19 May 2011
EMA/CHMP/557664/2011
Committee for Medicinal Products for Human Use (CHMP)

Assessment Report
For
Yervoy
(ipilimumab)

Procedure No.: EMEA/H/C/002213

Assessment Report as adopted by the CHMP with all information of a commercially confidential nature deleted

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Table of contents

List of abbreviations

ADCC	antibody-dependent cellular cytotoxicity
AE	adverse event
AEX	anion exchange
ALC	absolute lymphocyte count
ALT	alanine aminotransferase
ALP	Alkaline phosphatase
ALT	aspartate aminotransferase
ANC	absolute neutrophil count
AUC	area under the concentration-time curve
BOR	best overall response
BORR	best overall response rate
BMS	Bristol-Myers Squibb
CCIT	container closure integrity testing
CDC	complement-dependent cytotoxicity
CHO	Chinese hamster ovary
CEX	cation exchange
CI	confidence interval
CL	clearance
Cmax	maximum concentration
Cmin	trough concentration
Cminss	trough concentration at steady state
CNS	central nervous system
CPP	critical process parameters
CR	complete response
CSR	clinical study report
CTLA-4	cytotoxic T lymphocyte antigen 4
CV	coefficient of variation
DCR	disease control rate
DTIC	dacarbazine
ECOG	Eastern Cooperative Oncology Group
ELISA	enzyme linked immunosorbent assay
EU	European Union
GCP	good clinical practice
GFR	glomerular filtration rate
GI	gastrointestinal
GLP	good laboratory practice
HA	hydroxyapatite
HAHA	human anti-human antibodies
HBsAG	hepatitis B surface antigen

HLA	human leukocyte antigen
HR	hazard ratio
ICH	International Conference on Harmonization
IFNa	interferon alfa
IL-2	interleukin-2
IP	intraperitoneally
irAE	immune-related adverse event
IRC	Independent Review Committee
ITT	intent to treat
IV	intravenously
KD	dissociation constant
KLH	keyhole limpet hemocyanin
LDH	lactate dehydrogenase
mAb	monoclonal antibody
MTD	maximum tolerated dose
ORR	overall response rate
OS	overall survival
PD	progressive disease
PFS	progression-free survival
PFSR	progression-free survival rate
PK	pharmacokinetic
PP	process parameters
PPK	population pharmacokinetic
PR	partial response
PV	pharmacovigilance
RMP	risk management plan
SAE	serious adverse event
SAWP	Scientific Advice Working Party
SD	stable disease
SIV	simian immunodeficiency virus
SmPC	Summary of Product Characteristics
T-HALF	terminal elimination half-life
TIL	tumor infiltrating lymphocyte
Tmax	time to maximum concentration
TNF	tumor necrosis factor
TSE	transmissible spongiform encephalopathy
UF/DF	ultrafiltration/diafiltration
ULN	upper limit of normal
VC	volume of central compartment
VF	viral filtration
VI	viral inactivation

VP	Volume of peripheral compartment
Vss	volume of distribution at steady state
WBC	white blood cells
WCB	working cell bank
WHO	World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant Bristol-Myers Squibb Pharma EEIG submitted on 5 May 2010 an application for Marketing Authorisation to the European Medicines Agency (EMA) for Yervoy, through the centralised procedure falling within the Article 3(1) and point 1 of Annex of Regulation (EC) No 726/2004.

The applicant applied for the following indication treatment of advanced melanoma in adults who have received prior therapy.

The legal basis for this application refers to:

Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application

The application submitted is composed of administrative information, complete quality data, non-clinical and clinical data based on applicants' own tests and studies and/or bibliographic literature substituting/supporting certain test(s) or study(ies).

Information on Paediatric requirements

Pursuant to Article 7 of Regulation (EC) No 1901/2006, the application included an EMA Decision P/63/2010 for the following condition(s):

- Treatment of melanoma in all subsets of the paediatric population.

on the granting of a class waiver

Information relating to orphan market exclusivity

Similarity

Not applicable.

Market Exclusivity

Not applicable.

Scientific Advice:

The applicant received Scientific Advice from the CHMP on 17 november 2005 and 25 June 2009. The Scientific Advice pertained to quality and clinical aspects of the dossier.

Licensing status

The product was not licensed in any country at the time of submission of the application.

A new application was filed in the following countries: Australia, Canada, Switzerland and USA.

A Marketing Authorisation was granted for Yervoy in the USA on 25 March 2011.

1.2. Steps taken for the assessment of the product

The Rapporteur and Co-Rapporteur appointed by the CHMP and the evaluation teams were:

Rapporteur: **Barbara van Zwieten-Boot** Co-Rapporteur: **Arantxa Sancho-Lopez**

- The application was received by the EMA on 5 May 2010.
- The procedure started on 26 May 2010.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 15 August 2010 The Co-Rapporteur's first Assessment Report was circulated to all CHMP members on 16 August 2010.
- During the meeting on 23 September 2010, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 24 September 2010.
- The applicant submitted the responses to the CHMP consolidated List of Questions on

  12 January 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 11 March 2011.
- During the CHMP meeting on 17 March 2011, the CHMP agreed on a list of outstanding issues to be addressed in writing and/or in an oral explanation by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 18 April 2011.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 4 May 2011.
- During the meeting of May 2011, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Yervoy on 19 May 2011. The applicant provided the letter of undertaking on the follow-up measures to be fulfilled post-authorisation on 19 May 2011.

2. Scientific discussion

2.1. Introduction

Melanoma is an aggressive form of skin cancer. The incidence of melanoma varies between different European countries the estimated incidence is about 3.5 /100.000 men and 2.5/ 100.000 women per year. Approximately half the incidence is in people between the age of 35 and 65 years, with a median age at diagnosis of 57 years. The last decades the incidence has been increased continuously. The increase in incidence affects all ages. Although more than 95% of the tumours are found in the skin, melanoma is not exclusively a skin cancer. Sites of primary extracutaneous melanoma include ocular, mucosal, gastrointestinal, genitourinary, leptomeninges and lymph nodes.

About 20% of the patients diagnosed with melanoma develop metastases, and these patients have a median survival of about seven months. Melanoma can spread by local extension (through lymphatic's) and/or by haematogenous routes. Systemic therapy, surgery and radiotherapy, all can be used in the treatment of metastatic melanoma. Spontaneous regression of melanoma has been reported with an incidence of less than 1%. Complete resection of isolated metastases to one anatomic site (lung, gastrointestinal tract, bone or brain) may occasionally achieve long term survival. Systemic treatment may consist of chemotherapy, and/or immunotherapy. Palliative radiotherapy is indicated for symptomatic relief of metastases to brain, bones and viscera.

Chemotherapy with dacarbazine (DTIC) may achieve objective response rates of about 20%, of which less than 5% is complete remission. Higher response rates have been seen using combination chemotherapy, however no increase in over-all survival has been demonstrated with combination regimens when compared to dacarbazine alone. Immunotherapeutic agents used for metastatic melanoma are interferon-alfa (IFNa) and interleukine2 (IL-2). Recurrent melanoma is resistant to most standard systemic therapy and no standardized effective second line treatment is established.

Ipilimumab (MDX-010, BMS-734016), a fully human anti-human CTLA-4 (CD152) monoclonal antibody of the IgG1-κ isotype, is an immunomodulatory agent that is being developed for use in the treatment of cancer. The proposed mechanism of action for ipilimumab is interference of the interaction of CTLA-4, expressed on a subset of activated T cells, with B7 (CD80/CD86) molecules on professional antigen-presenting cells. This results in T-cell potentiation due to blockade of the inhibitory modulation of T-cell activation promoted by the CTLA-4/B7 interaction. The resulting T-cell activation, proliferation, and lymphocyte infiltration into tumours, leads to tumour cell death. The mechanism of action of ipilimumab is indirect, through enhancing T-cell mediated immune response. The commercial dosage form proposed for the European Union (EU) is a 5 mg/ml concentrate for solution for infusion.

The applicant submitted this marketing authorisation application for Yervoy (ipilimumab) in the treatment of advanced melanoma in adults who have received prior therapy.

The proposed target population for Yervoy was patients with a diagnosis of unresectable stage III or IV melanoma who, in response to at least 1 cycle first-line therapy, have relapsed following an objective response, failed to demonstrate an objective response, or could not tolerate IL-2, dacarbazine and/or temozolomide therapy due to unacceptable toxicity.

The CHMP provided Scientific Advice (SA) to the applicant on the clinical development of ipilimumab. At the time of the SA, the Applicant proposed a phase III, blinded, three-arm clinical trial by which the three arms encompassed Yervoy combined with MDX-1379 (a tumour specific peptide vaccine), Yervoy alone and MDX-1379 alone.

2.2. Quality aspects

2.2.1. Introduction

Ipilimumab drug substance is manufactured by Lonza Biologics, Inc., Portsmouth, NH, USA. Ipilimumab is produced from large-scale cell culture using a Chinese hamster ovary (CHO) cell line and is purified using standard chromatography and filtration steps. The long-term stability studies support a 36-month shelf life for drug substance when stored refrigerated (2°-8°C) and protected from light.

Ipilimumab concentrate for solution for infusion, also referred to ipilimumab injection, is available as 50 mg/10 mL (5 mg/mL) or 200 mg/40 mL (5 mg/mL) single-use vial presentations. Both presentations are manufactured using the same 5 mg/mL bulk solution. Overall the long-term stability data support a 36-month shelf life when stored refrigerated (2°-8°C) and protected from light and freezing.

Three different manufacturing processes for the manufacturing of ipilimumab have been described: process A (hybridoma cells), process B-reduced-scale (CHO cells) and process B-commercial-scale (CHO cells). The process validation batches as well as the stability batches are produced with process B-commercial-scale material. Batches from all three processes are used in clinical studies, but the pivotal clinical studies are performed with process B-commercial-scale material. Regarding pre-clinical studies only material from process A and the first small scale batch from process B are included in the studies. Process B-commercial-scale is the proposed commercial process.

2.2.2. Active Substance

Ipilimumab is a fully human monoclonal antibody produced by recombinant DNA technology in a CHO mammalian cell expression system. Ipilimumab consists of four polypeptide chains with two identical heavy chains of 447 amino acids each and two identical kappa light chains of 215 amino acids each. Each heavy and light chain pair is linked through an interchain disulfide bond. The predicted molecular weight is 147,991 Daltons.

Manufacture

Ipilimumab is produced as a secreted protein in large-scale cell culture employing a CHO cell line that was transfected with an expression vector containing the coding sequences for both heavy and light chains of ipilimumab. This cell line is maintained with a Master Cell Bank and a Working Cell Bank (WCB) both of which have been tested consistent with ICH guidance documents.

The upstream manufacturing process is initiated with the thaw of a frozen vial from a WCB. The culture is initially propagated in flasks to inoculate a seed bioreactor. Subsequently, contents are transferred to a second seed bioreactor followed by a production bioreactor. The production bioreactor is harvested when a specified set of criteria are met.

The primary recovery steps are designed to clarify the material obtained from the production bioreactor for downstream processing. The cell culture is harvested through a continuous flow centrifuge and clarified by depth filtration. At the completion of the primary recovery process, the material is transferred to the purification area.

The downstream manufacturing process consists of three chromatographic steps, two orthogonal dedicated viral inactivation/clearance steps, UF/DF steps, a formulation step, final filtration and fill. The downstream process is designed to remove host cell proteins, DNA, and cell culture media components from the process stream.

A description of the formulation of the drug substance batch, the batch formula and the controls during formulation has been provided. Drug substance stability studies have all been conducted using formulated bulk drug substance. The holding times for the unformulated bulk as well as formulated bulk drug substance for the lots used for drug product production are presented.

Overall the drug substance manufacturing process has been sufficiently validated. The validation protocols included pre-defined acceptance criteria. Reprocessing steps are appropriately described and validated. The applicant has committed to perform an additional in-process stability study for each in-process holding point using an updated test panel. Moreover a cumulative in-process stability study at laboratory scale will be performed. The testing of clearance of HCP is performed using a generic CHO HCP assay. This assay is not considered the most suitable for its purpose based on the difficulties to fully demonstrate its sensitivity and accuracy. The applicant is asked to continue the development and validation of a process-specific HCP assay. The process validation is supported by a control strategy with a full set of process parameters (PPs). A subset of the PPs was designated as critical process parameters (CPPs). CPPs have been defined for the upstream and downstream process step and must be met to ensure the consistent performance of the manufacturing process. The acceptable ranges established for the PPs/CPPs are derived from data collected during development studies, production lots and scale-down ranging studies. Justification of the PP's and CPP's choice has been provided. Batch analysis data for the commercial validation batches as well as representative batches of the small-scale process demonstrate consistent production of DS. The formulation of the bulk is part of the drug substance manufacture at Lonza has been described in detail. In order to fully validate it, BMS is recommended to perform a formal mixing validation study at scale to confirm the complete mixing of polysorbate 80. All compendial raw materials used in the process are controlled to meet Ph. Eur. requirements. The identified raw materials of biological origin used in the process are low Transmissible Spongiform Encephalopathy (TSE) risk materials.

Development: cell banks

Initially hybridoma cells were generated by the fusion of mouse myeloma cells with spleen cells from a Cytotoxic T-Lymphocyte Antigen 4 (CTLA-4) immunized transgenic mouse (HuMAb-Mouse). In the HuMAb-Mouse, the murine genes coding for antibody sequences have been inactivated and human antibody coding sequences have been introduced. A hybridoma clone, produced anti-CTLA-4 antibody, was selected and its product was used in Phase I clinical studies (Process A).

For Phase II clinical studies and beyond, a recombinant CHO cell line was developed which expressed the same antibody sequence produced by the hybridoma. The genealogy of the CHO cell line is described in detail. A research cell bank was established from the ipilimumab-producing CHO cell line. A MCB was prepared from the research cell bank. These cell banks used in the manufacturing process were subsequently prepared from the MCB. The analyses performed on the MCB and WCB were adequately addressed, however, it should still be demonstrated that genetic stability of the End of Production cells is indeed not affected the process conditions.

Characterization

Three lots of ipilimumab drug substance manufactured by the proposed commercial process have undergone comprehensive physicochemical characterization. These characterization tests include amino acid analysis, molar absorptivity, amino acid sequence, molecular weight by mass spectroscopy, circular dichroism and differential scanning calorimetry. In addition to these physicochemical analyses, the biological activity of ipilimumab has been evaluated through analysis of binding to CTLA-4, Fc-receptor binding, antibody-dependent cellular toxicity (ADCC) and complement-dependent cytotoxicity (CDC).

Ipilimumab drug substance contains product-related variants that contain modifications at the amino- and carboxy-termini, N-linked glycoforms, deamidated and oxidized amino acids, charge variants, and high and low molecular weight species. These variants are common in monoclonal antibodies produced by mammalian cell cultures and are not expected to affect overall in vivo biological activity. However the degree of some of these variants (deamidated or oxidized) are considered as stability indicating. The overall biochemical characterization program has resulted in a comprehensive understanding of the structure, biological properties, product related variants, impurity profile and degradation pathways of this monoclonal antibody.

Some aggregates can be detected by the analytical ultracentrifugation (AUC), but remain unnoticed with the current SE-HPLC. However, AUC is not considered a suitable method for routine testing and release. The applicant is recommended to continue with their identification in order to ensure their monitoring with the routine release procedures (improved SE-HPLC or otherwise). The CEX-HPLC method is promising, and seems to be an important stability indicating test. With this respect, the applicant is recommended to review the acceptance criteria and justification limits after 30 batches have been tested for release.

Controls of Drug Substance

The identity, quality and purity of ipilimumab drug substance is controlled by employing a battery of tests validated in accordance with ICH guidelines.

A sufficient number of batches of ipilimumab drug substance have been manufactured at Lonza using the commercial process designated as Process B-commercial-scale. The analytical results for these lots have all met pre-established acceptance criteria and show that product of consistent quality can be manufactured. The results also compare very well with those obtained from lots manufactured by the same process but at a reduced scale and provide a linkage between ipilimumab used throughout primary clinical trials and that planned for commercial introduction.

The applicant will review the specifications after manufacturing of an additional, specified number of batches of DS.

Reference Standard

The reference material has been replaced several times during development. The current reference standard was derived from a representative drug substance lot manufactured by the proposed commercial process. Due to the nature of any standard material, the applicant should aim at a lower frequency of standard.

Container Closure System

Drug substance is filled in to single-use, pre-sterilized containers. Compendial endotoxins, sterility, biological reactivity, physicochemical and particulates testing are performed on the containers. Suitability of these containers has been demonstrated.

Stability

The analytical tests used to assess stability were a subset of those used for release testing and were suitable for determining the critical quality attributes purity and potency. At the recommended storage condition, no statistically significant trends were observed for any of the selected critical quality attributes analyzed. All batches were manufactured by Process B-commercial-scale at Lonza and were stored in containers of the same composition as the containers described above. In addition, an appropriate post-approval stability protocol is proposed which will be used for the first three

commercial batches and one batch annually thereafter. All stability studies were performed with formulated bulk drug substance.

Overall the stability data support the conclusion that ipilimumab drug substance as well as the reprocessed ipilimumab drug substance is stable for 36-months at the recommended storage conditions of 2°-8°C with protection from light.

2.2.3. Finished Medicinal Product

Ipilimumab injection is prepared as a sterile, preservative-free, clear and colourless isotonic solution at pH 7.0 (Tris HCl buffer) for intravenous (IV) administration. Light (few) particulates are allowed which are removed by filtration prior to patient administration by infusion with no loss in strength or potency. Ipilimumab injection is available in 50 mg/vial (50 mg/10 mL) and 200 mg/vial (200 mg/40 mL), single-use presentations. For both presentations, the same drug substance solution (5 mg/mL), which contains sodium chloride, pentetic acid and polysorbate 80 as stabilizers and mannitol to assure proper osmolality, is filled directly into Type I flint glass vials. Both vial presentations are stoppered with 20-mm gray butyl coated serum stoppers and sealed with 20-mm aluminium flip-off seals. Sufficient overfill is present for both presentations for vial.

