDX010-20 for unresectable and metastatic melanoma and preliminary supportive data from Study CA184024. The sponsor believed the favourable benefit risk ratio for Yervoy and the first demonstrated survival advantage for patients with this devastating disease represent a major advance in the management of unresectable and metastatic melanoma in Australia.

## Advisory Committee Considerations

The ACPM, having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, recommended approval of the submission for the indication:

*As monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.*

The ACPM noted that there are currently no approved therapies for the second line treatment of advanced melanoma.

In making this recommendation, the ACPM considered that the pivotal study demonstrated a statistically and clinically significant improvement in overall survival (OS) for subjects in the ipilimumab monotherapy arm, compared to those in the gp100 vaccine arm. Patients with advanced melanoma who have already failed one line of treatment have a poor prognosis, as evidenced by the median survival of only 6.4 months for patients in the vaccine only arm. Prolongation of life by an additional 3.7 months is therefore considered clinically significant.

The drug causes significant toxicity, including fatalities, although the overall effect of the drug on mortality was favourable. In general, the toxicities appear manageable as the incidence of discontinuation due to adverse events in the ipilimumab monotherapy arm was only 10% higher than that in the vaccine arm.

The ACPM agreed with the Delegate that given the poor prognosis of these patients and the lack of alternative therapies the risk-benefit balance for the drug in this setting is favourable. The Committee recommended approval of the 're-induction' regimen as proposed by the sponsor, as there were no accepted therapies for patients who failed second-line therapy.

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy, considered there is a favourable benefit-risk profile for this product.

## Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Yervoy/Winglore concentrate solution for IV infusion containing ipilimumab 50mg/10mL and 200mg/40mL for the indication:

> *As monotherapy, for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.*

### *Additional Conditions of Registration*

*Drug Product batches from different Drug Substance batches*

It is a condition of registration that batches of *ipilimumab* imported into Australia are not released for sale until:

1. Samples of each batch have been tested and approved by the TGA Office of Laboratories and Scientific Services (OLSS);
2. The manufacturer's release data of each batch have been evaluated and approved by OLSS;
3. Evidence of satisfactory shipping conditions to Australia of each batch have been evaluated and approved by OLSS. Note that until such time as acceptance criteria to evaluate temperature excursions are provided, all shipments of ipilimumab drug substance and drug product that are shipped with **any** deviation from the recommended storage temperature must be evaluated as satisfactory by the TGA before release of the product.

These batch release conditions will be reviewed and will be modified on the basis of actual batch quality and consistency. If the any of these batches are derived from common drug substance batches then material should be provided derived from unique drug substance batches.

These conditions remain in place until the sponsor is notified officially in writing of any change.

# Attachment 1. Product Information

The following Product Information was approved at the time this AusPAR was published. For the current Product Information please refer to the TGA website at www.tga.gov.au.

**PRODUCT INFORMATION**

**YERVOY ®**
**(ipilimumab)**

**5mg per 1mL concentrate solution for infusion**

## NAME OF THE MEDICINE

YERVOY ® (ipilimumab): 5 mg/mL concentrate solution for infusion

Each 1 mL of concentrate contains 5 mg ipilimumab.
One 10 mL vial contains 50 mg of ipilimumab.
One 40 mL vial contains 200 mg of ipilimumab.

## DESCRIPTION

CAS: 477202-00-9. YERVOY (ipilimumab (rch)) is a recombinant, fully human monoclonal antibody that binds to the cytotoxic T lymphocyte-associated antigen 4 (CTLA-4). Ipilimumab is an IgG1 kappa immunoglobulin with an approximate molecular weight of 148 kDa. Ipilimumab is produced in mammalian (Chinese hamster ovary) cell culture.

YERVOY is a sterile, preservative free liquid for intravenous (IV) administration, which may contain a small amount of visible translucent-to-white, amorphous ipilimumab particulates. YERVOY has a pH of 7.0 and an osmolarity of 260-300mOsm/kg. It is supplied at a nominal concentration of 5 mg/mL ipilimumab in 50-mg and 200-mg single-use vials.

Each 1 milliliter contains 5 mg of ipilimumab and 0.1mmol sodium (or 2.30mg sodium).

Inactive ingredients are: trometamol hydrochloride (2-amino-2-hydroxymethyl-1,3-propanediol hydrochloride), sodium chloride, mannitol (E421), pentetic acid (diethylenetriaminepentaacetic acid), polysorbate 80, sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment), water for injections.

## PHARMACOLOGY

### Mechanism of action

Cytotoxic T-lymphocyte antigen-4 (CTLA-4) is a negative regulator of T-cell activation. Ipilimumab is a T-cell potentiator that specifically blocks the inhibitory signal of CTLA-4, resulting in T-cell activation, proliferation, and lymphocyte infiltration into tumours, leading to tumour cell death. The mechanism of action of ipilimumab is indirect, through enhancing T-cell mediated immune response.

### Pharmacodynamic effects

In patients with melanoma who received YERVOY, the mean peripheral blood absolute lymphocyte counts (ALC) increased throughout the induction dosing period. In Phase 2 studies, this increase occurred in a dose-dependent fashion. In MDX010-20 (see Clinical Trials), YERVOY

given with or without gp100 at 3 mg/kg increased ALC throughout the induction dosing period, but no meaningful change in ALC was observed in the control group of patients who received an investigational gp100 peptide vaccine alone.

In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA-DR+ CD4+ and CD8+ T cells and a mean decrease in the percent of naive (CCR7+ CD45RA+) CD4+ and CD8+ T cells was observed after treatment with YERVOY, consistent with its mechanism of action. A mean increase in the percent of central memory (CCR7+ CD45RA-) CD4+ and CD8+ T cells and a smaller, but significant, mean increase in the percent of effector memory (CCR7- CD45RA-) CD8+ T cells also was observed after treatment with YERVOY.

**Immunogenicity**

Less than 2% of patients with advanced melanoma who received YERVOY in Phase 2 and 3 clinical studies developed antibodies against ipilimumab. None had any infusion-related or peri-infusional hypersensitivity or anaphylactic reactions. Neutralizing antibodies against ipilimumab were not detected. Overall, no apparent association was observed between antibody development and adverse events, or clearance of ipilimumab (see Pharmacokinetics).

## PHARMACOKINETICS

The pharmacokinetics of YERVOY were studied in 498 patients with advanced melanoma who received induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. $C_{max}$, $C_{min}$ and AUC of YERVOY were found to be dose proportional within the dose range examined.

Upon repeated dosing of YERVOY administered every 3 weeks, clearance did not vary over time, and minimal systemic accumulation was observed with an accumulation index of 1.5 or less for $C_{max}$, $C_{min}$ and AUC. YERVOY steady-state was reached by the third dose when administered once every 3 weeks. The average YERVOY serum trough concentrations achieved at steady-state with 3 mg/kg induction regimen was 21.8 μg/ml.

Based on a population pharmacokinetic analysis, the following pharmacokinetic parameters of YERVOY were obtained: a mean terminal half-life of 15 days; a geometric mean systemic clearance of 15.3 ml/h; and a geometric mean volume of distribution at steady-state of 7.22 L.