Pharmaceutical Development

Extensive formulation development studies for ipilimumab injection included the selections of buffer type, pH, and ionic strength, and the evaluation of pharmaceutically acceptable surfactants, metal ion chelators, and tonicity modifiers. These studies focused on optimizing the final formulation composition to allow for the maintenance of binding activity and structural integrity of ipilimumab. The proposed commercial formulation is able to effectively minimize the formation of high molecular weight species and breakdown products, and other physical and chemical modifications that might otherwise adversely affect product quality and stability.

Tris hydrochloride buffer at pH 7.0 was selected for the final drug product formulation as the optimal buffer to maintain the physical and chemical stability of ipilimumab. Among several surfactants tested, polysorbate 80 provided protection against protein aggregation and precipitation. Therefore, polysorbate 80 at the lowest effective concentration was selected for the ipilimumab commercial formulation.

Pentetic acid (DTPA) was found to have the optimal protective effect against potential metal-induced oxidation of ipilimumab and was therefore selected for the drug product formulation.

Adjustment for proper isotonicity was achieved using mannitol and is suitable to support IV infusion of the undiluted product. Alternatively, the drug product may be further diluted with 0.9% Sodium Chloride Injection, or 5% Dextrose Injection, to concentrations ranging from 1 mg/mL to 4 mg/mL. Use time studies demonstrated that ipilimumab injection is also compatible with multiple IV containers, IV sets, syringes and filters.

Manufacture of the product

The manufacturing process of ipilimumab injection consists of the pooling and mixing of the contents of the drug substance containers followed by sterile filtration, aseptic filling into sterile glass vials, stoppering with sterile rubber closures, and sealing with aluminum seals. It is confirmed that each drug substance batch complies with the DS release specifications.

Suitable controls are in place particularly for verification of sterile filtration via filter integrity testing and in-process vial weight check during aseptic filling. For the 50 mg/10 mL and the 200 mg/40 mL

presentation, three validation lots each were manufactured and placed on long-term stability. All pre-established process validation acceptance criteria were met and the process controls assure consistent drug product manufacturing. The applicant has confirmed that bioburden is tested before final sterile filtration and has a limit of NMT 10 cfu/100 mL in line with guideline CPMP/QWP/486/95.

PPs and CPPs are clearly defined, and validation is based on these pre-defined limits. Validation parameters were met, except for the In Process Weight Checks, for on batch. The CPP limits for the In Process Weight Checks were amended hereafter.

After packaging, drug product vials are shipped to the manufacturing site where secondary packaging and release occurs. Validation of the shipment has been provided on request. The secondary commercial packaging for ipilimumab injection includes a paperboard folding carton which provides the drug product vial with adequate protection from light throughout the shelf life.

Compatibility of ipilimumab injection with the stopper was adequately demonstrated under accelerated and long-term conditions with vials stored in horizontal and upright orientations. A stopper leachables study was conducted. All leachable levels were below their limits of detection except for acetone, isopropyl alcohol, and tert-butyl alcohol. The highest levels of leachables seen were thoroughly evaluated as to potential safety issues and none were identified.

With the exception of Tris hydrochloride, pentetic acid, and hydrochloric acid used as a formulation buffer, all of the excipients in ipilimumab injection comply with the current Ph.Eur. requirements.

Pentetic acid is required to meet acceptable in-house specifications. None of excipients have an animal/human origin. It is also noted that neither the DS specification nor the DP specifications include any test for excipients. The applicant will add in-process test for Polysorbate 80 and DTPA to ensure proper control of these excipients.

Product specification

Control of Drug Product

The identity, quality and purity of drug product are assured by employing a similar battery of release tests used for testing of drug substance. Specific compendial tests for sterility and volume in the container are included. During the procedure the applicant has updated the specification for appearance to be in line with the Ph.Eur. monograph for monoclonal antibodies.

A sufficient number of lots of Ipilimumab Injection, 50 mg/10 mL, and Ipilimumab Injection, 200 mg/40 mL, have been manufactured using drug substance made by Process B-commercial scale at Lonza. The analytical results for these lots have all met the set of proposed acceptance criteria and show that product of consistent quality can be manufactured. These results compare very well with those obtained from drug substance manufactured by the same process but at a reduced scale and provide a link between ipilimumab used throughout primary clinical trials and that planned for commercial introduction. The applicant will review the specifications after manufacturing of 30 batches of DP.

Reference Standards and Materials

The reference standard is the same used for testing of drug substance. This is appropriate since the drug product solution is of the same composition and approximate protein concentration as compared to the drug substance solution.

Container Closure System

Container closure integrity testing (CCIT) was conducted using a Microbial Ingress Challenge Test on primary packaging components (both 10-cc tubing and 50-cc molded Type I flint glass vials) that had

been processed at the proposed commercial site. Results of these studies indicated that each vial/stopper/seal combination evaluated maintains its integrity after exposure to the stressed environmental conditions and confirmed the suitability of the chosen container closure system which meets current USP/Ph.Eur. requirements.

Stability of the product

A long-term stability study is conducted to justify a 36-month shelf life for the drug product stored at 2-8°C with protection from light. The analytical tests used to assess stability were a subset of those used for release testing and are overall considered suitable for determining critical quality attributes for purity and potency.

The stability data for the 50 mg/10 mL and the 200 mg/40 mL presentations were obtained from three validation lots respectively. 36 months of stability data for both presentations lots were available with no trends observed at the recommended storage condition of 2-8°C. Both presentations as they have shown equivalent stability profiles under both recommended and stress conditions. Except for volume, the container-closure systems used for both presentations are considered equivalent.

At the recommended storage condition, no statistically significant trends were observed for any of the selected critical quality attributes analyzed. All lots were manufactured from drug substance produced by Process B-commercial scale at Lonza. The long-term stability studies were conducted through 36 months. In addition, an appropriate post-approval stability protocol is proposed that will be used for the first three commercial lots and one lot annually thereafter. During the stability studies the vials were stored in a horizontal position and the product is in contact with the container closure. In accordance with EU GMP guidelines, any confirmed out of specification result, or significant negative trend, should be reported to the Rapporteur and the EMA.

Adventitious agents

The MCB, WCB and End-of Production Cell Bank were all tested to demonstrate sterility and absence of mycoplasma and viruses. Specifications exist which describe the acceptance and release criteria for all raw materials including those of biological origin. A raw materials risk assessment for TSE has been conducted and appropriate certifications have been obtained from the vendors. Pre-harvest samples are tested for bioburden, mycoplasma and viruses. No raw materials of human origin are used in the manufacturing process for ipilimumab injection drug product.

A complete viral clearance study using scaled-down column chromatography, and viral inactivation/removal steps was conducted consistent with the principles contained in ICH Q5A. The virus validation studies are deemed adequately designed and well performed. The viral safety has been sufficiently assured.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

The development, manufacture and control of the drug substance and drug product have been presented in a satisfactory manner. The different aspects of the chemical, pharmaceutical and biological documentation are in compliance with existing guidelines.

The manufacture of the drug substance have been adequately described, controlled and validated. The drug substance has been well characterised with regard to its physicochemical and biological characteristics. Adequate analytical methods have been established and appropriate specifications have been set. It is noted that the testing of clearance of HCP is performed using a generic CHO HCP assay. This is not considered the most suitable test for this purpose based on the difficulties on validation.

With this respect, the applicant is asked to continue the development and validation of a process-specific HCP assay.

The manufacturing process of the drug product has been satisfactorily described and validated. The results of tests carried out indicate satisfactory consistency and uniformity of important quality characteristics. The quality of the drug product is controlled by adequate test methods and specifications.

The viral safety and the safety concerning other adventitious agents including TSE have been sufficiently assured.

The applicant is recommended to undertake some minor quality issues having no impact on the benefit-risk balance of the product.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

Based on the review of the data on quality, the application for Yervoy is considered approvable.

2.3. Non-clinical aspects

2.3.1. Introduction

The pivotal toxicology studies supporting the safety of ipilimumab were conducted in compliance with Good Laboratory Practice (GLP) regulations and International Conference on Harmonization (ICH) guidelines.

2.3.2. Pharmacology

Primary pharmacodynamic studies

The scientific rationale for the clinical use of ipilimumab for the management and treatment of cancer was supported by discussions of the role of T-cell immunity during carcinogenesis, the role of CTLA-4 during T-cell activation and the effect of blocking CTLA-4 function, the role on other stimulatory and inhibitory signals in the T-cell activation process, the anti-tumour activity of anti-mouse CTLA-4 blocking antibodies in murine tumour models and the effect of CTLA-4 blockade on development of experimental autoimmunity in mice.

In vitro studies

In vitro, ipilimumab binds to human CTLA-4 with high affinity (KD = 5.25 ± 3.62 nM) and blocks in vitro binding of B7.1 (CD80) and B7.2 (CD86) to human CTLA-4 at EC50 values of approximately 0.2 µg/mL with maximal blockade between 6 to 20 µg/mL and 1 to 3 µg/mL respectively. Therefore, ipilimumab concentrations are targeted at Ctrough concentration of 20 µg/ml.

In competition experiments ipilimumab was able to inhibit CTLA-4 binding to B7.1/B7.2 with maximal inhibition at concentrations between 6 to 20 µg/mL and 1 to 3 µg/mL for B7.1 and B7.2 respectively (study MDX-010-008R).

In vitro data indicate that ipilimumab does not elicit CDC up to concentrations of 50 µg/ml. However, this is lower than the concentrations reached in human plasma after the 3mg/kg dose (Cmax ~85 µg/ml). In vitro data indicate that ADCC could occur in vivo. However, given the lack of

effects on T cell numbers in the in vivo studies it is likely that ADCC does not occur in vivo at biological relevant levels.

Ipilimumab did not show cross-reactivity with or binding to CTLA-4 from rats, mice or rabbits, but showed specific binding to cynomolgus monkey recombinant CTLA-4 and activated T-cells (study MDX-010-011-R).

As part of the functional characterization of ipilimumab, in vitro assays were conducted to determine whether ipilimumab could elicit cytotoxicity of target cells mediated by activation of complement (CDC) or by activation of FcγRs expressed on immune effector cells (ADCC). Ipilimumab did not mediate complement-dependent cytotoxicity of activated T cells in vitro. Under in vitro conditions, ipilimumab mediated variable levels of ADCC, which was unrelated to the level of CTLA-4 expression, and suggest that treatment with ipilimumab could produce depletion of activated T cells. Furthermore, in contrast to the in vitro studies, non-clinical and clinical studies showed no depletion of T cells.

In vivo studies

- Mouse studies

The MC-38 colon carcinoma tumour line was implanted into the human CTLA-4 transgenic mice to evaluate the anti-tumour activity of ipilimumab.

Ipilimumab administered at a dose of 10 mg/kg resulted in a delay in tumour growth or complete inhibition of tumour growth when administered 3 or 4 times every 3 days, but was not active when administered for 2 doses only given every 3 days.

Ipilimumab or control IgG antibody were administered intraperitoneally (IP) at a dose of 10 mg/kg on Study Days 0, 3, 6, and 10 (tumour cell implantation was performed on Day 0). Ipilimumab treatment produced complete rejection of tumours in 4 out of 10 mice, and delayed time to reach tumour target size in the remaining mice. Control animals showed progressive tumour growth in 9 out of 10 mice.

Following multiple treatments of ipilimumab, tumours were rejected (10-50% of mice) or tumour growth delayed, whereas rapid tumour growth and no tumour rejection were observed in mice treated with human IgG1 control antibody.

- Cynomolgus monkey studies

Intravenous studies were conducted to determine the effect of ipilimumab on immune responses to T-cell dependent antigens. The antigens used for this assessment were hepatitis B surface antigen (HBsAg) vaccine, a melanoma cell-based vaccine (Sk-mel), DNP (2,4-Dinitrophenyl)-Ficoll keyhole limpet hemocyanin (KLH) and simian immunodeficiency virus (SIV) DNA vaccines (purified plasmid DNA) expressing the proteins for the gag (pSIVgag), env (pSIVenv), and pol (pSIVpol) portions of SIV. In one study, the SKmel tumour line was transfected to express GM-CSF.

Ipilimumab at 10 mg/kg was effective in enhancing the antibody response to HBsAg (study 0992-128, 1416-128, SUV00006), SK-mel (studies 01-3460, 1416-128, SUV00006) and KLH (study DS06064). In studies where no statistical significance was achieved ($p > 0.05$) between ipilimumab-treated and control animals, the ipilimumab-treated group produced higher antibody titers to the injected antigens than the control group. DNP (2,4-dinitrophenyl)-Ficoll does not produce a measurable humoral response (study SUV00006), and therefore, ipilimumab, as expected, was not effective.

In one study, a comparison between weekly doses of 1 mg/kg of ipilimumab to doses of 0.1, 1 and 10 mg/kg administered approximately every 4 weeks was conducted (study 1416-128). In this study a clear increase in the magnitude of the response was only seen in animals treated with ipilimumab every 4 weeks at 10 mg/kg. In the same study also a comparison of the pharmacodynamic activity of

equal doses (10 mg/kg) of ipilimumab produced by Process A (hybridoma-derived) and Process B (Chinese hamster ovary [CHO]-cell derived) was also conducted. The magnitude of the enhancement of the antibody response to the test antigen was similar, demonstrating the functional comparability of ipilimumab produced by these processes.

In these monkey studies also immunophenotypic analysis of the T cells and T cell subset was performed in several studies. There were no ipilimumab -related changes in the frequencies of CD4+ or CD8+ T cells, or on these T-cell subpopulations expressing CD69, CD25, or HLA-DR activation markers (studies 0992-128, 01-3460, 1416-128, SUV00006).

Measurement of the levels of intracellular cytokines was performed in 3 studies: It was concluded that despite the variability and lack of robustness in response using these investigative methods, the overall trend in results was consistent with the proposed effect of ipilimumab on T-cell responses.

The cellular immune responses were extensively characterised in study SUV00006, measured indices included the percentage of T (incl. Treg), B and monocytic cells as well as the activation status of these cells. There were no gross alterations in cellular subsets for the treatment groups. In this study an increase in the percentage of CD4+ central memory T cells was observed within 2 weeks of antibody treatment.

The Applicant concluded that results from the in vivo studies conducted in human CTLA-4 transgenic mice bearing colon carcinoma tumours and in cynomolgus monkeys challenged with T cell-dependent antigens suggest that ipilimumab should expand antigen-specific immune responses in humans, and supports the use of ipilimumab for the treatment of patients with cancer.

Secondary pharmacodynamic studies

No secondary pharmacodynamic studies were conducted.

Safety pharmacology programme

Evaluation of the potential effects of intravenous administration of ipilimumab on the cardiovascular, central/peripheral nervous or respiratory systems were included as part of the pivotal (GLP) repeat-dose toxicity studies in monkeys.

No drug-related findings were observed in standard clinical evaluations of cardiovascular, respiratory or neurologic function (including behaviour, posture, coordination, neurologic exams that included peripheral and cranial nerve evaluations, peripheral reflexes, proprioception, or eye movements, and in the 1-month study, electrocardiograms) conducted in monkeys as part of the repeat-dose toxicity studies for up to 6 months with ipilimumab.

In the 1-month (weekly doses for 4 weeks) intermittent-dose study of ipilimumab at 10 mg/kg alone or in combination with BMS-663513 (an anti-CD137 monoclonal antibody), safety assessments were conducted prior to the first dose, at Day 22, and after an approximate 10-week dose-free observation period. These assessments included physical assessment of general body condition, and the respiratory, gastrointestinal, integumentary, circulatory (including body temperature), cardiovascular, lymphatic, urogenital, central nervous system ophthalmologic, otologic, and musculoskeletal systems. The results of these evaluations did not show any drug-related changes in cardiovascular, neurologic, or respiratory function.

In the 6-month study in cynomolgus monkeys in which ipilimumab was administered intravenously (10 mg/kg), as a single agent or in conjunction with a vaccine (SK-mel cells) on Days 0, 28, 56, 84 and 140, no drug-related findings involving the safety pharmacology endpoints were reported.

Assessments of similar parameters and frequency performed in other repeat-dose studies also did not show any drug-related findings.

The specificity of ipilimumab and its molecular size limit possible access to ion channels in the myocardium, and ipilimumab is not expected to affect ion currents or channel selectivity as can occur with a variety of small molecule drugs.

Pharmacodynamic drug interactions

The pharmacodynamic activity of ipilimumab when administered in combination with immunomodulatory antibodies to human CD137 (BMS-663513, 2 studies) or to PD-1 receptor (MDX-1106, 1 study) was studied in cynomolgus monkeys. From these studies, co-treatment with BMS-663513 did not affect the ability of ipilimumab to modulate antibody responses to a T cell-dependent antigen. Results of the study conducted in combination with MDX-1106 did not provide direct information on potential drug interaction.

An assessment of the effect of dexamethasone on the anti-tumour activity of anti-mouse CTLA-4 monoclonal antibody (mAb) was made (study MDX-010-001-R). Administration of systemic corticosteroids may be required in clinical studies with ipilimumab to treat immune-related adverse events; thus, it was of interest to determine how concurrent or sequential treatment with dexamethasone affects anti-CTLA-4 mAb anti-tumour effects. These studies showed that concurrent treatment with dexamethasone reduced the anti-tumour activity elicited by anti-CTLA-4 mAb; however, administration of dexamethasone after multiple anti-CTLA-4 mAb treatments did not negate the anti-tumour effect elicited by CTLA-4 blockade. Therefore, these data support the use of corticosteroids for the treatment of immune related adverse events (irAEs) which may occur during anti-CTLA-4 immunotherapy.

2.3.3. Pharmacokinetics

Methods of analysis

The Applicant developed different methods of analysis for the determination of ipilimumab in plasma and serum which were improved and validated along the development programme. A first non-validated flow cytometric assay was used to quantify serum ipilimumab in the 2-week intermittent-dose studies. An ELISA method was developed and validated for the determination of ipilimumab in plasma of monkey and human. This method was used in the 79-day comparability, 6-month and 3-month toxicology studies. This method was further developed to determine ipilimumab in serum and plasma of cynomolgus monkeys in the single-dose IV comparability study, the 1-month intermittent-dose combination toxicity study, the repeat-dose pharmacology study and the 1-month intermittent-dose combination toxicity study. Validation criteria were tightened for these two second methods. The Applicant developed and validated three different methods to determine anti-ipilimumab antibodies in serum and plasma. Two of them were ELISA based assays, and the third one was an electrochemiluminiscence method. It should be highlighted that the bridging ELISA (bivalent anti-ipilimumab antibodies) was not validated for cynomolgus monkey plasma, only for human plasma. This method was used in the 3-month intermittent-dose study. It is not known whether the presence of anti-ipilimumab antibodies interfered with the detection of ipilimumab.

Absorption

All studies were performed in cynomolgus monkey and ipilimumab was administered intravenously.

In the *single dose* kinetics, the half life time of ipilimumab is long, 8 to 15 days depending on the study, as was the mean residence time. Consistent with the long T1/2, the CLT was low (0.17-0.21 mL/h/kg). The Vss is similar to the plasma volume of monkeys.

Studies with every 3rd day dosing. Serum concentrations increased in males in a manner proportional (study 0919-128) or greater than dose proportional (study 71114-100) to the dose increment between 3 and 10 mg/kg. Consistent with the long half-life predose concentrations doubled in these studies between Day 4 and Day 7, indicative of accumulation of ipilimumab when dosed every 3 days.

Studies with weekly dosing. In study DS060604 10 mg/kg ipilimumab was or was not combined with BMS-663513 (anti-CD137 agonistic antibody). BMS-663513 did not affect the kinetics of ipilimumab. Data from 8 animals followed up after the last administration revealed a long half-life (approximately 12 days). Also in study SUV00106 where ipilimumab was administered together with MDX1106 an increase in serum concentration of ipilimumab was seen after repeated dosing. A dose proportional increase in serum concentration was seen between 3 and 10 mg/kg dose group.

Studies with monthly dosing. In two studies plasma concentrations of ipilimumab tended to increase with repeated dosing (study 1416-128, 01-3460). This increase was most pronounced between the first and second dose, and also visible after the third dose. No significant increase was visible after subsequent dosing (only study 01-3460). This trend for accumulation was not observed in a third study (SUV0006). In all studies ipilimumab was still detectable in predose samples, thus 4 weeks after the last dose. There was a greater-than-proportional increase in exposure as the monthly dose increased from 1 to 10 mg/kg (study 1416-128).

In all studies serum/plasma concentrations of ipilimumab were similar between males and females and between animals receiving ipilimumab only or ipilimumab in combination with another substance (BMS-663513, MDX1106 or Oligo-CpG).

During the development ipilimumab has been produced in three different processes. Two non-clinical bridging studies were performed comparing processes. There were no differences in pharmacokinetics (PK) parameters. Of note, these studies were not powered to test bioequivalence.

The immunogenic potential of ipilimumab, as measured by the formation of ipilimumab specific antibodies, was evaluated in all pivotal toxicity studies, as well as a number of exploratory studies. Ipilimumab generally was not immunogenic in monkeys. When including the animals with a weak antibody response, a value of 12% was calculated for the frequency of anti-ipilimumab-Ab positive animals.

Distribution

No radiolabeled tissue distribution/mass balance or metabolism studies with ipilimumab were conducted in animals. Serum protein binding was not evaluated. Following a single 10-mg/kg IV dose of ipilimumab to male and female cynomolgus monkeys (single-dose IV comparability study, DS07167, and 79-day intermittent-dose comparability study, 1416-128), the Vss (81 ± 14 and 44 ± 6.1 mL/kg, respectively) was similar to the plasma volume of monkeys, suggesting that ipilimumab does not distribute out of the plasma compartment.

Metabolism and excretion

No studies were conducted to evaluate the metabolism, metabolic pathways and excretion of ipilimumab in animals.

Pharmacokinetic drug interactions

Monoclonal antibodies are expected to be metabolised into small peptides and amino acids via biochemical pathways that are independent of cytochrome P450 enzymes. Consequently, ipilimumab is not expected to have interactions with molecules that are metabolized by these enzymes.

However, in a GLP- compliant intermittent-dose study (DS06064) conducted to determine the potential toxicity of ipilimumab administered alone or in combination with BMS-663513, there was no difference between the Cmax or AUC(0-48 h) values for monkeys receiving ipilimumab alone and monkeys receiving ipilimumab in combination with BMS-663513. These results do not provide any evidence of a PK drug-drug interaction between ipilimumab and BMS-663513 in monkeys.

2.3.4. Toxicology

The cynomolgus monkey was selected as the toxicology species because ipilimumab binds specifically to macaque CTLA-4, but not to homologous CTLA-4 in other traditional toxicology species (mouse, rat, rabbit), and has pharmacologic activity only in primates. Since ipilimumab is administered intravenously to humans, the IV route was evaluated in all monkey studies.

All pivotal studies were conducted with product that was comparable to clinical material in use at the time the studies were conducted based on comprehensive analytical evaluations of drug product and pharmacokinetic equivalence.

Single dose toxicity

Pivotal single-dose studies with ipilimumab were not conducted since the initial doses in repeat-dose studies were considered adequate to characterize its acute toxicity. No acute toxicity was noted in monkeys following ipilimumab doses up to 30 mg/kg in the repeat-dose toxicology studies. Further, no adverse toxicities were observed in a single-dose exploratory comparative pharmacokinetics study in monkeys of ipilimumab at 10 mg/kg.

Repeat dose toxicity

A summary of the repeated-dose toxicity studies is provided in Table 1.

Table 1 – Overview of repeated-dose toxicology studies

Study ID	Sex/ Number	Dose (mg/kg)	Day of dosing	Antigen	NOEL (mg/kg/day)	Major findings
126-002	2F	3	1,4,7	-	3	-
0919-128	2M	3	1,4,7	-	10	Small increase CD3+ cells.
	2/sex	10	1,4,7	-		
7114-100	2M	3	1,4,7	-	3	30: > leukocyte, WBC, lymph, neutr, mono,
	2/sex	30	1,4,7	-		
ds06064	5/sex	10	1, 8, 15, 22	KLH	10	-
	5/sex	10[b]	1, 8, 15, 22	KLH		
0992-128	2/sex	10	1, 29	HBsAg		> 10+ CpG: lymphocyte count
	2/sex	10[c]	1, 29	HBsAg		
1416-128	3/sex	1	1, 29, 57	HBsAg, SKmel	10	-
	3/sex	1	10 x weekly	HBsAg, SKmel		

	3/sex	10	1, 29, 57	HBsAg, SKmel		
	3/sex	10[a]	1, 29, 57	HBsAg, SKmel		
1-3460	2/sex	10[a]	0, 28, 56, 84, 140	-		↓ organ weight (testes, thyroid)
	3/sex	10[a]	0, 28, 56, 84, 140	SKmel		

a: process A material
b: ipilimumab was given together with BMS-663513
c: ipilimumab was administered together with CpG

At 30 mg/kg ipilimumab dosed for 2 weeks, haematological effects were noted, decreased erythrocyte count (10%), haemoglobin (10%) and haematocrit (5%) in males at day 14. Potential relationship of these findings with ipilimumab treatment could not be excluded and for further studies of longer duration, 10 mg/kg was selected as the highest dose tested. Slight decreases in red blood cell parameters were also observed in a 4-week repeat dose study even in control group.

Three out of 100 cynomolgus monkeys in the ipilimumab non-clinical toxicology program presented severe adverse effects. Fatal colitis and persistent dermatitis/rash observed in two animals along the toxicology programme were considered by the Applicant as immune-related adverse event (irAEs) linked with the intended pharmacologic basis of CTLA-4 blockade.

Apart from these cases of severe adverse events, ipilimumab generally did not result in adverse toxicities in any other monkeys when administered IV at doses up to 30 mg/kg for 1 week, 10 mg/kg administered weekly for 1 month, 1 mg/kg weekly for 10 weeks, or 10 mg/kg monthly for up to 6 months.

Decreased mean testes weights and ratios, and thyroid/body weight and thyroid /brain weight ratios were noted in animals treated for 6 months with ipilimumab and SK-mel cells, without accompanying histopathologic findings.

Genotoxicity

No standard genotoxicity battery of studies was performed with ipilimumab.

Carcinogenicity

Carcinogenicity studies for ipilimumab were not conducted.

Reproduction Toxicity

Reproductive, developmental, or juvenile toxicology studies have not been submitted with ipilimumab.

In tissue cross-reactivity studies, ipilimumab specifically bound to activated lymphocytes expressing CTLA-4 in several normal human and/or cynomolgus monkey tissues. In addition, ipilimumab bound specifically to connective tissue in human and cynomolgus monkey placenta and to connective tissue in cynomolgus monkey ovary; no specific binding was observed in human ovary. CTLA-4 protein expression on placental fibroblasts has been previously reported and may be involved in the maintenance of pregnancy. However, the role of CTLA-4 in pregnancy is still unclear.

Despite specific binding of ipilimumab to cynomolgus monkey ovarian tissue, no gross or microscopic ovarian findings were observed in ipilimumab toxicity studies conducted in monkeys and therefore is not expected to have any biological or toxicological relevance, especially since similar binding was not observed with human ovaries. The lack of specific binding in the remaining human and cynomolgus

monkey tissues was expected and consistent with reports that indicate that CTLA-4 is primarily transiently expressed on activated mononuclear cells.

In repeat-dose toxicology studies, drug-related changes in reproductive organ weights were limited to decreases in absolute and relative testicular (27 to 50%) weights in the 6- month study at 10 mg/kg; however, there were no corresponding microscopic changes in these organs.

No formal reproductive, developmental, or juvenile studies were submitted to support the proposed indication.

Toxicokinetic data

Systemic exposure to ipilimumab generally increased as a function of dose in a greater than dose-proportional manner, and there was a trend for ipilimumab to accumulate, which is consistent with its long half-life (up to ~ 13 ± 4 days) relative to the dosing interval (~ 3 ± 28 days). There were no gender-related differences in pharmacokinetics or evidence of a difference in the toxicity profiles between ipilimumab manufactured through different processes. When present, antibodies usually correlated with rapid elimination of circulating levels of ipilimumab.

Local Tolerance

In the intravenous repeat-dose studies in monkeys with ipilimumab no substantial irritation was observed at injection sites of ipilimumab. Ipilimumab was administered from preformulated (ready-to-use) vials at the clinical concentration (generally ~5 mg/mL). However, injection rates were faster and varied from ~3 to 10 mL/min (up to 50 mg/min) in the nonclinical studies compared with 90-min clinical infusion (total dose of 210 mg for a 70 kg person, up to 2.3 mg/min), thus, providing a safety factor of approximately up to ~22-fold based on infusion rate.

Other toxicity studies

Antigenicity

The immunogenic potential of ipilimumab, as measured by the formation of ipilimumab-specific antibodies, was evaluated in all pivotal toxicity studies, as well as a number of exploratory studies. As indicated previously, ipilimumab generally was not immunogenic in monkeys. When including the animals with a weak antibody response, a value of 12% was calculated for the frequency of anti-ipilimumab-Ab positive animals.

Immunotoxicity

As a selective immunomodulator, ipilimumab was expected to have effects on the immune system. The immunologic effects of ipilimumab (including special assessments of biomarkers of mechanism of action) were studied in the pivotal and exploratory repeat-dose studies in monkeys. That is, in addition to standard immune hematologic (i.e., leukocyte counts and differentials) and clinical chemistry (i.e., globulins) assessments and gross and histopathologic examinations of lymphoid tissues included in the repeat-dose studies, specialized immune parameters were incorporated into several of the studies including peripheral blood lymphocyte phenotyping (including activated T-cell and regulatory T-cell subsets), lymphocyte phenotyping in spleen, inguinal lymph node, and colon epithelium, anti-nuclear antibody assessments, T cell-dependent antibody response assessments, DTH assessments, and intracellular staining of ex vivo stimulated cytokine (IL-2, TNF-α and/or IFN-γ) production by monkey peripheral blood T cells. The T-cell dependent response as elicited by KLH administration clearly showed the effect of ipilimumab.

2.3.5. Ecotoxicity/environmental risk assessment

According to the CHMP guideline "Guideline on the Environmental Risk Assessment of Medicinal Products for Human Use" (ref. EMEA/CHMP/SWP/4447/00, dated 01 June 2006), 'Vitamins, electrolytes, amino acids, peptides, proteins, carbohydrates and lipids are exempted because they are unlikely to result in significant risk to the environment. Similarly, vaccines and herbal medicinal products are also exempted due to the nature of their constituents'.

Ipilimumab is a natural substance (protein composed of natural amino acids), the use of which will not alter the concentration or distribution of the substance in the environment. Therefore, ipilimumab is not expected to pose a risk to the environment.

2.3.6. Discussion on non-clinical aspects

Ipilimumab binds to human and cynomolgus CTLA-4, but not to CTLA-4 of other potential test species. As a result ipilimumab showed specific binding to activated, but not resting, T cells from the cynomolgus monkey and from humans. These data make the cynomolgus monkey a relevant test species, however the affinity of ipilimumab for monkey CTLA-4 is approximately 2-4 times lower when compared to humans CTLA-4; therefore the potency/activity of ipilimumab may be lower in cynomolgus monkeys when compared to humans.

In vitro data indicate that ipilimumab does not elicit CDC up to concentrations of 50 µg/ml. However, this is lower than the concentrations reached in human plasma after the 3mg/kg dose (Cmax ~85 µg/ml). In vitro data indicate that ADCC could occur in vivo. However, given the lack of effects on T cell numbers in the in vivo studies it is likely that ADCC does not occur in vivo at biological relevant levels.

The anti-tumour activity of ipilimumab was tested in a human CTLA-4 transgenic, mouse CTLA-4 knock out mouse. Anti-tumour activity was only seen when ipilimumab was administered at or near the time of the expected peak of the primary (anti-tumour) immune response. For the current application the relevance of this study, and other cited anti-tumour studies using homologous mouse tumour models is limited because in all these studies the (blocking) CTLA-4 antibody was administered at the time or shortly after tumour inoculation i.e. at time of a (primary) immune response against the tumour.

In cynomolgus monkeys ipilimumab (10 mg/kg) administered concurrently with T cell antigens enhanced the antigen-specific antibody response. Immunophenotypic analysis of the T cell compartment indicated that there were no ipilimumab-related changes in the frequencies of CD4+ or CD8+ T cells, nor in the expression pattern of various subpopulation/activation markers (e.g. CD69, CD25, or HLA-DR). Thus administration of ipilimumab does not appear to result in an over-stimulation of the T cell compartment.

There was no pharmacological justification for dose chosen in these studies. The results with the KLH-test and the immunogenicity data with SKmel indicated that the dose of 10 mg/kg is certainly an active level, but no dose-response was studied, and the dose inducing the maximum pharmacological effect is not known.

According to ICH S7A Guideline on safety pharmacology studies for human pharmaceuticals (CPMP/ICH/539/00), biotechnology-derived products that achieve highly specific receptor targeting, it is often sufficient to evaluate safety pharmacology endpoints as a part of toxicology and/or pharmacodynamic studies, and therefore safety pharmacology studies can be reduced or eliminated for these products. In ipilimumab development, these endpoints were included as part of the pivotal repeat-dose toxicology studies, performed in compliance with GLP Principles.

Most of the PK parameters have been calculated/measured at only one dose level, i.e. 10 mg/kg, therefore only little is known on the effect of the dose on PK parameters. In addition there was no discussion on the possible PK/PD relationship. This may be due to the special character if the PD endpoint (enhancement of the immune response) which may be difficult to qualify/quantify.

There were no differences in PK between males and females. When studied serum concentrations increased dose- or supradose-proportional. This indicates that the dose may affect the PK profile of ipilimumab. A dose effect on PK parameters due to target mediated drug disposition can occur for substances with specific and high affinity binding such as ipilimumab.

An anti-ipilimumab-antibody response was detected in 12% of the monkeys receiving ipilimumab, although it should be noted that this frequency is likely to be underestimated due to interference of (serum) ipilimumab with the antibody detection assay. It is difficult to assess whether the exposure was sufficient in the antibody positive animals.

Ipilimumab was well tolerated at all doses in monkeys following treatment for up to 6 months with no clinical manifestations of major target-organ toxicity or autoimmunity in the majority of monkeys.

The most notable concern identified during non-clinical testing was a low incidence of serious irAEs, manifested as colitis or dermatitis, in 2 of over 100 monkeys dosed with ipilimumab. These inflammatory responses are consistent with the proposed key role of CTLA-4 in maintaining self-tolerance in the immune system and subsequent immunostimulation afforded by blockade of this receptor and are similar in nature to the primary adverse events seen with clinical ipilimumab therapy. It is assumed that these observations should be taken as a general indication that ipilimumab might be associated with immune-related serious adverse effects, which cannot always predicted in character from animal studies.