YERVOY clearance increased with increasing body weight and with increasing lactate dehydrogenase (LDH) at baseline; however, no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis. YERVOY clearance was not affected by age (range 26-86 years), gender, hepatic function (as measured by albumin and alkaline phosphatase), concomitant use of budesonide, renal function (estimated GFR 22 ml/min or greater), performance status, HLA-A2*0201 status, positive immunogenicity status, and prior use of systemic anticancer therapy. The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups.

No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

## CLINICAL TRIAL EFFICACY INFORMATION

### Clinical Trials

The efficacy of YERVOY at the recommended dose of 3 mg/kg in previously treated patients with advanced melanoma was investigated in a Phase 3 study (MDX010-20) and in a Phase 2 study (CA184022). YERVOY has not been investigated in patients with active or a history of serious chronic viral infections, including hepatitis B, hepatitis C, or human immunodeficiency virus (HIV). Clinical studies excluded patients without liver metastasis who had a baseline AST > 2.5 x ULN or patients with liver metastasis who had a baseline AST greater than > 5 x ULN. Patients with a baseline total bilirubin≥ 3 x ULN were also excluded.

#### *Study MDX010-20*

A Phase 3, double-blind study enrolled patients with advanced melanoma who had previously been treated with regimens containing one or more of the following: IL-2, dacarbazine, temozolomide, fotemustine, or carboplatin. Patients were randomized in a 3:1:1 ratio to receive YERVOY 3 mg/kg in combination with an investigational gp100 peptide vaccine (gp100), YERVOY 3 mg/kg monotherapy, or gp100 alone. All patients in this study were HLA-A2*0201 type; this HLA type supports the immune presentation of gp100. Patients received YERVOY every 3 weeks for 4 doses as tolerated (induction therapy). Patients with apparent tumour burden increase before completion of the induction period were continued on induction therapy as tolerated if they had adequate performance status. Assessment of tumor response to YERVOY was conducted after completion of induction therapy.

Additional treatment with YERVOY (re-induction therapy) was offered to patients who developed progressive disease (PD) after initial clinical response (partial response [PR] or complete response [CR]) or after stable disease (SD, per the modified WHO criteria) lasting longer than 3 months from the first tumour assessment. The primary endpoint was overall survival (OS) in the YERVOY+ gp100 group vs. the gp100 group. Key secondary endpoints were OS in the YERVOY+ gp100 group vs. the YERVOY monotherapy group and in the YERVOY monotherapy group vs. the gp100 group. Other secondary endpoints included best overall response rate (BORR) up to Week 24 and duration of response.

A total of 676 patients were randomized: 137 to the YERVOY monotherapy group, 403 to the YERVOY + gp100 group, and 136 to the gp100 alone group. The majority of patients had received all 4 doses during induction. Thirty-two evaluable patients received a re-induction dose: 8 in the YERVOY monotherapy group, 23 in the YERVOY + gp100 group, and 1 in the gp100 group. Duration of follow-up ranged up to 55 months. Baseline characteristics were well balanced across treatment groups. The median age was 57 years. The majority (71-73%) of patients had M1c stage disease and 37-40% of patients had an elevated LDH at baseline. A total of 77 patients had a history of previously treated brain metastases.

The YERVOY-containing regimens demonstrated a statistically significant advantage over the gp100 group in OS. The hazard ratio (HR) for comparison of OS between the YERVOY monotherapy and gp100 groups was 0.66 (95% CI: 0.51, 0.87; p = 0.0026). This result was consistent with the HR for comparison between the YERVOY + gp100 group and the gp100 group (HR 0.68 [95% CI: 0.55, 0.85]; p = 0.0004). Overall survival results are shown in Figure 1. Median and estimated rates of OS at 1 year and 2 years are presented in Table 1.

**Figure 1: Overall Survival in Study MDX010-20**

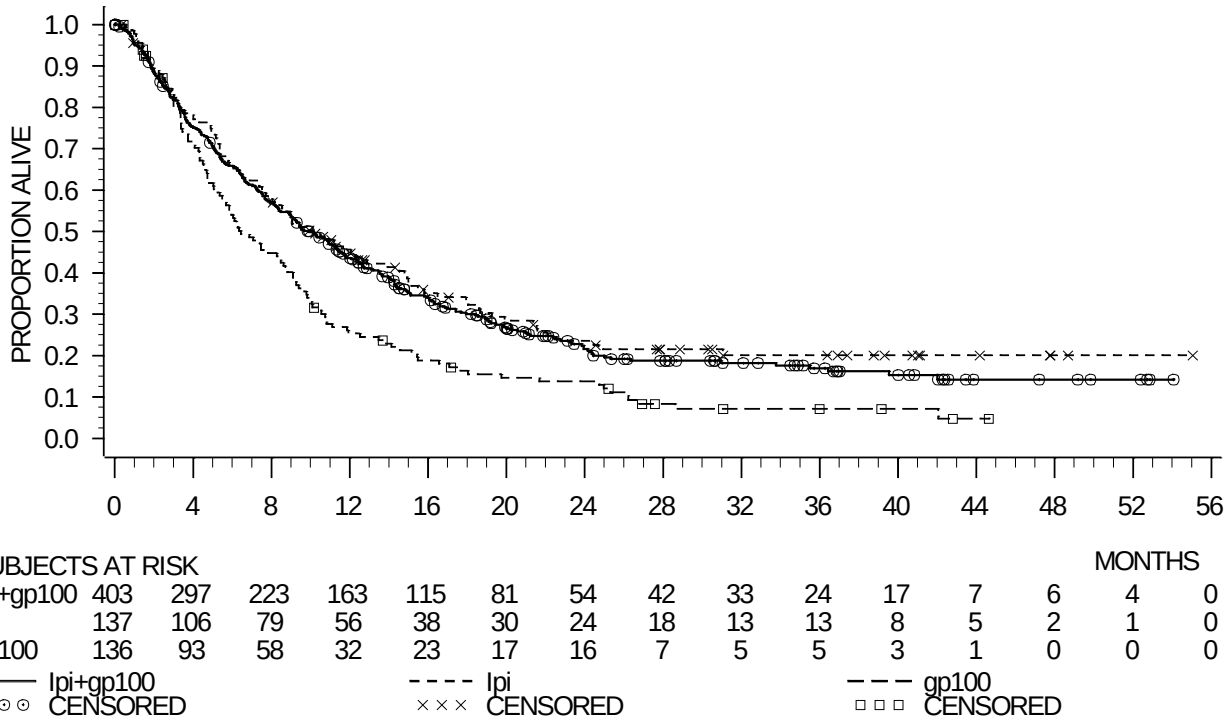



**Table 1. Median and estimated rates of OS at 1 year and 2 years.**

**Table 1: Overall Survival in MDX010-20**

| | **YERVOY n= 137** | YERVOY+ gp100[a] n= 403 | gp100[a] n= 136 |
|---|---|---|---|
| Median Months (95% CI) | **10 months (8.0, 13.8)** | 10 months (8.5, 11.5) | 6 months (5.5, 8.7) |
| OS at 1 year % (95% CI) | **46% (37.0, 54.1)** | 44% (38.6, 48.5) | 25% (18.1, 32.9) |
| OS at 2 years% (95% CI) | **24% (16.0, 31.5)** | 22% (17.2, 26.1) | 14% (8.0, 20.0) |

[a] Combination of YERVOY + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

In the YERVOY 3 mg/kg monotherapy group, median OS was 22 months and 8 months for patients with SD and those with PD, respectively. At the time of this analysis, medians were not reached for patients with CR or PR.