In a 6-month toxicity study in cynomolgus monkeys, ipilimumab in a dose of 10 mg/kg with monthly intervals (4 times over these 6 months) was not associated with adverse drug-related toxicity, but a possible treatment-related reduction in thyroid and testes weight have been noted. Although it may be likely that these observations are due to the low number of animals and the biological variability, potential similar findings on the testes and thyroid have been reported for anti-CTLA-4 therapy. Therefore a potential treatment-related effect on these organs cannot be ruled out.

Reproductive and developmental toxicology studies were not performed with ipilimumab. As part of the routine histopathological examination of organs collected in toxicity studies, the male and female reproductive organs were evaluated including assessments of sperm and follicle/ovum morphology and maturation. There were no histopathologic changes in these organs that could be attributed to ipilimumab.

Human IgG1 is expected to cross the placental barrier; in the second and third trimester of pregnancy. The effects of ipilimumab on the development of the immune system in foetuses are not clear, therefore the use of ipilimumab in pregnant women is generally not recommended. Women of child-bearing potential should use effective contraception during treatment with ipilimumab. Given the short life-expectancy and physiologic status of advanced melanoma adult patients and the potential benefits from the use of ipilimumab in pregnant women despite its potential risks, a combined embryofoetal, pre/post-natal development study is ongoing. As indicated in the Risk Management Plan, final results of this study will be submitted when available. Human IgG1 is known to be secreted in the first human milk gift, the colostrum, the potential for infant exposure to ipilimumab via breast milk also exists. The use of ipilimumab during pregnancy is probably only theoretical due to the serious disease stage (see section 4.6 and 5.3 of the Summary of Product Characteristics).

In accordance with ICH S6 (R1) guideline and ICH S1A Guideline on the need for carcinogenicity studies of pharmaceuticals (CPMP/ICH/140/95) no studies on genotoxicity and carcinogenicity were

conducted, which was acceptable. In addition, considering the lack of relevance of the rodent species for ipilimumab, the limited value of short-term carcinogenicity studies with homologous products (as reflected in the draft reviewed version of the guideline), and the advanced condition intended to be treated by ipilimumab, the lack of conventional carcinogenicity studies is acceptable.

Local tolerance was assessed as part of the toxicity studies. No substantial irritation at the ipilimumab injection-site was observed.

2.3.7. Conclusion on the non-clinical aspects

The most notable concern identified during non-clinical testing was a low incidence of serious irAEs, manifested as colitis or dermatitis, for which no safety margin could be determined. It is assumed that these observations should be taken as a general indication that ipilimumab might be associated with immune-related serious adverse effects.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

2.4.2. Pharmacokinetics

Pharmacokinetics of ipilimumab has not been studied in healthy volunteers and most data were from patients with advanced melanoma. Non-compartmental PK analysis was conducted in the studies with intensive PK data. These studies comprehend comparison of the two manufacturing process products, single and multiple dose PK of ipilimumab, dose-proportionality and time dependency. A population pharmacokinetic (PPK) model was developed, using the to-be-marketed product, to evaluate covariate factors and to evaluate concentration-effect relationships.

Two methods have been used to quantify ipilimumab in plasma and serum. The latter assay was validated according current standards while the earlier method used less stringent criteria in the beginning but validation was updated. No cross-validation of the 2 methods was conducted, but sufficient data are present with the commercial scale batch / serum ELISA (PPK analysis).

Development of antibodies against ipilimumab was measured throughout the clinical program. Finally, a three tier ECL method was developed and validated but there remain some questions regarding the sensitivity of the serum and plasma assay in presence of ipilimumab and the specificity of the assay as predose samples were scored as positive for anti-ipilimumab antibodies. As indicated in the RMP, the applicant commits to improve the specificity and sensitivity of the serum ECL assay to detect antibodies, which will be used for ongoing and future clinical studies.

Absorption

Bioavailability

Ipilimumab was only administered intravenously throughout the program. Thus, no bioavailability study was conducted.

Bioequivalence

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. The second process, Process B, referred to the manufacturing process in a recombinant Chinese hamster ovary (CHO) cell line. This process was initially based on a reduced bioreactor scale (Process B -reduced scale) that was subsequently scaled up to commercial scale (Process B-commercial scale).

Based on the direct comparison in study MDX010-15, PK of ipilimumab derived from Process A and Process B-reduced scale are comparable. For upscaling from Process B -reduced scale to Process B - commercial scale, no direct comparison of the PK of ipilimumab has been made. The across study comparison indicated that there were no major differences in pharmacokinetics after upscaling. Both the reduced scale and commercial scale products have been used in the phase 3 study and the commercial scale product, intended for marketing, has been used in the PPK analysis.

Distribution

No plasma protein binding study was conducted.

PK parameters derived by *non-compartmental methods* with extensive sampling during induction therapy with ipilimumab from MDX010-15 and pooled data at 10 mg/kg from BMS studies CA184007 and CA184008 are presented in Table 2.

Table 2 – Summary of PK parameters in melanoma subjects (MDX010-15, CA184007 and CA 184008)

Study Protocol	**Process** [a]	**Matrix**	**Dose**	**Treatment Dose (mg/kg)**	**Sample size**	**Mean Pharmacokinetic Parameters of Ipilimumab Mean (CV%)** [b]					
						Cmax (µg/mL)	Tmax (hr) (Range)	AUC (0-21d) (µg.h/mL)	T-HALF (day)	CL (mL/hr)	VSS (L)
MDX010-15	A	Plasma	Dose #1	3	N=12	84.5 (38%)	1.75 (1.5-4)	12383 (32%)	17 (11)[c]	13.8 (8.1)	5.9 (1.6)
MDX010-15	B-reduced scale	Plasma	Dose #1	2.8	N=13	79.9 (24%)	2.5 (1.5-5.5)	12081 (44%)	16 (9.5)[c]	12.8 (6.8)	5.5 (2.1)
MDX010-15	B-reduced scale	Plasma	Dose #1	10	N=7[d]	300 (24%)	2 (1.5-7)	37706 (24%)	15 (8.3)[c]	15.7 (6.2)	6.7 (2.3)
MDX010-15	B-reduced scale	Plasma	Dose #4	10	N=13[d]	441 (36%)	2.5 (1.25-48)	55433 (35%)	15 (9.4)[c]	N/A[e]	N/A[e]
CA184007 & CA184008	B-commercial scale	Serum	Dose #1	10	N=15	205 (19%)	1.58 (1.5-1.75)	34176 (19%)	9.45 (3.17)	18.3 (5.88)	5.75 (1.69)
CA184007 & CA184008	B-commercial scale	Serum	Dose #3	10	N=16	223 (24%)	1.58 (1.45-24)	48924 (24%)	15.6 (6.89)	N/A[e]	N/A[e]

[a] All the data in this table are from the formulation manufactured by Process B and assayed by STM1693 and Human Serum ELISA Metod.
[b] Arithmetic means (SD) except Cmax and AUC which are expressed as geometric mean (CV%), and Tmax as median (range).
[c] Values manually converted from hours to days.
[d] These are from different cohorts (MDX010-15)
[e] CL and VSS in the third/fourth dose are not calculated (not available, N/A)

The PK of ipilimumab was also characterized by *population pharmacokinetic analysis* from 498 subjects with advanced (Stage III or IV) melanoma who were enrolled in four Phase 2 studies (CA184004, CA184007, CA184008, and CA184022) receiving induction doses ranging from 0.3 to 10 mg/kg administered once every 3 weeks for 4 doses. The PPK of ipilimumab was characterized by a linear two-compartment model with zero-order input 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).

Cmax, Cmin and AUC of ipilimumab were found to be dose proportional within the dose range examined. Upon repeated dosing of YERVOY administered every 3 weeks, clearance was found to be time-invariant, and minimal systemic accumulation was observed as evident by an accumulation index 1.5 fold or less for Cmax, Cmin and AUC. Ipilimumab steady-state was reached by the third dose administered once every 3 weeks. Based on population pharmacokinetic analysis, the geometric mean volume of distribution was at steady-state of 7.22 l with CV% of 10.5%. The average (±SD) ipilimumab serum trough concentrations achieved at steady-state with a 3 mg/kg induction regimen was 21.8 µg/ml (± 11.2).

Other covariates tested were: age, gender, albumin, alkaline phosphatase, estimated glomerular filtration rate (GFR), concomitant budesonide, prior IL-2 therapy, prior systemic therapy, performance status (ECOG), immunogenicity (HAHA status), presence of allele HLA-A2*0201, and metastatic stage. The effect of race was not examined as there were insufficient data in non-Caucasian ethnic groups. The effects of these demographic and clinical covariates were not statistically significant or the magnitude of the effect was considered to be of minimal clinical relevance (less than ± 20% effect on the typical value of a model parameter relative to the reference value)

Elimination

Based on the PPK analysis, the half-life of ipilimumab was between 10 and 17 days with a mean (SD) of 15 (4.62) days, which is consistent with the elimination half-life of other IgG antibodies. The geometric mean systemic clearance was of 15.3 ml/h with percent coefficient of variation (CV%) of 38.5% (ranging from 12.8-18.3 ml/min across studies).

No formal metabolism studies were conducted as ipilimumab is a human monoclonal immunoglobulin and not metabolized by cytochrome P450 enzymes, it is degraded to small peptides and individual amino acids.

Dose proportionality and time dependencies

Dose proportionality assessment was examined in study MDX010-15 from single dose data ranging from 2.8 mg/kg to 20.0 mg/kg. Ipilimumab exposure AUC(0-21d) and AUC(INF) appeared less than dose proportional. However, Cmax, elimination half-life and volume of distribution were reasonably comparable across the dose range of ~ 3 to 20 mg/kg.

Across CA184 studies, the mean Cmin value prior to Dose 4 for patients who received 0.3, 3, and 10 mg/kg ipilimumab were 2.1 (N=30), 21.8 (N=33), and 57.4 (N=193) µg/mL, respectively. Thus, the mean Cmin values increased in the ratio of 1: 11: 28, respectively, suggesting an approximate dose-proportional increase in ipilimumab exposure.

Overall, the PK of ipilimumab seemed dose proportional over the dose range 0.3 mg/kg to 10 mg/kg. Ipilimumab accumulation ratio of 1.5 was consistent with the estimated half-life of approximately 2 weeks and dosing every 3 weeks.

Special populations

The PPK analysis indicated that ipilimumab clearance increased with increasing body weight and with increasing lactate dehydrogenase (LDH) at baseline. Particularly, ipilimumab clearance increased by 20% over the reference typical value only for LDH values in excess of 550 IU/L (2.4-fold upper limit of normal [ULN]). This difference is not clinically relevant. Therefore no dose adjustment is required for elevated LDH or body weight after administration on a mg/kg basis.

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, 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 PK of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

Pharmacokinetic interaction studies

No formal drug-drug interaction study was carried out because ipilimumab is a protein and does not undergo metabolism by the cytochrome P450 enzymes.

The clearance of human monoclonal antibody, such as ipilimumab, is rarely affected by other drugs except immunosuppressants. Thus, an integrated PPK analysis was conducted to assess the impact of budesonide, a glucocorticoid, on the PK of ipilimumab with data from 3 Phase 2 studies. Concomitant treatment with 9 mg oral budesonide had no effect on the PK of ipilimumab. However, as systemic immunosuppressants could interfere with the pharmacodynamic activity of ipilimumab, a warning on the concomitant use of immunosuppressive agents, including systemic corticosteroids, has been included in the Product information.

Pharmacokinetics using human biomaterials

No in vitro studies were conducted.

2.4.3. Pharmacodynamics

Primary and Secondary pharmacology

Activated T Cells increase after ipilimumab treatment

To investigate the effect of ipilimumab on the peripheral immune system, activated T-cells were examined by flow cytometry of peripheral blood. In study CA184004, the mean percent of activated HLA-DR+ CD4+ and CD8+T cells increased after treatment with ipilimumab. There was no difference in increase in percentage activated T cells between the 3 mg/kg and 10 mg/kg dose. The percentage activated T-cells did not increase from week 4 to week 12. The percentage activated HLA-DR+ CD4+ en CD8+ T-cells at baseline was high in study CA184004 probably due to the tetanus booster administered prior to baseline blood collection in study CA184004.

Comparable data were obtained in study CA184007 after treatment with 10 mg/kg ipilimumab. Although flow cytometry on samples from CA184007 did not distinguish between HLA-DR+ and CD69+ status, based on earlier ipilimumab clinical studies (MDXCTLA4-01, MDXCTLA4-02, MDX010-15, MDX010-19), the increase in percent of activated T cells is likely derived primarily from the HLA-DR+ population. No other meaningful and consistent changes in the percent of T cell subset, B cell or NK cells have been reported following 10 mg/kg ipilimumab administration, including intestinal homing T cells (CCR9+), CD25+ T cells, B cells (CD19+), or NK cells (CD16+56+).

Absolute Lymphocyte Count (ALC)

ALC is a composite measure of all circulating T and B lymphocytes. Baseline ALC has been shown to be positively associated with overall survival (OS) in patients with a variety of cancers including myeloma, lymphoma, carcinoma, and sarcoma. In MDX010-20, this same positive association between baseline ALC and OS was also observed, independent of treatment group. In studies MDX010-20, CA184004, CA184007, CA184008, and CA184022, ALC was found to be a pharmacodynamic biomarker of immune cell activation by 3 and 10 mg/kg ipilimumab. In the Phase 2 studies CA184022 and CA184004, ALC increased on average after ipilimumab treatment in a dose-dependent fashion. For patients treated with 3 or 10 mg/kg ipilimumab, ALC continued to increase over the induction-dosing period, supporting the induction period dosing of one dose every 3 weeks. The magnitude of change in ALC after treatment with either 0.3 mg/kg ipilimumab (CA184022) or gp100 peptide vaccine alone (MDX010-20) was significantly different from, and smaller than, that after ipilimumab treatment at doses of 3 mg/kg or above.

Ipilimumab Enhanced Humoral Response In an Antigen-Specific Fashion

In CA184004, humoral response to T-cell-dependent antigens (tetanus or influenza) or T-cell-independent antigens (pneumococcal) was measured before and after receiving vaccine or booster and ipilimumab. No difference was observed between the 3 mg/kg and 10 mg/kg groups. Increases in humoral titers to influenza vaccine were observed in the majority of patients who received a vaccine but in only one patient who did not receive the influenza vaccine. Responses to pneumococcal and tetanus antigens were observed even in patients who never received vaccination on study. These results are consistent with RT-PCR of whole blood collected from patients with melanoma treated with ipilimumab in CA184004, which demonstrated an increase in expression of immunoglobulin lambda chain (IGL) mRNA.

Baseline Tumour Immunology Biomarkers

In the biomarker study, CA184004, tumour biopsies were taken before and after ipilimumab dosing. There was no consistent pattern in necrosis or presence of tumour-infiltrating lymphocytes in the biopsies pre and post-treatment.

Secondary pharmacology

In study CA184007, the effect of prophylactic oral budesonide 9 mg on the safety of ipilimumab 10 mg/kg was investigated. Oral budesonide 9 mg did not affect the incidence of GI irAEs. The temporal association between stool calprotectin and GI irAEs was not examined due to the lack of specificity observed in CA184007, CA184008 and CA184022. Thus, stool calprotectin is not recommended as a screening assay for GI inflammation in ipilimumab treated patients.

For MDX010-20, the patient's ability to develop or maintain disease control in the presence and absence of systemic steroids was analyzed. Of 137 patients in the ipilimumab monotherapy group, 34 patients had received steroids prior to best overall response assessment and 103 did not receive any steroids prior to best overall response assessment. The rate of CR, PR, or SD, not followed by PD, was 8.8% for patients who received steroids and 14.6% for patients who did not receive steroids.

Of 403 patients in the ipilimumab + gp100 group, 92 patients had received steroids prior to best overall response assessment and 311 did not receive any steroids best overall response assessment. Between these 2 subgroups of patients, the rate of CR, PR, or SD, not followed by PD, was similar (7.6% for patients who received steroids and 8.4% for patients who did not receive steroids).

Additionally, for those patients who had a response, maintenance of clinical response following ipilimumab treatment was similar with or without the use of systemic corticosteroids.

No formal QTc prolongation study was conducted. Effect of ipilimumab 3 and 10 mg/kg does not seem to produce clinically significant changes in ECG intervals or rhythm.

Relationship between plasma concentration and effect

Exposure-response analyses indicated that safety and efficacy were correlated with ipilimumab Cmin at steady-state (Cminss). Baseline LDH and performance status along with Cminss were significant predictors of OS. The risk of death increased with increasing LDH at baseline and ECOG performance status greater than zero and decreased with increasing Cminss. The probability of immune related adverse events (irAEs) especially Grade ≥ 3 also increased in a Cminss dependent fashion.

2.4.4. Discussion on clinical pharmacology

The PK of ipilimumab (including that on the commercial product) has been sufficiently studied. Effects of antibodies against ipilimumab on the PK of ipilimumab are uncertain as questions remain on the sensitivity of the assay as previously indicated. Further optimisation of the specificity and sensitivity of the serum ECL assay to detect antibodies can be handled after approval for ongoing and future clinical studies, as indicated in the RMP.

Based on population pharmacokinetic results, no specific dose adjustment is necessary in patients with mild to moderate renal dysfunction.

Being a human monoclonal antibody that is not metabolized by cytochrome P450 enzymes or other drug metabolizing enzymes, ipilimumab 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 interactions.

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 was dose dependent. In MDX010 20, YERVOY at 3 mg/kg with or without gp100 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. This biomarker has been proposed as prognosis factor related to OS, although there is not a clear and definitive relationship between this measure and survival, there is a documented trend in this sense. The threshold of baseline ALC associated with a shorter OS has been proposed in approximately $< 1 \times 10^9$. The Applicant submitted a report which explored the relationship between ALC and the biologic action of ipilimumab. ALC may be considered as biomarker of the ipilimumab action, however, the relation between OS and ALC cannot be supported because the pivotal study was not designed to show that association.

In peripheral blood of patients with melanoma, a mean increase in the percent of activated HLA DR+ 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.

Preliminary data suggested that an increase in tumour-infiltrating lymphocytes in tumour biopsies occurred more often in patients who benefited from ipilimumab treatment, although no relation with ipilimumab dose was observed.

The most common drug-related adverse events were immune-related in nature, consistent with the mechanism of action of the drug and generally medically manageable with topical and/or systemic immunosuppressants. Prophylactic oral budesonide 9 mg did not affect the incidence of GI irAEs Grade ≥ 2 diarrhoea.

In addition, data from the pivotal study MDX010-20 was reviewed to analyse patient's ability to develop or maintain disease control in the presence and absence of systemic steroids. It was concluded that the development or maintenance of clinical activity following ipilimumab treatment was similar with or without the use of systemic corticosteroids. Therefore, the use of systemic corticosteroids at baseline, before starting YERVOY, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of YERVOY. However, systemic corticosteroids or other immunosuppressants can be used after starting YERVOY to treat immune-related adverse reactions. The use of systemic corticosteroids after starting YERVOY treatment does not appear to impair the efficacy of YERVOY (see section 4.4 of the Summary of Product Characteristics).

No formal QTc prolongation study was conducted. As ipilimumab is an IgG monoclonal antibody against CTLA-4, no effects on ECG are anticipated. Effect of ipilimumab 3 and 10 mg/kg does not seem to produce clinically significant changes in ECG intervals or rhythm.

2.4.5. Conclusions on clinical pharmacology

Overall, the pharmacokinetics of ipilimumab has been adequately studied. Further optimisation of the specificity and sensitivity of the serum ECL assay to detect antibodies can be handled after approval for ongoing and future clinical studies, as indicated in the RMP.

2.5. Clinical efficacy

The clinical aspects of the application were supported by one phase 3 pivotal study MDX010-20 and seven supportive phase 1/2 studies. During the procedure, data from a phase 3 study CA184024 was also submitted. The designs of the studies are summarised in the table below.

Table 3 – Clinical study designs

Study nr	Phase	Type of study	Patients	Aim	Primary endpoint
MDX010-20 Pivotal study	Phase 3	Randomized, double-blind, 3 groups multicenter study In 125 sites in Europe, North America, South America and Africa	HLA-A2*0201-positive, previously treated, unresectable stage III or IV melanoma 3 mg/kg q3 wk x 4 +/- gp 100 or gp100 alone (induction) followed by re-induction	Compare OS of patients administered ipilimumab in combination with gp 100 versus those administered ipilimumab placebo in combination with gp100	Overall survival Secondary endpoints: BORR, major durable response rate, duration of response, PFS, time to progressio n
CA184022	Phase 2	Randomized, double-blind, dose-ranging, 3 group multi centre study In 66 sites in 13 countries	Previously treated unrespectable Stage III and IV melanoma 0.3, 3, or 10 mg/kg q3 wk X 4 (induction) followed by maintenance dosing q 12 wk	Estimate BORR in patients receiving ipilimumab doses 0.3, 3 and 10 mg/kg	BORR Secondary endpoints: OS, DCR, PRS, time to response, and duration of response
CA184004	Phase 2	Randomized, double-blind, 2-group, biomarker study	Unrespectable Stage III or IV melanoma 3 or 10 mg/kg q3 wk x 4	Analyze pre-treatment characteristic of patients and/or	Biomarker Secondary endpoints:

		In 14 sites in 7 countries	(induction) followed by maintenance dosing q 12 wk	tumour with clinical tumour response, in other to identify candidate markers predictive of response and/or serious toxicity to ipilimumab dosed at 3 or 10 mg/kg q 3 weeks	BORR, OS, DCR, PFS, time to response, and duration of response
MDX010-08	Phase 2	Randomized, double-blind, 2 group study In 12 sites in the US	Chemo therapy naïve metastatic melanoma 3 mg/kg q4 wk x 4 +/- DTIC (induction)	To determine the safety and activity profile of multiple doses of ipilimumab and to determine whether the addition of cytotoxic chemotherapy would augment the effects of ipilimumab	ORR Secondary endpoints: OS, DCR, PFS, duration of response, and time to response
CA184008	Phase 2	Open-label, single-group study In 50 sites in Europe and North America	Previously treated, unrespectable Stage III or IV melanoma 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q 12 wk	To evaluate the BORR	BORR Secondary endpoints; OS, DCR, PFS, time to response, and duration of response
CA184007	Phase 2	Randomized, double-blind, 2 group study In 11 sites in 6 countries in Europe, North America, and South America	Unresectable Stage III or IV melanoma 10 mg/kg q3 x 4 +/- budesonide (induction) followed by maintenance dosing q 12 wk	To estimate the rate of Grade ≥ 2 diarrhoea in patients treated ipilimumab at 10 mg/kg given with either prophylactic oral budesonide or placebo	Safety Secondary endpoints: BORR, OS, DCR, PFS, time to response, and duration of response
CA184042 Stage 1	Phase 2	Open-label study In 8 sites in US	Stage IV melanoma with brain metastases 10 mg/kg q3 wk x 4 (induction) followed by maintenance dosing q 12 wk	To assess the disease control rate determined after Week 12 using the modified WHO (mWHO) tumor assessment criteria	DCR Secondary endpoints: BORR, PFS, and duration of response
MDX010-15 Group B	Phase 1/2	Open-label study In 5 sites in US	Unresectable Stage III or IV melanoma 10 mg/kg q3 wk x 4 (induction)	Determine the safety and pharmacokinetic profile of single and multiple doses of ipilimumab derived from a transfectoma or a hybridoma cell line	Secondary endpoints: BORR DCR, time to response, and duration of responses
MDX010-28 Survival	Phase 2		Patients enrolled in MDXCTLA-02, MDX010-08 or MDX010-15		OS

Follow-up Study					
CA184024	Phase 3	Randomized, double-blind, 2 groups multicenter study	Previously untreated patients with unresectable Stage III or IV melanoma 10 mg/kg q3 wk x 4 +/- dacarbazine (induction) followed by maintenance	To compare overall survival in patients receiving dacarbazine plus 10mg/kg ipilimumab vs. dacarbazine with placebo.	OS Secondary endpoints: BORR, PFS, DCR

BORR= best overall response rate; DCR= disease control rate; DTIC= dacarbazine; ORR= overall response rate; OS= overall survival

Three of the clinical studies (MDX010-20, CA184022 and CA 184004) evaluated the recommended dose of 3 mg/kg administered once every 3 weeks (q3w) for 4 doses; in MDX010-08, 3 mg/kg was administered every 4 weeks (q4w) for 4 doses. Phase 2 studies CA184008, CA 184007, CA 184042 and MDX010-15 and Phase 3 study CA184024 evaluated ipilimumab at 10 mg/kg.

2.5.1. Dose response studies

No formal dose response studies were included in the application. Data from phase 1 and 2 studies was reviewed to support the dose used in the pivotal trial.

Study MDX010-15 (phase 1/2)

The primary objective of this study was to determine the safety and pharmacokinetic profile of single and multiple doses of ipilimumab. One of the secondary objectives of this study was determination of the single-dose maximum tolerated dose (MTD) of ipilimumab.

Of the 90 patients enrolled for this study, 88 were treated, with 2.8 to 10 mg/kg multiple doses or with 7.5 mg/kg to 20 mg/kg single dose.

The applicant concluded that ipilimumab at single doses up to 20 mg/kg and multiple doses up to 10 mg/kg every 3 weeks for 4 doses was tolerable with a safety profile consistent with that demonstrated in other studies of ipilimumab (see clinical safety section). The single-dose MTD of ipilimumab was not identified.

Study CA184022 (phase 2)

The primary objective of the study was to estimate best overall response rate (BORR) (as per modified World Health Organization (mWHO) criteria) in patients with previously treated, therapy-refractory or intolerant, Stage III (unresectable) or Stage IV melanoma receiving ipilimumab at doses 0.3, 3, and 10 mg/kg. Estimation of differences in BORR in patients receiving 3 vs 0.3 mg/kg, 10 vs 0.3 mg/kg and 10 vs 3 mg/kg was one of the secondary objectives of this study.

For this study 73, 72 and 72 patients were treated with respectively 0.3, 3 or 10 mg/kg ipilimumab induction therapy, every 3 weeks for a total of 4 separate doses followed by maintenance period in which ipilimumab was administrated every 12 weeks.

Tumour response for the induction phase was assessed at weeks 12, 16, 20 and 24. During the maintenance period tumour assessment was performed every 6 weeks. After week 48, tumour assessment was preformed every 12 weeks. Tumour response was evaluated by independent radiology review committee (IRC) based on mWHO criteria and by the investigators. The IRC assessment was considered primary. Tumour response as assessed by the IRC was based on the change from baseline in total tumour volume of index and non-index lesions.

Of the 217 randomized patients, 214 patients were treated in the induction period, of which 20 patients were also treated during the maintenance period. Approximately 60% of the patients randomized to the 0.3 and 3 mg/kg group received 4 doses induction therapy and 40% of the patients randomized to the 10 mg/kg group received 4 doses induction therapy.

As assessed by the IRC, none of the patients who received 0.3 mg/kg ipilimumab responded. The BORR in the 3 mg/kg treatment group was 4.2% (3/72 patients) and 11.1% (8/72 patients). In the 10 mg/kg group 2/8 responders achieved CR and 6/8 responders achieved PR. The results indicated a statistically significant trend (p=0.0015) of increased BORR with increased dose, suggesting a dose effect.

Other studies

For the pivotal study, a dose of 3 mg/kg ipilimumab was used. The rationale of the Applicant for using this dose was that preliminary studies provided evidence of clinical activity of ipilimumab at doses of 1 and 3 mg/kg in patients with metastatic melanoma.

In study MDXCTLA-4, a single infusion of ipilimumab at 3 mg/kg was associated with PR in 1 of 17 patients. In Protocol MDX010-05, patients were administered an initial dose of ipilimumab at 3 mg/kg followed by either 1 mg/kg (n=27) or 3 mg/kg (n=29) every 3 weeks; all doses in were administered in combination with the same gp100 vaccine as used in MDX010-20. A dose response was observed based on durable responses, suggesting that the 3 mg/kg dose might have more clinical activity than the 1 mg/kg dose. In study MDX010-08, patients were administered ipilimumab 3 mg/kg q4 weeks as monotherapy (n=37) or in combination with dacarbazine (n=37). In the monotherapy group, 2 patients had PRs (both ongoing at > 1year) (ORR 5%) and in the combination group 2 patients had CRs (both ongoing at >1.5 years) and 4 patients had PRs (1 ongoing at > 1.5 years) (ORR 17%). Together, these data indicted that ipilimumab at 3 mg/kg every 3 to 4 weeks was associated with clinical activity. Higher doses of ipilimumab had not been adequately studied at the time the pivotal study was initiated.

2.5.2. Main study: MDX010-20

Methods

Study MDX010-20 is a randomized, double-blind, multicenter study comparing ipilimumab (MDX-010) monotherapy, ipilimumab in combination with a melanoma peptide vaccine (gp100), and gp100 monotherapy in HLA-A*0201-positive patients with previously treated unresectable stage III or IV melanoma.

Study Participants

The inclusion criteria were the following:

- Histologic diagnosis of malignant melanoma
- Measurable unresectable Stage III or Stage IV melanoma:
- At least 18 years of age
- Positive for HLA-A2*0201
- Patient demonstrated 1 of the following in response to at least 1 cycle of 1 or more regimens containing 1 or more of the following: IL-2, dacarbazine, temozolomide, fotemustine and/or carboplatin: 1) relapse following an objective response (PR/CR); 2)failed to demonstrate an objective response (PR/CR); or 3) inability to tolerate treatment due to unacceptable toxicity

- At least 28 days since treatment with chemotherapy, biochemotherapy, surgery, radiation, or immunotherapy, and 14 day for gamma knife treatment and recovered from any clinically significant toxicity experienced during treatment (prior treatment must be completed by the time of study drug administration);
- Women met one of the following criteria: post-menopausal for at least 1 year; surgically incapable of bearing children; or utilizing a reliable form of contraception. Women of childbearing potential had a negative serum β-human chorionic gonadotropin (HCG) hormone pregnancy test conducted during screening and a negative urine β-HCG pregnancy test conducted prior to study drug administration
- Men who could have fathered a child agreed to use of male contraception for the duration of their participation in the trial
- Life expectancy ≥ 4 months
- Eastern Cooperative Oncology group (ECOG) performance status of 0 or 1
- Required values for initial laboratory tests:
    - White blood cell (WC) count ≥ 2500/μL
    - Absolute neutrophil count (ANC) ≥ 1500/μL
    - Platelet count ≥ 100* 10^3/μL
    - Haematocrit (Hct) ≥ 30%
    - Haemoglobin (Hb) ≥ 10/μL
    - Creatinine ≤ 2 upper limit of normal (ULN)
    - Aspartate aminotransferase (AST) ≤ 2 *ULN, except for patients with ≤ 2 *ULN attributed to liver metastases
    - Total Bilirubin ≤ 2 *ULN, except patients with Gilbert's Syndrome, who must have had a total bilirubin < 3.0 mg/dL

Amongst the exclusion criteria were the following: Primary ocular melanoma; Active, untreated central nervous system (CNS) metastasis.

Treatments

Subjects were randomized in a 3:1:1 ratio to receive ipilimumab plus gp100, ipilimumab monotherapy, or gp100 monotherapy, respectively. The regimens were as follows:

- Ipilimumab plus gp100: ipilimumab (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);

- Ipilimumab monotherapy: ipilimumab (3 mg/kg q3 weeks up to 4 doses) plus vaccine placebo (q3 weeks up to 4 doses); or

- gp100 monotherapy: ipilimumab placebo (q3 weeks up to 4 doses) plus gp100 (2 mg Peptide A and 2 mg Peptide B q3 weeks up to 4 doses).

A complete induction cycle consisted of 4 doses of ipilimumab/ipilimumab placebo plus 4 doses of gp100/vaccine placebo and is referred to as 4 doses of study drug. Likewise, each re-induction cycle consisted of 4 doses of study drug.

Objectives

The primary objective was to compare OS of subjects administered ipilimumab in combination with melanoma peptide vaccine versus those administered ipilimumab placebo in combination with melanoma peptide vaccine.

The secondary objectives of this study were: comparison of OS of subjects administered ipilimumab plus gp100 vs. those administered ipilimumab in combination with placebo, and of subjects administered gp100 monotherapy vs. those administered ipilimumab monotherapy, determination of the safety, evaluation of best overall response rate (BORR), determination of major durable response rate, duration of response, progression-free survival (PFS), time-to-progression and evaluation of health-related Quality of Life (HRQoL).

Outcomes/endpoints

The primary endpoint was overall survival, defined for each patient as the time between randomization date and death. If a patient was still alive, the patient was censored at the last known alive date. The primary efficacy analysis compared the difference in OS between ipilimumab plus gp100 vs. gp100.

The Survival rate at 12, 18 and 24 months was defined as the probability that a patient is alive at these time points following randomization date.

Secondary endpoints included BORR determined from Week 12 to Week 24 and confirmed at least 4 weeks later, disease control rate (DCR), duration of response, time to response, PFS, PFS rate (PFSR) at Week 12, and time-to-progression, delayed response, Health-related Quality of Life and safety. Tumour response status was assessed by the investigator.

Sample size

The original number of patients (750) that should be enrolled for the study was based on a primary endpoint of BORR. Due to advice of Health Authorities, the primary endpoint was changed to overall survival. Based on the new OS endpoint, the sample size was revised. A total of 481 events were required in all 3 groups (assuming that the events are distributed with ratios as 3:1:1 in ipilimumab plus gp100, ipilimumab monotherapy, and gp 100 monotherapy, respectively). On the basis of these assumptions 650 patients were to be enrolled into the study.

Randomisation

A centralised randomization scheme was used to assign subjects in a 3:1:1 ratio to the ipilimumab plus gp100, ipilimumab monotherapy, or gp100 monotherapy group. The randomization was stratified according to 1) baseline TNM status (M0, M1a or M1b versus M1c); and 2) prior treatment with IL-2 or not. A stratified randomization list was independently generated before the study was initiated using a block size of 20.

Blinding (masking)

This was a double-blind study: for masking of the "none" treatment matching placebos were used. Matching vaccine placebo for gp100 existed of 0.9% sodium chloride which was subcutaneously administrated. For ipilimumab a matching placebo was used that was like ipilimumab administered as an IV infusion.

Statistical methods

The statistical analysis plan (SAP) had 6 amendments, the major change being in primary endpoint (from ORR to BORR to OS), as advised by Health Authorities.

Sample size was ultimately set for the comparison of overall survival between patients administered ipilimumab in ipilimumab + gp100 and those administered gp100. On the basis of a simulation using the collected blinded survival data from this study and historical literature data, the hazard ratios for the overall survival of ipilimumab + gp100 versus gp100 at 8 months, 12 months, and 24 months were assumed to be 1, 0.2017, and 0.6126, respectively. Based on these assumptions, the median overall survival times of ipilimumab + gp100 and gp100 are 10.8 and 8.6 months, respectively. Therefore, a total of 385 events and a total of 500 enrolled patients for these 2 groups are required to achieve a 90% power to detect the difference of overall survival between these 2 groups at the 0.05 significance level, log-rank test using EAST 5. Approximately a total of 481 events are required in all 3 groups

(assuming that the events are distributed with ratios at 1:3:1 in gp100, ipilimumab + gp100, ipilimumab, respectively) to observe 385 events in ipilimumab + gp100 and gp100 treatment groups.