Efficacy was demonstrated across the primary and secondary endpoints. Additional efficacy results are presented in Table 2.

**Table 2: Efficacy of YERVOY in MDX010-20**

| | **YERVOY n= 137** | YERVOY + gp100[a] n= 403 | gp100[a] n= 136 |
|---|---|---|---|
| BORR (up to Week 24) % (95% CI) | **10.9% (6.3, 17.4)** | 5.7% (3.7, 8.4) | 1.5% (0.2, 5.2) |
| YERVOY vs gp100 | **p= 0.0012** | | |
| YERVOY + gp100 vs gp100 | p= 0.0433 | | |
| CR (%) | **1.5%** | 0.2% | 0 |
| PR (%) | **9.5%** | 5.5% | 1.5% |
| SD (%) | **17.5%** | 14.4% | 9.6% |
| Median Duration of Response (range) | **Not Reached (2.8-44.2+)** | 11.5 months (1.9-44.4+) | Not Reached (2.0-5.6+) |

[a] Combination of YERVOY + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

Tumour responses were observed as late as 5.5 months from the start of YERVOY therapy.

For patients who required re-induction therapy, the BORR was 38% (3/8 patients) in the YERVOY monotherapy group, 13% (3/23 patients) in the YERVOY + gp100 group, and 0% in the gp100 group. The disease control rate (DCR , defined as CR+PR+SD) was 75% (6/8 patients), 65% (15/23 patients), and 0%, respectively.

The development or maintenance of clinical activity following YERVOY treatment was similar with or without the use of systemic corticosteroids.

***Study CA184022***

The activity of three doses of YERVOY was investigated in a blinded, randomized Phase 2 study in patients with advanced melanoma. Patients who progressed after or were intolerant to prior therapy were enrolled in the study. A total of 217 patients were randomized to three groups: 0.3 mg/kg (n= 73), 3 mg/kg (n= 72), and 10 mg/kg (n= 72). In this study, some objective responses were observed after initial evidence of tumour burden increase, including new lesions. Clinical response, disease control, and survival were similar regardless of the HLA subtype.

## INDICATIONS

YERVOY, as monotherapy, is indicated for the treatment of patients with unresectable or metastatic melanoma who have failed or are intolerant to prior therapy.

## CONTRAINDICATIONS

Hypersensitivity to the active substance or to any of the excipients.

## PRECAUTIONS

YERVOY is associated with inflammatory adverse reactions resulting from increased or excessive immune activity (irAEs), likely to be related to its mechanism of action. Early diagnosis and appropriate management are essential to minimize life-threatening complications. Signs and symptoms suggestive of irAEs relating to the gastrointestinal tract (diarrhoea, increased stool frequency, bloody stool), liver (liver function test [LFT] elevations), skin (rash) and endocrine system must be considered inflammatory and YERVOY-related unless an alternative etiology is identified. While most irAEs occurred during the induction period, some irAEs occurred weeks to months after the last dose of YERVOY.

Due to the mechanism-based inflammatory reactions observed with YERVOY, corticosteroid or other immunosuppressive therapy may be required for management of severe irAEs. YERVOY-specific management guidelines for irAEs are described below.

### Immune-related gastrointestinal events

YERVOY is associated with serious immune-related gastrointestinal events. Fatalities due to gastrointestinal perforation have been reported in clinical trials (see ADVERSE REACTIONS).

In patients who received YERVOY 3 mg/kg monotherapy in a Phase 3 study of advanced melanoma (MDX010-20, see Clinical Trials), the median time to onset of severe or fatal (Grade 3-5) immune-related gastrointestinal events was 8 weeks (range 5 to 13 weeks) from the start of treatment. In this study, with protocol-specified management guidelines, resolution occurred in most cases (90%), with a median time from onset to resolution of 4 weeks (range 0.6 to 22 weeks).

Patients must be carefully monitored for gastrointestinal symptoms that may be indicative of immune-related colitis, diarrhoea, or gastrointestinal perforation. The presentation may include diarrhoea, increase in the frequency of bowel movements, abdominal pain, or haematochezia, with or without fever. Diarrhoea or colitis occurring after initiation of YERVOY therapy must be evaluated to exclude infectious or alternate etiologies. In clinical trials, immune-related colitis was associated with evidence of mucosal inflammation, with or without ulcerations, and lymphocytic infiltration.

Management recommendations for diarrhoea or colitis demonstrated or suspected to be immune-related are based on severity of symptoms (per National Cancer Institute-Common Terminology Criteria for Adverse Events [NCI-CTCAE v3] for diarrhoea and colitis). Patients with mild to moderate (Grade 1 or 2) diarrhoea (an increase of up to 6 stools per day) or suspected colitis (eg, abdominal pain or blood in stools) may remain on YERVOY therapy. Symptomatic treatment (eg, loperamide, fluid replacement) and close monitoring are advised. If mild to moderate symptoms recur or persist for 5-7 days, the scheduled dose of YERVOY should be omitted; corticosteroid therapy (eg, prednisone 1 mg/kg orally once daily or equivalent) is recommended. If resolution to Grades 0-1 or baseline occurs, YERVOY may be resumed at the next scheduled dose. Doses omitted for toxicity must not be replaced (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) diarrhoea or colitis (see DOSAGE AND ADMINISTRATION). For severe symptoms, high-dose IV corticosteroid therapy is recommended. (In clinical trials, methylprednisolone 2 mg/kg/day have been used.) Once diarrhoea and other symptoms are controlled, the initiation of corticosteroid taper should be based on clinical judgment. In clinical trials, rapid tapering (over periods < 1 month)

resulted in recurrence of diarrhoea or colitis in some patients. Patients must be evaluated for evidence of gastrointestinal perforation or peritonitis.

The experience from clinical trials on the management of corticosteroid-refractory diarrhoea or colitis is limited. However, addition of alternative immunosuppressive agents to the corticosteroid regimen may be considered. In clinical trials, a single dose of infliximab 5 mg/kg was added unless contraindicated. Infliximab must not be used if gastrointestinal perforation or sepsis is suspected. Refer to the Product Information for infliximab.

**Immune-related hepatotoxicity**

YERVOY is associated with serious immune-related hepatotoxicity. Fatal hepatic failure has been reported in clinical trials of YERVOY (see ADVERSE REACTIONS).

In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe or fatal (Grade 2-5) immune-related hepatotoxicity ranged from 3 to 9 weeks from the start of treatment. In this study, with protocol-specified management guidelines, time to resolution ranged from 0.7 to 2 weeks.