For the primary efficacy analysis, the difference in OS between ipilimumab plus gp100 vs. gp100 monotherapy was compared using stratified log-rank test. The 2 stratification factors were baseline TNM status (M0, M1a, or M1b versus M1c), and prior or no prior treatment with IL-2. The median estimates with 95% confidence intervals (CIs) were computed using Brookmeyer and Crowley method.

The secondary efficacy analysis of survival compared the OS of ipilimumab monotherapy to gp100 monotherapy and ipilimumab plus gp100 to ipilimumab monotherapy. Treatment differences for the BORR were compared using the stratified CMH test. The duration of response was summarized by treatment group using descriptive statistics for responder patients only. The HRQoL was compared for treatment differences using an Analysis of Covariance (ANCOVA) model.

Safety parameters were summarized using descriptive statistics (frequency tabulation).

Results

Participant flow

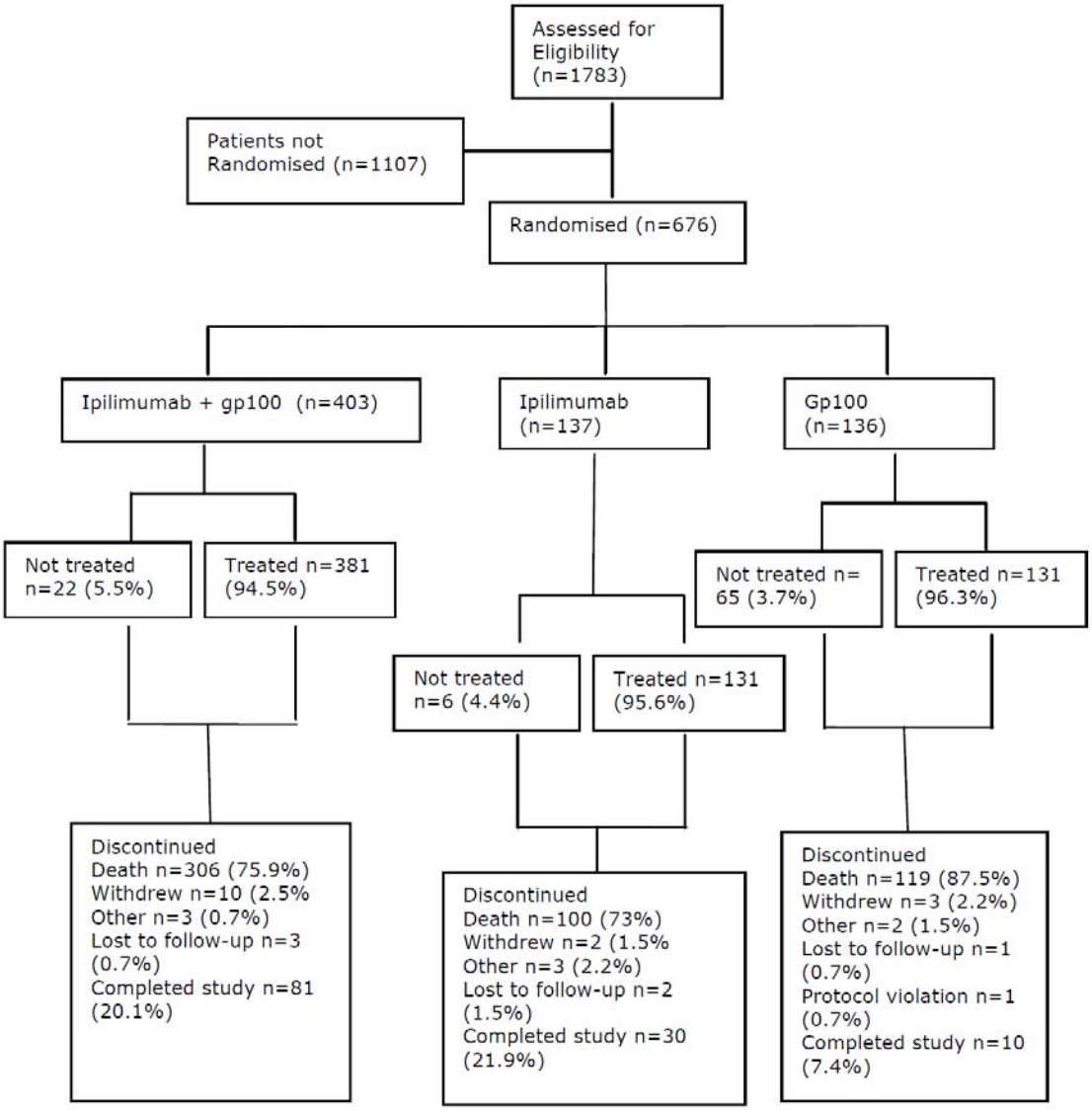


Figure 1 – Study MDX010-20 Participants flow

Recruitment

Subjects were randomized between 27-Sep-2004 and 24-July-2008. Enrolment into the study was closed effective 25-July-2008. Data was unblinded on 15 January 2009.

Conduct of the study

A number of amendments to the protocol were made. Initially, the primary endpoint was BORR. As indicated previously, the primary endpoint was changed to overall survival further to advice of Health Authorities, including that of the CHMP Scientific Advice. Accordingly, the sample size was amended.

Baseline data

Demographic summary and baseline characteristics in Study MDX010-20 are presented in the table below.

Table 4 – Demographic and Baseline Characteristics (ITT population) MDX010-20

Characteristic	Ipi+gp100 n=403	Ipi n=137	gp100 n=136	Total n=676
Age (years)				
Mean	55.6	56.8	57.4	56.2
Median	57.0	57.0	57.0	57.0
Sex (n %)				
Male	247 (61)	81 (59)	73 (54)	401 (59)
Female	156 (39)	56 (41)	63 (46)	275 (41)
Race (n %)				
White	380 (94.3)	129 (94.2)	129 (94.9)	638 (94.4)
Black	3 (0.7)	1 (0.7)	1 (0.7)	5 (0.7)
Hispanic	18 (4.5)	7 (5.1)	5 (3.7)	30 (4.4)
Other	2 (0.5)	0	1 (0.7)	3 (0.4)
M Stage				
M0	5 (1.2)	1 (0.7)	4 (2.9)	10 (1.5)
M1a	37 (9.2)	14 (10.2)	11 (8.1)	62 (9.2)
M1b	76 (18.9)	22 (16.1)	23 (16.9)	121 (17.9)
M1c	285 (70.7)	100 (73.0)	98 (72.1)	483 (71.4)
Prior IL-2				
No	315 (78.2)	105 (76.6)	103 (75.7)	523 (77.4)
Yes	88 (21.8)	32 (23.4)	33 (24.3)	153 (22.6)
LDH				
>ULN	148 (36.7)	53 (38.7)	54 (39.7)	255 (37.7)
≤ULN	255 (63.3)	84 (61.3)	82 (60.3)	421 (62.3)

ULN=upper limit of normal; Min=minimum; Max=maximum; (n%)

Almost all patients included in the MDX010-20 study had had prior surgery related to cancer, and all patients had received prior systemic therapies; IL-2, dacarbazine, temozolomide, fotemustine and/or carboplatin. Over ninety percent (91.9%) of the patients received prior chemotherapy. In the ipilimumab monotherapy group 40.1% of the patients received prior immunotherapy, whereas of the imipilimumab+gp100 group 47.9% of the patients received prior immunotherapy. Prior immune treatment options included: interferon alfa (2A or 2B), interleukin 2 or 7 and/or investigational immunotherapy (PEG-interferon alfa 2A or 2B). In the ipilimumab group 43.8% of the patients had prior radiotherapy and in the ipilimumab+gp100 group 38.2% had prior radiotherapy.

Initial diagnosis of melanoma by treatment is presented in the table below.

Table 5 – Initial diagnosis of melanoma (ITT population)

	Ipi+gp100 (N=403)	Ipi (N=137)	gp100 (N=136)	Total (N=676)
Disease Stage at Initial diagnosis (n %)				
Stage 0	0	1 (0.7)	0	1 (0.1)
Stage I	65 (16.1)	29 (21.2)	33 (24.3)	127 (18.8)
Stage II	108 (26.8)	33 (24.1)	36 (26.5)	177 (26.2)
Stage III	92 (22.8)	31 (22.6)	32 (23.5)	155 (22.9)
Stage IV	77 (19.1)	31 (22.6)	19 (14.0)	127 (18.8)
Unknown	59 (14.6)	12 (8.8)	16 (11.8)	87 (12.9)
Histopathologic type at initial diagnosis (n %)				
Melanoma in situ	8 (2.0)	3 (2.2)	2 (1.5)	13 (1.9)
Malignant melanoma, NOS	118 (29.3)	41 (29.9)	28 (20.6)	187 (27.7)
Superficial spreading melanoma	79 (19.6)	18 (13.1)	28 (20.6)	125 (18.5)
Nodular melanoma	76 (18.9)	21 (15.3)	26 (19.1)	123 (18.2)
Lentigo maligna melanoma	8 (2.0)	7 (5.1)	1 (0.7)	16 (2.4)
Acral lentiginous melanoma	17 (4.2)	5 (3.6)	8 (5.9)	30 (4.4)
Desmoplastic melanoma	6 (1.5)	3 (2.2)	2 (1.5)	11 (1.6)
Epithelioid cell melanoma	8 (2.0)	5 (3.6)	5 (3.7)	18 (2.7)
Spindle cell melanoma	10 (2.5)	8 (5.8)	4 (2.9)	22 (3.3)
Balloon cell melanoma	0	0	1 (0.7)	1 (0.1)
Blue nevus, malignant	1 (0.2)	0	0	1 (0.1)
Malignant melanoma in giant pigmented nevus	3 (0.7)	1 (0.7)	0	4 (0.6)
Other	15 (3.7)	14 (10.2)	6 (4.4)	35 (5.2)
Unknown	52 (12.9)	10 (7.3)	25 (18.4)	87 (12.9)
Missing	2 (0.5)	1 (0.7)	0	3 (0.4)

Numbers analysed

The study populations are summarised in **Error! Reference source not found.**. The primary efficacy population was ITT (all randomized).

Table 6 – Study Population by Treatment Group (MDX10-20-All Subjects)

	Ipi+gp100 n=403	Ipi n=137	gp100 n=136	Total n = 676
Study populations (n %)				
Intent-to-Treat	403 (100.0)	137 (100.0)	136 (100.0)	676 (100.0)
Safety - efficacy analyses	381 (94.5)	131 (95.6)	131 (96.3)	643 (95.1)
Safety - safety analyses	380 (94.3)	131 (95.6)	132 (97.1)	643 (95.1)
Per-protocol	315 (78.2)	106 (77.4)	101 (74.3)	522 (77.2)
Re-induction - efficacy analyses	23 (5.7)	8 (5.8)	1 (0.7)	32 (4.7)
Re-induction - safety analyses	29 (7.2)	9 (6.6)	2 (1.5)	40 (5.9)
≥ 1 Cycle	29 (7.2)	9 (6.6)	2 (1.5)	40 (5.9)
≥ 2 Cycles	4 (1.0)	3 (2.2)	0	7 (1.0)
≥ 3 Cycles	1 (0.2)	0	0	1 (0.1)

[a] All randomized, as randomized; includes subjects who were randomized but not treated.
[b] All treated, as randomized
[c] All treated, as treated; 1 subject was randomized to Ipi+gp100 but treated with gp100. Therefore, the dosing and safety analyses count this subject in the gp100 treatment group.
[d] Safety population for Re-induction; includes all subjects who received re-induction treatment (safety analyses) regardless of eligibility.

Outcomes and estimation

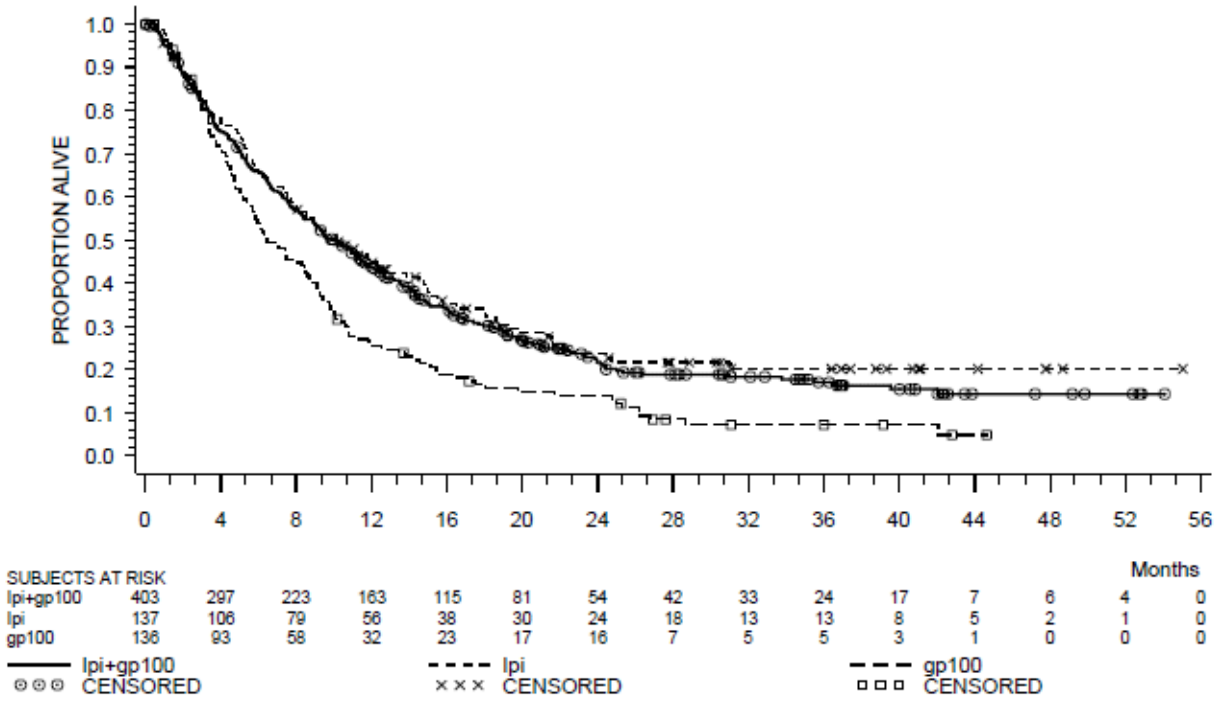
Primary endpoint: Overall survival

The primary endpoint overall survival is presented in the table and figure below. The median follow-up, assessed for 151 patients known to be alive, was 21.0 months for the ipilimumab+ gp100 group, 27.8 months for the ipilimumab monotherapy group and 17.2 months for the gp100 monotherapy group.

Table 7 – Overall Survival by Treatment (MDX010-20 Study - ITT Population)

	Ipi+gp100 (n=403)	Ipi (n=137)	gp100 (n=136)	Total (n=676)
Number of events	306	100	119	525
Median (months)	9.95	10.12	6.44	9.10
95% CI for median	(8.48, 11.50)	(8.02, 13.80)	(5.49, 8.71)	(8.31, 10.12)
HR vs. gp100 with 95% CI	0.68 (0.55, 0.85)	0.66 (0.51, 0.87)		
Log-rank p value vs. gp100	0.0004	0.0026		
HR vs. Ipilimumab with 95% CI	1.04 (0.83, 1.30)			
Log-rank p value vs Ipilimumab	0.7575			

Cox model for Hazard ratios (HR) and log-rank test p-values were stratified by baseline M-stage at randomization (M0, M1a, M1b vs. M1c) and prior treatment with IL-2 (Yes vs. No).
95% confidence intervals (CI) for median were computed using Brookmeyer and Crowley method. 95% confidence intervals (CI) for HR were computed using Cox model.



GROUP	# DEATHS / # RANDOMIZED	MEDIAN (95% CI)
Ipi+gp100	306/403	9.95 (8.48 - 11.50)
Ipi	100/137	10.12 (8.02 - 13.80)
gp100	119/136	6.44 (5.49 - 8.71)

Figure 2 – Overall Survival by Treatment (MDX010-20 Study - ITT Population)

Secondary endpoint: Best Overall Response Rate

Best overall response rate results are presented in the table below.

Table 8 – Best Overall Response Based on Modified WHO Criteria by Treatment (MDX010-20 Study - ITT Population)

	Ipi+gp100 (n=403)	Ipi (n=137)	gp100 (n=136)	Total (n=676)
Best overall response (n[%])				
CR	1 (0.2)	2 (1.5)	0	3 (0.4)
PR	22 (5.5)	13 (9.5)	2 (1.5)	37 (5.5)
SD	58 (14.4)	24 (17.5)	13 (9.6)	95 (14.1)
PD	239 (59.3)	70 (51.1)	89 (65.4)	398 (58.9)
NE	83 (20.6)	28 (20.4)	32 (23.5)	143 (21.2)
BORR (n[%])[a]	23 (5.7)	15 (10.9)	2 (1.5)	40 (5.9)
95% CI	(3.7, 8.4)	(6.3, 17.4)	(0.2, 5.2)	(4.3, 8.0)
P value vs. gp100[b]	0.0433	0.0012		
P value vs. ipi[b]	0.0402			

Secondary endpoint: Progression-Free Survival

PFS results are presented in the figure below.

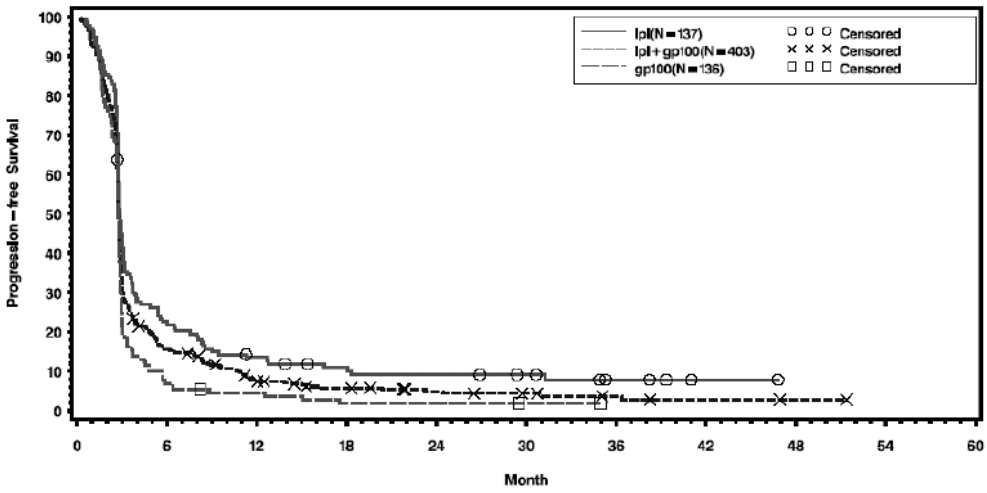
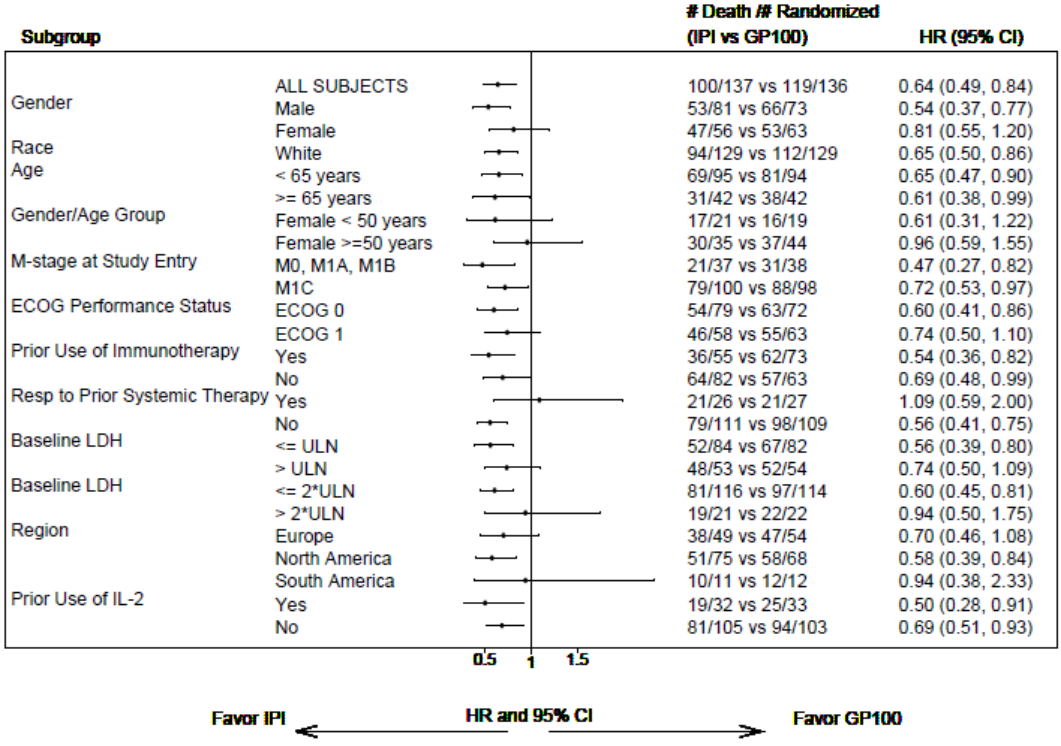


Figure 3 – Progression-free Survival by Treatment (MDX010-20 Study - ITT Population)

Ancillary analyses

Subgroup comparisons for OS were performed across pre-specified categories : M-stage (M0, M1a or M1b versus M1c), prior IL-2 baseline LDH (≤ ULN versus > ULN), age (<65 years versus ≥ 65 years), sex, response to prior systemic therapy, and region for MDX010-20. Of note, for women above 50 years of age the HR was close to 1.



Note: Dataset: Randomized pre-treated subjects. Analyses were not performed for subgroups with <10 subjects in either group.

Figure 4 – Overall Survival Hazard Ratio and 95% Confidence Interval for subgroup Analysis (Ipilimumab monotherapy vs gp100) MDX010-20

Summary of main study

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy as well as the benefit risk assessment (see later sections).

Table 9 – Summary of Efficacy for trial MDX010-20

Title: A Randomized, Double-blind, Multicenter Study Comparing MDX-010 Monotherapy, MDX-010 in Combination with a Melanoma Peptide Vaccine, and Melanoma Vaccine Monotherapy in HLA-A*0201 Positive Patients with Previously Treated Unresectable Stage III or Stage IV Melanoma			
Study identifier	MDX010-20, EUDRACT 2004-005059-32, IND 9186		
Design	Phase 3, randomized, double-blind, multicenter		
	Duration of main phase: Duration of Run-in phase: Duration of Extension phase:	Induction phase: 12 weeks not applicable not applicable	
Hypothesis	Superiority of Ipilimumab + gp100 *vs* gp100		
Treatments groups	Ipilimumab + gp100 (Ipi + gp100)	Induction cycle every 3 weeks for total of 4 doses Ipilimumab: 3 mg/kg IV infusion gp100: 2 mL or 2mg of Peptide A + 2 mL or 2 mg of Peptide B, SC Possibility of re-induction	
	Ipilimumab + placebo (Ipi)	Induction cycle every 3 weeks for total of 4 doses Ipilimumab: 3 mg/kg IV infusion gp100 placebo: sterile 0.9% sodium chloride SC Possibility of re-induction	
	Placebo + gp100 (gp 100)	Induction cycle every 3 weeks for total of 4 doses Ipilimumab placebo gp100: 2 mL or 2mg of Peptide A + 2 mL or 2 mg of Peptide B, SC Possibility of re-induction	
Endpoints and definitions	Primary endpoint: Overall survival (OS)	Time between randomization date and death.	
	Secondary endpoints: Best overall response rate (BORR)	Best overall response (BOR) based on investigator's assessment (modified WHO criteria)	
	Secondary endpoints: Progression free survival (PFS)	Time between randomization date and the date of progression or death.	
Database lock	7 October 2009		

Results and Analysis

Analysis description	**Primary Analysis**			
Analysis population and time point description	Intent to treat (all randomized patients) Primary efficacy treatment comparison: Ipi + gp100 *vs* gp100 Secondary efficacy treatment comparisons: Ipi + gp100 *vs* Ipi and Ipi *vs* gp100			
Descriptive statistics and estimate variability	Treatment group	Ipi+gp100	Ipi	gp100
	No. of subjects	403	137	136
	Overall survival No. of events	306	100	119
	Median (months)	9.95	10.12	6.44

	95% CI for median (months)	(8.48, 11.50)	(8.02, 13.80)	(5.49, 8.71)
	HR vs gp100 (95% CI)	0.68 (0.55, 0.85)	0.66 (0.51, 0.87)	
	HR vs Ipi (95% CI)	1.04 (0.83, 1.30)		
	P-value (stratified logrank) vs gp 100	0.0004	0.0026	
	P-value (stratified logrank) vs Ipi	0.7575		
	BORR (CR and PR) N (%)	23 (5.7)	15 (10.9)	2 (1.5)
	95% CI for proportion	(3.7, 8.4)	(6.3, 17.4)	(0.2, 5.2)
	P-value (Cochran-Mantel-Haenszel (CMH)) vs gp 100	0.0433	0.0012	
	P-value (Cochran-Mantel-Haenszel (CMH)) vs Ipi	0.0402		
	PFS Median (months)	2.76	2.86	2.76
	95% CI for median (months)	(2.73, 2.79)	(2.76, 3.02)	(2.73, 2.83)
	HR vs gp100 (95% CI)	0.81 (0.66, 1.00)	0.64 (0.50, 0.83)	
	HR vs Ipi (95% CI)	1.25 (1.01, 1.53)		
	P-value (stratified logrank) vs gp 100	0.0464	0.0007	
	P-value (stratified logrank) vs Ipi	0.0371		
Note:	log-rank test p-values were stratified by M-stage (M0, M1a, M1b vs. M1c) from the randomization list and prior treatment with IL-2 (Yes vs. No)			

Analysis performed across trials (pooled analyses and meta-analysis)

Not applicable.

Clinical studies in special populations

Patients with significant hepatic and renal impairment were excluded from the study.

Supportive studies

Seven supportive studies were submitted in the application (CA184022, CA184004, MDX010-08, CA180008, CA184007, CA184042, MDX010-15 and MDX010-28). Ipilimumab was administrated to all patients included in the supportive studies (none of the studies contained a control arm). The primary

endpoint for most studies was BORR. During the application, the applicant also provided supportive data from Study CA184024, a randomized, placebo-controlled Phase 3 study evaluating OS in patients with previously untreated, advanced melanoma.

In general the response rates to ipilimumab monotherapy, obtained in the supportive studies were comparable to the BORR reported for the pivotal MDX010-20 study.

Study CA1840042

This was an open label multi-centre phase II study with a two-stage design. The study is still ongoing, and only results from an interim analysis of the first stage were submitted. The primary objective of the study was to assess the disease control rate (DCR) determined after week 12 using mWHO tumour assessment criteria, after ipilimumab monotherapy. Secondary endpoints were overall response rate and DCR of non-central nervous system lesions and global tumour burden using the mWHO tumour assessment criteria (Therasse P. Eur J Cancer 2002;38:1817–23) and immune response criteria (irRC). For the first stage of the study 28 patients with stage IV melanoma with brain metastases, were enrolled (Arm A). Included patients had not received corticosteroid therapy for a minimum of 10 days before their first dose of ipilimumab. During induction phase patients were treated with 10 mg/kg ipilimumab every 3 weeks for 4 doses.

This study of ipilimumab in patients with advanced melanoma specifically included patients with brain metastases. Confirmed objective responses in the non-CNS compartment were associated with confirmed objective responses in the brain with 5/8 (17.9%) of patients achieving global and CNS based confirmed PRs, respectively. Likewise, disease control (CR, PR and SD) in non-CNS compartment was associated with disease control in the brain with a disease control rate of 7/28 (25%) and 8/28 (28.6%), respectively.

Study CA184004

This was an exploratory study to determine potential predictive markers of response and/or toxicity in patients with unresectable stage III or IV malignant melanoma. In total 101 patients were enrolled and 82 were randomized in a 1:1 ratio to be treated with 4 doses 3 or 10 mg/kg ipilimumab 3q weeks. Before randomization the patients were stratified by use of prior immunotherapy for malignant melanoma. Secondary objectives were BORR (assessed according to mWHO criteria), DCR, PFS rate at week 12, PFS, OS, survival rate at 1 year, duration of response, time to response, safety, estimate the sensitivity and specificity of any candidate marker for prediction of clinical response and toxicity to ipilimumab.

After the induction phase (4 doses ipilimumab), patients with stable disease (SD) or better through week 24 tumour assessment, could receive maintenance ipilimumab (3 mg/kg or 10 mg/kg every 3 months). Pre- and post-treatment biomarker assessments were performed including baseline blood for single-nucleotide polymorphisms, and pre- and post-treatment immune monitoring and tumour biopsy. All patients also had pre- and post treatment serial, triplicate ECG assessment.

Tumour assessments were performed every 4 weeks from week 12 through 24 and every 12 weeks thereafter.

Increase in ALC was associated with benefit, defined as objective response or SD lasting until at least 24 weeks from first dose (P=0.00042). Baseline expression of tumour FoxP3 or the immunoregulatory enzyme indoleamine 2,3-dioxygenase IDO was associated with benefit (P=0.014 and 0.012 respectively). Both genes are markers for T-cell suppression, suggesting that if expression of T-cell suppressive genes is determined in the tumour, response on ipilimumab is more likely.

Preliminary data suggested that an increase in tumour-infiltrating lymphocytes in tumour biopsies occurred more often in patients who benefited from ipilimumab treatment, although no relation with ipilimumab dose was observed..

Activation of circulating effectors T-cells and enhancement of humoral response to specific common antigens were observed, however the T-cell activation was not dose dependent. Biomarkers that were not predictive for benefit or safety were SNP genotypes, HLA allele A2*201, and medium-resolution HLA-A genotype.

Study CA184024

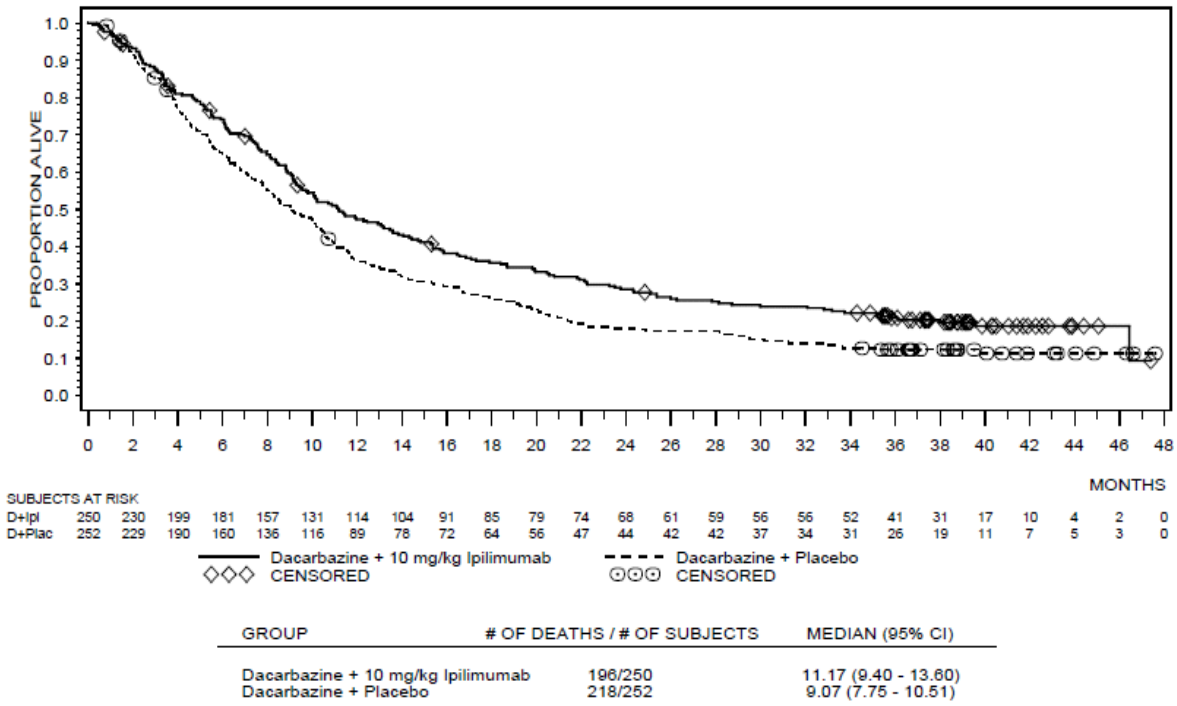
Study CA184024 is a randomized, placebo- controlled Phase 3 study evaluating OS in subjects with previously untreated, advanced (unresectable Stage III or IV) melanoma. The 2 treatment arms were ipilimumab plus dacarbazine (ipilimumab +DTIC; N=250) and placebo plus DTIC (DTIC; N=252). Randomization was 1:1 and was stratified by baseline TNM status (M0 vs M1a vs M1b vs M1c) and ECOG performance status (0 vs 1). In the CA184024 study patients were enrolled without regard to HLA status and prospective HLA testing was not performed. Ipilimumab was administered at a dose of 10 mg/kg every 3 weeks for 4 doses, followed by maintenance therapy with 10 mg/kg ipilimumab for eligible patients. The study has been finalised at the beginning of 2011; only high level results were available during the assessment of this application.

Results for OS are presented in the table below. There was a 2.1 month improvement in median survival in the ipilimumab+DTIC arm compared to DTIC with the HR of 0.716 was significant (p=0.0009). The Kaplan-Meier curve for OS is shown in Figure 5.

Table 10 – Study CA184024 Overall survival results

	Ipilimumab + DTIC n = 250	**DTIC n = 252**
Median (months) (95% CI)	11.17 (9.40, 13.60)	9.07 (7.75, 10.51)
Hazard ratio[a] (95% CI)	0.716 (0.588, 0.872)	
p-value	p=0.0009	

[a] Stratified Cox Model



GROUP	# OF DEATHS / # OF SUBJECTS	MEDIAN (95% CI)
Dacarbazine + 10 mg/kg Ipilimumab	196/250	11.17 (9.40 - 13.60)
Dacarbazine + Placebo	218/252	9.07 (7.75 - 10.51)

Figure 5 – Study CA184024 Overall Survival

The Kaplan-Meier estimates of survival rates at 1 year, 2 years and 3 years were consistently higher in the ipilimumab +DTIC arm compared with DTIC (Table 11).

Table 11 – Study CA184024 Kaplan-Meier survival results

Treatment Arms	
Ipilimumab + DTIC rate (95% CI)	**DTIC rate (95% CI)**
1 year: 47.3% (41.0, 53.6)	1 year: 36.3% (30.4, 42.4)
2 years: 28.5% (22.9, 34.2)	2 years: 17.9% (13.3, 22.8)
3 years: 20.8% (15.7, 26.1)	3 years: 12.2% (8.2, 16.5)

2.5.3. Discussion on clinical efficacy

For ipilimumab monotherapy a median overall survival of 10.12 months (95% CI; 8.02-13.80) was reported whereas the observed median overall survival for gp100 monotherapy was only 6.44 months (95% CI; 5.49-8.71). No statistically significant differences in overall survival between the ipilimumab monotherapy group and the combined therapy group were seen.