Hepatic transaminase and bilirubin must be evaluated before each dose of YERVOY as early laboratory changes may be indicative of emerging immune-related hepatitis (see DOSAGE AND ADMINISTRATION). Elevations in LFTs may develop in the absence of clinical symptoms. Increase in LFT or total bilirubin should be evaluated to exclude other causes of hepatic injury, including infections, disease progression, or medications and monitored until resolution. Liver biopsies from patients who had immune-related hepatotoxicity showed evidence of acute inflammation (neutrophils, lymphocytes, and macrophages).

For patients with elevated AST or ALT (> 5-≤ 8 x ULN) or total bilirubin (> 3-≤ 5 x ULN) that is suspected to be related to YERVOY, the scheduled dose of YERVOY should be omitted, and LFTs must be monitored until resolution. After toxicity resolves (AST and ALT ≤ 5 x ULN and total bilirubin ≤ 3 x ULN), YERVOY therapy may be resumed at the next scheduled dose. Doses omitted for toxicity must not be replaced (see DOSAGE AND ADMINISTRATION).

For patients with AST or ALT elevations > 8 x ULN that are suspected to be related to YERVOY, treatment must be permanently discontinued (see DOSAGE AND ADMINISTRATION), and high-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg daily or equivalent) is recommended. In such patients, LFTs must be monitored until normalization. Once symptoms have resolved and LFT elevations are normalized, the initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month. Elevations in LFTs during taper may be managed with an increase in the dose of corticosteroid and a slower taper.

For patients with significant LFT elevations that are refractory to corticosteroid therapy, addition of alternative immunosuppressive agents to the corticosteroid regimen may be considered. In clinical trials, mycophenolate mofetil was used in patients without response to corticosteroid therapy, or who had an LFT elevation during corticosteroid tapering that was not responsive to an increase in the dose of corticosteroids. Refer to the Product Information for mycophenolate mofetil.

**Immune-related skin toxicity**

YERVOY is associated with serious skin toxicity that may be immune-related. In clinical trials, fatal toxic epidermal necrolysis has been reported (see ADVERSE REACTIONS).

YERVOY-induced rash and pruritus are predominantly Grade 1 or 2 and responsive to symptomatic therapy. In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, the median time to onset of moderate to severe or fatal (Grade 2-5) skin toxicity was 3 weeks (range 0.9-16 weeks) from start of treatment. In this study, with protocol-specified management guidelines, resolution occurred in most cases (87%), with a median time from onset to resolution of 5 weeks (range 0.6 to 29 weeks).

YERVOY-induced rash and pruritus should be managed based on severity. Patients with mild to moderate (Grade 1 or 2) toxicity may remain on YERVOY therapy with symptomatic treatment (eg, antihistamines). For mild to moderate rash or pruritus that persists for 1 to 2 weeks and does not improve with topical corticosteroids, oral corticosteroid therapy should be considered (eg, prednisone 1 mg/kg once daily or equivalent).

For patients with severe (Grade 3) skin toxicity, the scheduled dose of YERVOY should be omitted. If initial symptoms improve to mild or resolve (Grade 1 or lower), YERVOY therapy may be resumed at the next scheduled dose. Doses omitted for toxicity must not be replaced (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with very severe (Grade 4) skin toxicity (see section DOSAGE AND ADMINISTRATION), and high-dose IV corticosteroid therapy (eg, methylprednisolone 2 mg/kg/day) is recommended to control initial symptoms. Once rash or pruritus is controlled, initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

**Immune-related neurological events**

YERVOY is associated with serious immune-related neurological events. In clinical trials, fatal Guillain-Barré syndrome has been reported (see ADVERSE REACTIONS). Myasthenia gravis-like symptoms have also been reported. Patients may present with muscle weakness. Sensory neuropathy may also occur.

Unexplained motor neuropathy, muscle weakness, or sensory neuropathy lasting > 4 days must be evaluated, and non-inflammatory causes such as disease progression, infections, metabolic syndromes and medications should be excluded. For patients with moderate (Grade 2) neuropathy (motor with or without sensory) likely related to YERVOY, the scheduled dose should be omitted. If neurologic symptoms resolve to baseline, the patient may resume YERVOY therapy at the next scheduled dose. Doses omitted for toxicity must not be replaced (see DOSAGE AND ADMINISTRATION).

YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to YERVOY (see DOSAGE AND ADMINISTRATION). Patients must be treated according to institutional guidelines, and the administration of IV corticosteroids (eg, methylprednisolone 2 mg/kg/day) should be considered.

Progressive signs of motor neuropathy must be considered immune-related and managed accordingly. YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) motor neuropathy regardless of causality (see DOSAGE AND ADMINISTRATION).

**Immune-related endocrinopathy**

YERVOY can cause inflammation of the endocrine system organs, specifically hypophysitis, hypopituitarism, adrenal insufficiency, and hypothyroidism and patients may present with nonspecific symptoms, which may resemble other causes such as brain metastasis or underlying disease. The most common clinical presentation includes headache and fatigue. Symptoms may also include visual field defects, behavioral changes, electrolyte disturbances, and hypotension. Adrenal crisis as a cause of the patient's symptoms must be excluded. Clinical experience with YERVOY-associated endocrinopathy is limited.

In patients who received YERVOY 3 mg/kg monotherapy in MDX010-20, time to onset of moderate to severe (Grade 2-4) immune-related endocrinopathy ranged from 7 to nearly 20 weeks from the start of treatment. Immune-related endocrinopathy observed in clinical trials was generally controlled with hormone replacement therapy.

If there are any signs of adrenal crisis such as severe dehydration, hypotension, or shock, immediate administration of IV corticosteroids with mineralocorticoid activity is recommended, and the patient must be evaluated for presence of sepsis or infections.

If there are signs of adrenal insufficiency but the patient is not in adrenal crisis, further investigations should be considered including laboratory and imaging assessment. Evaluation of laboratory results to assess endocrine function may be performed before corticosteroid therapy is initiated. If pituitary imaging or laboratory tests of endocrine function are abnormal, a short course of high-dose corticosteroid therapy (eg, dexamethasone 4 mg every 6 hrs or equivalent) is recommended to treat the inflammation of the affected gland, and the scheduled dose of YERVOY should be omitted (see DOSAGE AND ADMINISTRATION). It is currently unknown if the corticosteroid treatment reverses the gland dysfunction. Appropriate hormone replacement should also be initiated. Long-term hormone replacement therapy may be necessary.

Once symptoms or laboratory abnormalities are controlled and overall patient improvement is evident, treatment with YERVOY may be resumed and initiation of corticosteroid taper should be based on clinical judgment. Tapering should occur over a period of at least 1 month.

**Other immune-related adverse events**

The following additional adverse reactions suspected to be immune-related have been reported in patients treated with YERVOY 3 mg/kg monotherapy in MDX010-20: uveitis, eosinophilia, lipase elevation, and glomerulonephritis. In addition, iritis, hemolytic anaemia, amylase elevations, multi-organ failure, and pneumonitis have been reported in patients treated with YERVOY 3 mg/kg + gp100 peptide vaccine in MDX010-20 (see ADVERSE REACTIONS).

If severe (Grade 3 or 4), these events may require high-dose corticosteroids and discontinuation of YERVOY (see DOSAGE AND ADMINISTRATION). For YERVOY-related uveitis, iritis, or episcleritis, topical corticosteroid eye drops should be considered as medically indicated.

**Infusion reaction**

There were isolated reports of severe infusion reactions in clinical trials. In case of a severe infusion reaction, YERVOY infusion must be discontinued and appropriate medical therapy administered. Patients with mild or moderate infusion reaction may receive YERVOY with close monitoring.

**Patients requiring immunosuppressive therapy for life-threatening disease or condition**

Patients who require systemic immunosuppressive therapy for active autoimmune disease or for organ transplantation graft maintenance were not evaluated in clinical studies. Ipilimumab is a T-cell potentiator that activates the immune response (see PHARMACOLOGY) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection.

YERVOY must be administered with caution in patients with active, life-threatening autoimmune disease where further immune activation is potentially imminently life threatening. Clinical stabilization of ongoing active autoimmune disease must be achieved before initiation of YERVOY therapy. YERVOY should be administered only if the potential benefit justifies the potential risk in these patients.

**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 Clinical Trials).

**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 Pharmacokinetics).

**Patients on controlled sodium diet**

Each mL of this medicinal product contains 0.1 mmol (or 2.3 mg) sodium. To be taken into consideration when treating patients on a controlled sodium diet.

**EFFECTS ON FERTILITY**

Studies to evaluate the effect of ipilimumab on fertility have not been performed. Thus, the effect of YERVOY on male and female fertility is unknown.

**USE IN PREGNANCY (Category C)**

YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk.

There are no data on the use of ipilimumab in pregnant women. Animal reproduction studies have not been conducted. It is not known whether ipilimumab can cause foetal harm when administered to a pregnant woman or whether it can affect reproductive capacity.

Human IgG1 is known to cross the placental barrier; therefore, ipilimumab has the potential to be transmitted from the mother to the developing foetus.

## USE IN LACTATION

It is not known whether ipilimumab is secreted in breast milk; however, because human IgG1 is known to be secreted in human breast milk, there is potential for infant exposure to ipilimumab via nursing. A risk to the newborns/infants cannot be excluded. Women who are taking YERVOY should not breast-feed.

## PAEDIATRIC USE

The safety and efficacy of YERVOY in children below 18 years have not been established. The use of YERVOY in children or adolescents is not recommended.

## GENOTOXICITY AND CARCINOGENICITY

Studies to evaluate the genotoxic and carcinogenic potential of ipilimumab have not been performed.

## DRUG INTERACTIONS

Ipilimumab is a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes (CYPs) or other drug metabolizing enzymes, and is not expected to have an effect on CYPs or other drug metabolizing enzymes in terms of inhibition or induction. Therefore, ipilimumab is not expected to have pharmacokinetic-based drug-drug interactions. Except for treatment of irAEs, systemic immunosuppressants, including systemic corticosteroids, should be avoided as they could interfere with the pharmacodynamic activity of ipilimumab.

## EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Because of potential adverse reactions such as fatigue (see ADVERSE REACTIONS), patients should be advised to use caution when driving or operating machinery until they are reasonably certain that YERVOY does not adversely affect them.

## PATIENT COUNSELLING INFORMATION

Patients should be advised to report immediately any signs or symptoms suggestive of immune-related events as described in PRECAUTIONS. The importance of reporting any worsening of symptoms or severity should be emphasized. Patients should be strongly advised not to treat any of these symptoms with over-the-counter medications without consultation with a health care provider.

## ADVERSE REACTIONS

YERVOY has been administered to > 3000 patients in a clinical program evaluating its use with various doses and tumor types. Unless otherwise specified, the data described below reflect exposure to YERVOY monotherapy at 3 mg/kg (n= 131) in previously treated patients with advanced melanoma from a Phase 3 study (MDX010-20. See Clinical Trials). Patients received a median of 4 doses (range 1-4).

YERVOY is most commonly associated with adverse reactions resulting from increased or excessive immune activity (see PRECAUTIONS for the management of irAEs). Most of these adverse reactions, including severe reactions, resolved following initiation of appropriate medical therapy or withdrawal of YERVOY.

### Adverse Events reported in study MDX010-20

In patients who received 3 mg/kg YERVOY monotherapy in MDX010-20, the most frequently reported adverse events (≥ 10% of patients) were fatigue, diarrhoea, pruritus, rash, decreased appetite, vomiting, abdominal pain, cough, headache, pyrexia, and insomnia (Table 3). The majority of adverse events were mild to moderate (Grade 1 or 2). YERVOY therapy was discontinued for adverse reactions in 10% of patients.

Adverse events, regardless of causality, reported in >1% of patients treated with either YERVOY-containing regimen in MDX010-20 are presented in Table 3. This table includes adverse events that occurred at a greater incidence in a YERVOY group than in the gp100 group (before rounding).

These adverse events are presented by system organ class and by frequency.

**Table 3: Adverse Events Reported in ≥1% of patients treated with YERVOY**

| System Organ Class/ Preferred Term | Percentage (%) of Patients[a] | | |
|---|---|---|---|
| | YERVOY 3 mg/kg n=131 | YERVOY 3 mg/kg+gp100[b] n=380 | gp100[b] n=132 |
| **Gastrointestinal Disorders** | | | |
| Diarrhea | 33 | 38 | 20 |
| Vomiting | 24 | 20 | 22 |
| Abdominal pain | 23 | 23 | 23 |
| Colitis | 8 | 6 | 2 |
| Gastrointestinal haemorrhage | 4 | 6 | 2 |
| Stomatitis | 2 | 0 | 1 |
| Dysphagia | 2 | 1 | 2 |
| Retching | 2 | 1 | 0 |
| **General Disorders and Administration Site Conditions** | | | |
| Fatigue | 42 | 37 | 31 |
| Pyrexia | 13 | 21 | 18 |
| Chills | 7 | 6 | 5 |
| Injection site reaction | 4 | 50 | 38 |
| Chest pain | 1 | 2 | 2 |
| Vaccination site reaction | 1 | 4 | 4 |
| **Skin and Subcutaneous Tissue Disorders** | | | |
| Pruritus | 33 | 23 | 11 |
| Rash | 30 | 25 | 8 |
| Erythema | 8 | 7 | 5 |
| Vitiligo | 3 | 4 | 2 |
| Alopecia | 2 | 3 | 2 |
| Dry skin | 2 | 3 | 2 |
| Night Sweats | 2 | 4 | 3 |
| Dermatitis | 2 | 2 | 1 |
| Urticaria | 1 | 3 | 1 |
| Eczema | 1 | 2 | 0 |
| Skin hypopigmentation | 0 | 1 | 0 |
| **Metabolism and Nutrition Disorders** | | | |
| Decreased appetite | 27 | 23 | 22 |
| Hypokalaemia | 6 | 3 | 2 |

**Table 3: Adverse Events Reported in ≥1% of patients treated with YERVOY**

| System Organ Class/ Preferred Term | Percentage (%) of Patients[a] | | |
|---|---|---|---|
| | YERVOY 3 mg/kg n=131 | YERVOY 3 mg/kg+gp100[b] n=380 | gp100[b] n=132 |
| Hyperglycaemia | 4 | 2 | 0 |
| Hypoalbuminaemia | 3 | 1 | 3 |
| Hyponatraemia | 2 | 2 | 2 |
| **Musculoskeletal and Connective Tissue Disorders** | | | |
| Myalgia | 6 | 7 | 3 |
| Muscle spasms | 2 | 3 | 3 |
| **Infections and Infestations** | | | |
| Upper respiratory tract infection | 8 | 5 | 5 |
| Urinary tract infection | 7 | 3 | 5 |
| Sepsis | 3 | 1 | 0 |
| Lower respiratory tract infection | 2 | 3 | 1 |
| Gastroenteritis | 1 | 2 | 0 |
| Infectious hepatitis | 2 | 0 | 0 |
| Oral candidiasis | 1 | 2 | 2 |
| Cellulitis | 0 | 2 | 2 |
| **Respiratory, Thoracic and Mediastinal Disorders** | | | |
| Cough | 17 | 16 | 14 |
| Oropharyngeal pain | 2 | 2 | 2 |
| Wheezing | 2 | 1 | 0 |
| Nasal disorder | 1 | 3 | 1 |
| Sinus congestion | 0 | 1 | 0 |
| **Nervous System Disorders** | | | |
| Headache | 15 | 18 | 14 |
| Lethargy | 4 | 3 | 2 |
| Tremor | 2 | 1 | 0 |
| Brain oedema | 1 | 2 | 1 |
| Cranial neuropathy | 1 | 1 | 0 |
| Peripheral neuropathy | 1 | 1 | 1 |
| Aphasia | 0 | 1 | 1 |
| **Vascular Disorders** | | | |
| Hypotension | 8 | 3 | 5 |
| Flushing | 5 | 3 | 1 |
| Hypertension | 3 | 1 | 0 |
| Haematoma | 2 | 1 | 2 |
| Venous thrombosis | 2 | 2 | 1 |

**Table 3: Adverse Events Reported in ≥1% of patients treated with YERVOY**

| System Organ Class/ Preferred Term | Percentage (%) of Patients[a] | | |
|---|---|---|---|
| | YERVOY 3 mg/kg n=131 | YERVOY 3 mg/kg+gp100[b] n=380 | gp100[b] n=132 |
| Thrombosis | 1 | 1 | 0 |
| Haemorrhage | 0 | 6 | 1 |
| Lymphoedema | 0 | 3 | 2 |
| **Psychiatric Disorders** | | | |
| Insomnia | 12 | 9 | 11 |
| Depression | 5 | 5 | 5 |
| Anxiety | 4 | 8 | 8 |
| Decreased libido | 2 | <1 | 0 |
| **Blood and Lymphatic System Disorders** | | | |
| Lymphadenopathy | 2 | 1 | 2 |
| Eosinophilia | 2 | <1 | 0 |
| Neutropenia | 2 | 1 | 2 |
| Thrombocytopenia | 1 | 2 | 2 |
| **Investigations** | | | |
| Increased blood creatinine | 4 | 1 | 2 |
| Increased blood bilirubin | 2 | <1 | 2 |
| Decreased blood corticotrophin | 2 | 0 | 0 |
| Increased lipase | 1 | 2 | 0 |
| **Eye Disorders** | | | |
| Blurred vision | 4 | 4 | 4 |
| Conjunctivitis | 2 | 2 | 2 |
| Uveitis | 2 | <1 | 1 |
| Eye pain | 1 | 1 | 1 |
| Dry eye | 0 | 1 | 1 |
| **Hepatobiliary Disorders** | | | |
| Abnormal hepatic function | 5 | 3 | 5 |
| Hepatic failure | 2 | 1 | 0 |
| Hepatomegaly | 2 | 1 | 0 |
| Jaundice | 0 | 1 | 0 |
| **Endocrine Disorders** | | | |
| Hypopituitarism | 4 | 1 | 0 |
| Hypothyroidism | 4 | 2 | 2 |
| Adrenal insufficiency | 2 | 1 | 0 |
| Hyperthyroidism | 2 | 1 | 0 |

**Table 3: Adverse Events Reported in ≥1% of patients treated with YERVOY**

| System Organ Class/ Preferred Term | Percentage (%) of Patients[a] | | |
|---|---|---|---|
| | YERVOY 3 mg/kg n=131 | YERVOY 3 mg/kg+gp100[b] n=380 | gp100[b] n=132 |
| **Neoplasms Benign, Malignant and Unspecified (incl Cysts and Polyps)** | | | |
| Tumour pain | 5 | 4 | 4 |
| Cancer pain | 2 | 1 | 1 |
| **Cardiac Disorders** | | | |
| Arrhythmia | 3 | 5 | 5 |
| Atrial fibrillation | 2 | 1 | 2 |
| Cardiac failure | 2 | 1 | 0 |
| **Injury, Poisoning and Procedural Complications** | | | |
| Contusion | 2 | 1 | 2 |
| Excoriation | 2 | 1 | 2 |
| **Renal and Urinary Disorders** | | | |
| Renal failure | 3 | 1 | 2 |
| Haematuria | 2 | 1 | 2 |
| **Immune System Disorders** | | | |
| Contrast media allergy | 2 | 0 | 0 |
| Seasonal allergy | 2 | <1 | 0 |

a Incidences presented in this table are based on reports of adverse events regardless of causality.
b Combination of YERVOY + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

In addition, the following adverse reactions were reported in other clinical studies: large intestinal ulcer, oesophagitis, ileus, Myasthenia gravis-like syndrome, erythema multiforme, blepharitis, and psoriasis.

**Immune-Related Adverse Events (irAEs) in MDX010-20 (Table 4).**

**Table 4: Immune-Related Adverse Events in MDX010-20 (Induction Phase)**

| | Percentage (%) of Patients | | |
|---|---|---|---|
| | **YERVOY 3 mg/kg n= 131** | YERVOY 3 mg/kg+gp100 [a] n= 380 | Gp100 N=132 |
| **Any irAEs**[b] | | | |
| Any Grade | **60** | 57 | 32 |
| Grade 3/4 | **13** | 10 | 3 |
| **Gastrointestinal irAEs** | | | |
| Any Grade | **28** | 31 | 14 |
| Grade 3/4 | **8** | 5 | 1 |
| Colitis | **5** | 3 | 0 |
| Diarrhoea | **5** | 3 | 1 |
| Gastrointestinal haemorrhage | **0** | < 1 | 0 |
| Intestinal perforation | **0** | < 1 | 0 |
| Large intestine perforation | **0** | 1 | 0 |
| **Hepatic irAEs** | | | |
| Any Grade | **3** | 2 | 4 |
| Grade 3/4 | **0** | 1 | 2 |
| Abnormal hepatic function | **0** | 0 | 2 |
| Increased ALT | **0** | 1 | 0 |
| Increased AST | **0** | < 1 | 0 |
| Abnormal liver function test | **0** | < 1 | 0 |
| Hepatitis | **0** | < 1 | 0 |
| **Skin irAEs** | | | |
| Any Grade | **42** | 39 | 17 |
| Grade 3/4 | **1** | 2 | 0 |
| Rash | **1** | 2 | 0 |
| Dermatitis | **0** | < 1 | 0 |
| Erythema | **0** | < 1 | 0 |
| Leukocytoclastic vasculitis | **0** | < 1 | 0 |
| Pruritus | **0** | < 1 | 0 |
| Toxic epidermal necrolysis | **0** | < 1 | 0 |
| **Neurological irAEs** | | | |
| Any Grade | **0** | 1 | 0 |
| Grade 3/4 | **0** | < 1 | 0 |
| Meningitis | **0** | < 1 | 0 |
| **Endocrine irAEs** | | | |

**Table 4: Immune-Related Adverse Events in MDX010-20 (Induction Phase)**

| | Percentage (%) of Patients | | |
|---|---|---|---|
| | **YERVOY 3 mg/kg n= 131** | YERVOY 3 mg/kg+gp100 [a] n= 380 | Gp100 N=132 |
| Any Grade | **8** | 3 | 2 |
| Grade 3/4 | **4** | 1 | 0 |
| Hypopituitarism | **3** | 1 | 0 |
| Adrenal insufficiency | **0** | 1 | 0 |
| Hypogonadism | **0** | < 1 | 0 |
| Hypothyroidism | **0** | < 1 | 0 |
| Decreased blood corticotrophin | **1** | 0 | 0 |
| **Other irAEs** | | | |
| Any Grade | **4** | 3 | 2 |
| Grade 3/4 | **2** | 1 | 1 |
| Glomerulonephritis | **1** | 0 | 0 |
| Pneumonitis | **0** | < 1 | 0 |
| Eosinophilia | **0** | < 1 | 0 |
| Hemolytic anaemia | **0** | < 1 | 0 |
| Increased lipase | **1** | 1 | 0 |
| Increased amylase | **0** | 1 | 1 |

[a] Combination of YERVOY + gp100 is not a recommended regimen; gp100 peptide vaccine is an experimental control. See DOSAGE AND ADMINISTRATION for the recommended dosage.

[b] Includes the following irAEs with fatal outcomes occurring in either YERVOY-containing regimen at a frequency of <1%: gastrointestinal perforation, colitis, hepatic failure, toxic epidermal necrolysis, Guillain-Barré syndrome, and multi-organ failure

Adverse reactions observed in Phase 2 studies in patients receiving 3 mg/kg of YERVOY (n=111) were consistent with those in MDX010-20. Rates of irAEs in HLA-A2*0201 positive patients who received YERVOY in MDX010-20 were similar to those observed in the overall clinical program.

**Other Adverse Reactions reported in Clinical Trials**

The following serious adverse reactions were also reported in patients with advanced melanoma treated with YERVOY in clinical studies (regardless of dose or regimen; N= 1498). Adverse reactions presented elsewhere in the ADVERSE REACTIONS section are excluded.

**Infections and infestations**
*Uncommon:* septic shock
*Rare:* respiratory tract infection, upper respiratory tract infection

**Blood and lymphatic system disorders**
*Uncommon:* anaemia
*Rare:* polycythemia

**Immune System Disorders**
*Rare:* hypersensitivity

**Endocrine disorders**
*Rare*: secondary adrenocortical insufficiency, hyperpituitarism, autoimmune thyroiditis

**Metabolism and nutrition disorders**
*Common:* dehydration
*Uncommon:* hypophosphatemia
*Rare:* alkalosis, tumour lysis syndrome

**Psychiatric disorders**
*Uncommon:* confusional state
*Rare:* mental status change

**Nervous system disorders**
*Uncommon:* dysarthria, ataxia
*Rare*: Guillain-Barré syndrome, meningism

**Eye disorders**
*Rare:* episcleritis, scleritis, iritis, eye oedema

**Cardiac disorders**
*Rare:* myocarditis, cardiomyopathy

**Vascular disorders**
*Rare:* angiopathy, peripheral ischemia, vasculitis, temporal arteritis, Raynaud's phenomenon

**Respiratory, thoracic and mediastinal disorders**
*Uncommon:* lung infiltration
*Rare:* dyspnoea, acute respiratory distress syndrome, respiratory failure

**Gastrointestinal disorders**
*Uncommon:* peritonitis, enterocolitis, nausea, pancreatitis

**Hepatobiliary disorders**
*Uncommon:* autoimmune hepatitis

**Musculoskeletal and connective tissue disorders**
*Uncommon:* arthralgia, musculoskeletal pain, arthritis
*Rare:* polymyalgia rheumatica

**Renal and urinary disorders**
*Uncommon:* haematuria
*Rare:* autoimmune nephritis, proteinuria, renal tubular acidosis

**General disorders and administration site conditions**
*Uncommon:* multi-organ failure, infusion related reaction, oedema

## DOSAGE AND ADMINISTRATION

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 (IV) 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 to YERVOY should be conducted only after completion of induction therapy.

Additional treatment with YERVOY (re-induction with 4 doses) may be considered for patients who develop PD after prior CR or PR or after SD lasting longer than 3 months from the first tumour assessment. The recommended re-induction regimen of YERVOY is 3 mg/kg administered IV over a 90-minute period every 3 weeks for a total of 4 doses as tolerated, regardless of the appearance of new lesions or growth of existing lesions.

Liver function tests (LFTs) and signs or symptoms of immune-related adverse events (irAEs), including diarrhoea and colitis, must be assessed before initiation of YERVOY and during treatment (see Tables 5, 6 and PRECAUTIONS).

**Permanent discontinuation of treatment or omission of doses**

Management of immune-related toxicity may require omission of a dose or permanent discontinuation of YERVOY therapy and institution of corticosteroid or other immunosuppressive therapy (see PRECAUTIONS).

Dose reduction or delay is not recommended. Doses that are omitted due to emergent Immune-Related Adverse Events (irAEs) must not be replaced.

Guidelines for permanent discontinuation or omission of scheduled doses are described in Tables 5 and 6. Detailed guidelines for the management of Immune-Related Adverse Events (irAEs) are described in PRECAUTIONS.

**Table 5 When to Permanently Discontinue YERVOY**

| **Permanently discontinue YERVOY in patients with the following signs and symptoms of an irAE. Management of these toxicities may also require high-dose corticosteroid therapy. See PRECAUTIONS for detailed management guidelines.** | |
|---|---|
| **Severe Toxicity** | **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) that are demonstrated or suspected to be immune-related | § Grade 3 or 4 diarrhoea or colitis |
| **Hepatic:** | |
| Severe elevations in AST, ALT, or total bilirubin or symptoms of hepatotoxicity that are demonstrated or suspected to be immune-related | § AST or ALT > 8 x ULN or<br>§ 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 |
| **Neurologic:** | |
| New onset or worsening severe motor or sensory neuropathy | § Grade 3 or 4 motor or sensory neuropathy |
| **Other significant immune-related events[b]:**<br>(eg, nephritis, pneumonitis, pancreatitis, non-infectious myocarditis) | § ≥ Grade 3 immune-related events[c]<br>§ ≥ Grade 2 for immune-related eye disorders NOT responding to topical 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 inflammatory events that are considered immune-related should be graded according to CTCAE. Decision whether to discontinue YERVOY should be based on severity.

[c] Excluding patients with severe (Grade 3 or 4) endocrinopathy controlled with hormone replacement therapy.
ULN = upper limit of normal

**Table 6 When to Omit Scheduled Dose of YERVOY**

| **Omit YERVOY dose[a] in patients with the following signs and symptoms of an irAE. See PRECAUTIONS for detailed management guidelines.** | |
|---|---|
| **Mild to Moderate Toxicity** | **Action** |
| **Gastrointestinal:**<br>Moderate symptoms, such as diarrhoea or colitis, that are not controlled with medical management (including persistent [5-7 days] or recurrent mild to moderate [Grade 1 or 2][b] symptoms) and that are demonstrated or suspected to be immune-related<br>**Hepatic:**<br>Moderate elevations in transaminase (AST or ALT > 5 to ≤ 8 x ULN) or total bilirubin (> 3 to ≤ 5 x ULN) levels that are demonstrated or suspected to be immune-related<br>**Skin:**<br>Moderate to severe (Grade 3)[b] skin rash or widespread/intense pruritus regardless of etiology<br>**Endocrine:**<br>Severe inflammation of the endocrine glands, such as hypophysitis and thyroiditis that is not adequately controlled with hormone replacement therapy or high-dose immunosuppressive therapy<br>**Neurological:**<br>Moderate (Grade 2)[b] unexplained motor neuropathy, muscle weakness, or sensory neuropathy (lasting more than 4 days)<br>**Other moderate immune-related events**[c] | 1. Omit YERVOY dose until toxicity resolves to Grade 1 or Grade 0 (or returns to baseline).<br>2. If resolution occurs before the next scheduled dose, resume therapy at next scheduled dose.<br>3. If resolution has not occurred before next scheduled dose, continue to omit doses until resolution then resume treatment schedule.<br>4. Discontinue YERVOY if resolution to Grade 1 or Grade 0 (or baseline) does not occur. |

[a] No dose reduction or delay of YERVOY is recommended. Doses that are omitted for toxicity must not be replaced.

[b] Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events. Version 3.0 (NCI-CTCAE v3).

[c] Any other inflammatory events that are considered immune-related should be graded according to CTCAE. Decision whether to omit a scheduled dose of YERVOY should be based on severity.

ULN = upper limit of normal

## SPECIAL POPULATIONS

### Paediatric patients

The safety and efficacy of YERVOY in children below 18 years have not been established. No data are available. The use of YERVOY in children or adolescents is not recommended until further data become available.

### Elderly patients.

No overall differences in safety or efficacy were reported between the 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 PHARMACOKINETICS).

### 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 Clinical Trials).

## PREPARATION AND ADMINISTRATION INSTRUCTIONS

Ipilimumab solutions must not be administered as an IV push or bolus injection. A separate infusion line must be used for the infusion, and the line must be flushed with sterile sodium chloride 9 mg/ml (0.9%) solution for injection or 5% glucose injection at the end of infusion.

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products. YERVOY should not be infused concomitantly in the same IV line with other medicinal products.

YERVOY may be used for IV administration without dilution after transferring to an infusion container using an appropriate sterile syringe, or after diluting with sterile sodium chloride 9 mg/ml (0.9% solution) or 5% glucose injection solution to a concentration ranging from 4 mg/ml to 1 mg/ml. An in-line, sterile, non-pyrogenic, low protein binding filter (pore size of 0.2 µm or 1.2 µm) must be used for IV administration. Care must be taken to ensure aseptic handling when preparing the infusion.

Determine the number of vials of YERVOY needed (see DOSAGE AND ADMINISTRATION). Allow the vials to stand at room temperature for approximately 5 minutes. Withdraw the required volume of ipilimumab solution (5 mg/ml) using an appropriate sterile syringe and transfer into a sterile, evacuated glass bottle or IV bag (PVC or non-PVC).

Ipilimumab solution is compatible with:

§ Glass, polyvinyl chloride (PVC) and non-PVC bags.
§ PVC IV extension/administration sets.
§ Polyethersulfone (0.2 μm and 1.2 μm) and nylon (0.2 μm) in-line filters.

EACH VIAL OF YERVOY® IS FOR SINGLE USE IN ONE PATIENT ONLY. DISCARD ANY RESIDUE.

Any unused medicinal product or waste material should be discarded in accordance with local requirements.

Prior to administration, the ipilimumab should be inspected visually for particulate matter and discolouration. Discard the solution if any particulate matter or discolouration is observed.

## OVERDOSE

The maximum tolerated dose of YERVOY has not been determined. In clinical trials, patients received up to 20 mg/kg without apparent toxic effects.

In case of overdosage, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic treatment instituted.

In the event of an overdose or poisoning contact the Poisons Information Centre on 131126.

## PRESENTATION

50 mg of ipilimumab in 10 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium light blue "flip off" seal

200 mg of ipilimumab in 40 mL of concentrate solution for infusion is supplied in a vial (Type I glass) with a stopper (coated butyl rubber) and an aluminium purple "flip off" seal

Pack of 1 vial containing 10 mL.
Pack of 1 vial containing 40 mL.

Not all pack sizes may be marketed.

## STORAGE AND STABILITY CONDITIONS:

Unopen vial: 36 months

Solution for infusion: The chemical and physical in-use stability of the undiluted or diluted concentrate (between 1 mg/mL and 4 mg/mL) has been demonstrated for 24 hours at 25°C and 2°C to 8°C. However, to reduce microbiological hazard, use as soon as practicable after dilution. If storage is necessary, hold at 2°C to 8°C for not more than 24 hours.

This medicinal product does not contain any preservatives.

**Special precautions for storage**

Store in a refrigerator (2°C to 8°C).
Do not freeze.
Store in the original package in order to protect from light.

**POISONS SCHEDULE**: S4

**DISTRIBUTED BY:**

Bristol-Myers Squibb Australia Pty Ltd
556 Princes Highway
NOBLE PARK VIC 3174

**AUSTRALIAN REGISTRATION NUMBERS**:

YERVOY (ipilimumab): 50mg of ipilimumab in 10mL of concentrate solution for infusion (5mg in 1mL). Pack of one vial containing 10mL. AUST R 174319

YERVOY (ipilimumab): 200mg of ipilimumab in 40mL of concentrate solution for infusion (5mg in 1mL). Pack of one vial containing 40mL. AUST R 174322

**DATE OF TGA APPROVAL: 27 June 2011**

**Therapeutic Goods Administration**

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Reference/Publication #