Gp100 is considered to be an experimental anti-cancer agent and the effect of gp100 monotherapy on the OS of melanoma patients is not exactly known. However, no clinical benefit has yet been demonstrated for gp100 monotherapy vaccination. No placebo controlled clinical trials are published investigating the clinical effect of gp100 monotherapy in advanced melanoma patients. Other clinical trials (combination with IL-2) provide little information about the expected OS for melanoma patients after gp100 monotherapy.

The observed median OS of gp100 of 6.4 months was somewhat lower than those seen in recent phase III trials curve which are typically around 7-8 months (range 5.9 in Eisen up to 9.7 in Hauschild). The Applicant provided a sensitivity analysis showing that after addition of 1.5 months survival to the observed individual survival time of each gp100 patient, still a statistically significant OS benefit of ipilimumab treatment above gp100 treatment exits.

Results of the CA184024 phase 3 trial in melanoma patients treated with DTIC versus DTIC and ipilimumab were submitted to support the efficacy data obtained in the MDX010-20 study. The CA184024 study showed an OS of 11.2 months for patients treated with DTIC+Ipilimumab and an OS of 9.1 months for patients treated with DTIC alone with a HR of 0.716 (p=0.0009).

The CA184024 study results supported the results of the MDX010-20 study. The CHMP considered that based on all the available data, the efficacy in the claimed indication for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy was sufficiently supported.

Based on effect-response analysis in study CA184022 and the other 3 phase 2 CA184 studies, it is not fully elucidated if the dose of 3 mg/kg ipilimumab in study MDX010-20 is the optimal dose for the target patient group. In the CA184024 study the used ipilimumab dose was 10 mg/kg. Given the differences in study design between the CA184024 and the MDX010-20 including different lines of ipilimumab treatment and different co-medication, the efficacy and safety results of the 10 mg/kg dose and the 3 mg/kg dose are not directly comparable. At this moment 3 mg/kg will be the dose recommended for ipilimumab in for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. However, it is unknown whether a higher dose of 10 mg/kg would have been better. As a condition to the marketing authorisation, the applicant shall collect further efficacy (with survival endpoint) and safety data in a randomised study comparing 3 mg/kg versus 10 mg/kg ipilimumab in advanced melanoma.

By subgroup analysis, it has been shown that the observed OS benefit in study MDX010-20 was consistent within most of the subgroups of patients (M [metastases]-stage, prior interleukin-2, baseline lactate dehydrogenase, age, and sex). However, for women above 50 years of age, the data supporting an OS benefit of YERVOY treatment were limited. As the subgroup analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data. The efficacy and safety of ipilimumab in these patients should continue to be analysed in ongoing and future clinical trials, particularly in the dose comparison study to be conducted.

The impact of treatment on the Quality of life was investigated in the MDX010-20 study (data not shown). The Health-related Quality of Life (HRQoL) for patients with cancer is negatively impacted by both disease progression and treatment toxicities. Most changes from baseline in HRQoL domains were "no change" to "moderate" across the three treatment groups. The trend in global health status was towards a return to baseline.

Patients with active brain metastases or ocular melanoma were excluded from the pivotal study. Results of the CA1840042 study suggest that ipilimumab might be effective against brain metastases. Given the mechanism of action of ipilimumab, anti-tumour effector cells should cross the blood-brain barrier before ipilimumab can be effective against brain-metastasis. The blood-brain barrier will be disrupted in patients who were treated with radiotherapy against the brain metastasis and by that lymphocytes can migrate into the CNS. Efficacy of ipilimumab for these patients might be expected, however for patients who were not treated with radiotherapy the effect of ipilimumab treatment is questionable.

No data regarding the efficacy and safety of ipilimumab use in patients with ocular melanoma is provided. It is uncertain whether the immunogenicity of ocular and skin melanoma are comparable and

by that whether a similar effect of ipilimumab is to be expected for both tumour types. As no additional safety concerns are expected, the CHMP considered that these should not be an absolute contra-indication for ipilimumab treatment. It has however been included in the product information that patients with ocular melanoma, primary CNS melanoma and active brain metastases were not included in the pivotal clinical trial.

In the main study MDX010-20 only patients with a positive HLAA2*201 test were included. Results of the CA184004 study indicated that HLA phenotype A2*201 was not a predictive biomarker for the efficacy or safety of ipilimumab treatment. According to the supposed working mechanism of ipilimumab, the activity of ipilimumab is not directly HLA dependent.

2.5.4. Conclusions on the clinical efficacy

Overall, the CHMP considered that the efficacy in the claimed indication for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy has been demonstrated based on an improvement in overall survival.

Based on effect-response analysis, it is not fully elucidated if the dose of 3 mg/kg ipilimumab in study MDX010-20 is the optimal dose. At this moment 3 mg/kg will be the dose recommended for ipilimumab in for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy. As a condition to the marketing authorisation, the applicant shall collect further efficacy (with survival endpoint) and safety data in a randomised study comparing 3 mg/kg versus 10 mg/kg ipilimumab in advanced melanoma.

2.6. Clinical safety

Patient exposure

Safety data from 1,107 patients is presented (975 patients received ipilimumab at 3 mg/kg (622) and at 10 mg/kg (353)) treated in Phase 2 and 3. The safety data were obtained by one Phase 3 study (MDX010-20), 4 completed phase 2 studies (CA184008, CA184022, CA184007 and CA184004, and one interim Phase 2 study (CA184042).

Supplemental safety data from 568 treated patients of 14 completed studies, investigating ipilimumab for the treatment of metastatic melanoma or other cancers including prostate, renal, and breast were submitted.

Adverse events

Throughout the clinical program in advanced melanoma, the vast majority (>96%) of patients with metastatic melanoma experienced adverse events (AEs) of any grade during the induction phase, including in the gp100 monotherapy group as well as all ipilimumab treatment groups. Most common safety events of any grade reported in patients receiving ipilimumab were those affecting the GI tract and skin, these AEs are classified as irAEs which includes diarrhoea, pruritus and rash, each were more commonly reported in the ipilimumab groups than in the gp100 group. In addition, the incidences of colitis and endocrine insufficiency, were higher in the ipilimumab groups than in the gp100 group.

Dyspnoea and pleural effusion were numerically more common in the gp100 monotherapy group.

In patients receiving ipilimumab 3 mg/kg monotherapy, the frequency of treatment related Grade 3-4 AEs was 20.6% in the main study MDX010-20 and 14.4% in the pooled 3 mg/kg group. In most cases these events were Grade 3 in severity, with few reports of Grade 4 events (3.8% and 1.8%, respectively). The most common treatment-related Grade 3-4 AEs were colitis and diarrhoea.

Table 12 – Treatment-related AEs Reported in at Least 5% of Subjects During the Induction Phase – Treated Subjects

	NUMBER OF SUBJECTS (%)					
SYSTEM ORGAN CLASS PREFERRED TERM	MDX010-20 3 MG/KG IPI N = 131	MDX010-20 3 MG/KG IPI+ GP100 N = 380	MDX010-20 GP100 N = 132	CA184004/022 POOLED 3 MG/KG IPI N = 111	CA184004/ 007/008/022 POOLED 10 MG/KG IPI N = 325	CA184042 10 MG/KG IPI N = 28
ANY DRUG RELATED ADVERSE EVENT	103 (78.6)	338 (88.9)	104 (78.8)	88 (79.3)	274 (84.3)	23 (82.1)
GASTROINTESTINAL DISORDERS	61 (46.6)	176 (46.3)	49 (37.1)	52 (46.8)	156 (48.0)	13 (46.4)
DIARRHOEA	35 (26.7)	111 (29.2)	18 (13.6)	28 (25.2)	115 (35.4)	10 (35.7)
NAUSEA	30 (22.9)	71 (18.7)	23 (17.4)	19 (17.1)	53 (16.3)	4 (14.3)
VOMITING	16 (12.2)	34 (8.9)	9 (6.8)	6 (5.4)	33 (10.2)	1 (3.6)
COLITIS	10 (7.6)	19 (5.0)	1 (0.8)	6 (5.4)	30 (9.2)	3 (10.7)
ABDOMINAL PAIN	8 (6.1)	31 (8.2)	6 (4.5)	6 (5.4)	25 (7.7)	1 (3.6)
CONSTIPATION	3 (2.3)	17 (4.5)	2 (1.5)	7 (6.3)	10 (3.1)	1 (3.6)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS	56 (42.7)	169 (44.5)	25 (18.9)	50 (45.0)	177 (54.5)	10 (35.7)
PRURITUS	31 (23.7)	62 (16.3)	14 (10.6)	23 (20.7)	91 (28.0)	7 (25.0)
RASH	23 (17.6)	64 (16.8)	6 (4.5)	28 (25.2)	102 (31.4)	7 (25.0)
ERYTHEMA	7 (5.3)	16 (4.2)	4 (3.0)	2 (1.8)	1 (0.3)	2 (7.1)

	NUMBER OF SUBJECTS (%)					
SYSTEM ORGAN CLASS PREFERRED TERM	MDX010-20 3 MG/KG IPI N = 131	MDX010-20 3 MG/KG IPI+ GP100 N = 380	MDX010-20 GP100 N = 132	CA184004/022 POOLED 3 MG/KG IPI N = 111	CA184004/ 007/008/022 POOLED 10 MG/KG IPI N = 325	CA184042 10 MG/KG IPI N = 28
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	53 (40.5)	259 (68.2)	75 (56.8)	43 (38.7)	121 (37.2)	13 (46.4)
FATIGUE	31 (23.7)	87 (22.9)	26 (19.7)	29 (26.1)	74 (22.8)	11 (39.3)
PYREXIA	10 (7.6)	40 (10.5)	8 (6.1)	13 (11.7)	40 (12.3)	1 (3.6)
CHILLS	7 (5.3)	12 (3.2)	6 (4.5)	5 (4.5)	7 (2.2)	0
ASTHENIA	6 (4.6)	15 (3.9)	5 (3.8)	6 (5.4)	13 (4.0)	1 (3.6)
OEDEMA PERIPHERAL	3 (2.3)	10 (2.6)	1 (0.8)	1 (0.9)	3 (0.9)	3 (10.7)
INJECTION SITE PAIN	2 (1.5)	23 (6.1)	13 (9.8)	0	0	0
INJECTION SITE REACTION	2 (1.5)	105 (27.6)	26 (19.7)	0	0	0
INJECTION SITE ERYTHEMA	1 (0.8)	25 (6.6)	5 (3.8)	0	0	0
INJECTION SITE INDURATION	0	23 (6.1)	4 (3.0)	0	0	0
METABOLISM AND NUTRITION DISORDERS	16 (12.2)	48 (12.6)	11 (8.3)	11 (9.9)	48 (14.8)	4 (14.3)
DECREASED APPETITE	15 (11.5)	39 (10.3)	8 (6.1)	9 (8.1)	38 (11.7)	2 (7.1)
DEHYDRATION	2 (1.5)	7 (1.8)	1 (0.8)	3 (2.7)	17 (5.2)	2 (7.1)
INVESTIGATIONS	14 (10.7)	26 (6.8)	10 (7.6)	5 (4.5)	55 (16.9)	3 (10.7)

	NUMBER OF SUBJECTS (%)					
SYSTEM ORGAN CLASS PREFERRED TERM	MDX010-20 3 MG/KG IPI N = 131	MDX010-20 3 MG/KG IPI+ GP100 N = 380	MDX010-20 GP100 N = 132	CA184004/022 POOLED 3 MG/KG IPI N = 111	CA184004/ 007/008/022 POOLED 10 MG/KG IPI N = 325	CA184042 10 MG/KG IPI N = 28
WEIGHT DECREASED	4 (3.1)	10 (2.6)	2 (1.5)	3 (2.7)	19 (5.8)	2 (7.1)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS	13 (9.9)	65 (17.1)	20 (15.2)	15 (13.5)	27 (8.3)	2 (7.1)
MYALGIA	5 (3.8)	24 (6.3)	3 (2.3)	5 (4.5)	9 (2.8)	0
PAIN IN EXTREMITY	1 (0.8)	24 (6.3)	7 (5.3)	0	5 (1.5)	0
NERVOUS SYSTEM DISORDERS	9 (6.9)	55 (14.5)	17 (12.9)	10 (9.0)	37 (11.4)	3 (10.7)
HEADACHE	5 (3.8)	29 (7.6)	8 (6.1)	7 (6.3)	18 (5.5)	1 (3.6)

The most common treatment –related AEs associated with the use of ipilimumab were immune related (named immune-related AEs or irAEs). They primarily involve the GI tract and skin, and less frequently, the liver, endocrine glands, and nervous system. The early diagnosis of irAEs was

important to initiate therapy and minimize complications. Immune-related AEs were generally managed with either symptomatic therapy for Grade 1-2 events, systemic corticosteroids for Grade 3-4 events, or other immunosuppressants (e.g., infliximab, mycophenolate mofetil) for steroid-unresponsive GI or hepatic irAEs, as appropriate. Management of irAEs was usually paired with omission of dosing for mild or moderate events and permanent discontinuation for severe irAEs.

Adverse reactions reported in patients with advanced melanoma who were treated with ipilumumab 3 mg/kg in clinical trials (n= 767) are presented in Table 13.

Table 13 – Adverse reactions in patients with advanced melanoma treated with YERVOY 3 mg/kg (n= 767)[a]

Infections and infestations	
Uncommon	sepsis[b], septic shock[b], meningitis, gastroenteritis, diverticulitis, urinary tract infection, upper respiratory tract infection, lower respiratory tract infection
Neoplasms benign, malignant and unspecified (including cysts and polyps)	
Common	tumour pain
Uncommon	paraneoplastic syndrome
Blood and lymphatic system disorders	
Common	anaemia, lymphopenia
Uncommon	haemolytic anaemia[b], thrombocytopenia, eosinophilia, neutropenia
Immune system disorders	
Uncommon	hypersensitivity
Endocrine disorders	
Common	hypopituitarism (including hypophysitis)[c], hypothyroidism[c]
Uncommon	adrenal insufficiency[c], hyperthyroidism[c], hypogonadism
Metabolism and nutrition disorders	
Very common	decreased appetite
Common	dehydration, hypokalemia
Uncommon	hyponatremia, alkalosis, hypophosphatemia, tumour lysis syndrome
Psychiatric disorders	
Common	confusional state
Uncommon	mental status changes, depression, decreased libido
Nervous system disorders	
Common	peripheral sensory neuropathy, dizziness, headache, lethargy
Uncommon	Guillain-Barré syndrome[b,c], syncope, cranial neuropathy, brain oedema, peripheral neuropathy, ataxia, tremor, myoclonus, dysarthria
Eye disorders	
Common	blurred vision, eye pain
Uncommon	uveitis[c], vitreous haemorrhage, iritis[c], reduced visual acuity, foreign body sensation in eyes, conjunctivitis
Cardiac disorders	
Uncommon	arrhythmia, atrial fibrillation
Vascular disorders	
Common	hypotension, flushing, hot flush
Uncommon	vasculitis, angiopathy[b], peripheral ischaemia, orthostatic hypotension
Respiratory, thoracic and mediastinal disorders	
Common	dyspnea, cough
Uncommon	respiratory failure, acute respiratory distress syndrome[b], lung infiltration, pulmonary oedema, pneumonitis, allergic rhinitis
Gastrointestinal disorders	
Very common	diarrhoea[c], vomiting, nausea
Common	gastrointestinal haemorrhage, colitis[b,c], constipation, gastroesophageal reflux disease, abdominal pain
Uncommon	gastrointestinal perforation[b,c], large intestine perforation[b,c], intestinal perforation[b,c], peritonitis[b], pancreatitis, enterocolitis, gastric ulcer, large intestinal ulcer, oesophagitis, ileus[d]
Hepatobiliary disorders	
Common	abnormal hepatic function
Uncommon	hepatic failure[b,c], hepatitis, hepatomegaly, jaundice
Skin and subcutaneous tissue disorders	
Very common	rash[c], pruritus[c]
Common	dermatitis, erythema, vitiligo, urticaria, alopecia, night sweats, dry skin

Uncommon	toxic epidermal necrolysis[b,c], leukocytoclastic vasculitis, skin exfoliation
Musculoskeletal and connective tissue disorders	
Common	arthralgia, myalgia, musculoskeletal pain, muscle spasms
Uncommon	polymyalgia rheumatica, arthritis
Renal and urinary disorders	
Uncommon	renal failure[b], glomerulonephritis[c], renal tubular acidosis
Reproductive system and breast disorders	
Uncommon	amenorrhea
General disorders and administration site conditions	
Very common	fatigue, injection site reaction, pyrexia
Common	chills, asthenia, oedema, pain
Uncommon	multi-organ failure[b,c], infusion related reaction
Investigations	
Common	increased alanine aminotransferase[c], increased aspartate aminotransferase[c], increased blood bilirubin, weight decreased
Uncommon	abnormal liver function test, increased blood creatinine, increased blood thyroid stimulating hormone, decreased blood cortisol, decreased blood corticotrophin, increased lipase[c], increased blood amylase[c], decreased blood testosterone

a Frequencies are based on pooled data from 9 clinical trials investigating the YERVOY 3 mg/kg dose in melanoma.
b Including fatal outcome
c Additional information about these potentially inflammatory adverse reactions is provided in "Description of selected adverse reactions" and section 4.4. Data presented in those sections primarily reflect experience from a Phase 3 study, MDX010-20.
d Reported in recent studies outside the completed clinical trials in melanoma.

Like in the MDX010-20 study in the CA184024 study the most common safety events of any grade reported in patients receiving ipilimumab were adverse events classified as immune related (irAEs). Most frequent AE's affected the GI and the skin, the percentage of patients with a AE in GI and skin in the CA184024 study was comparable with the safety results of the MDX010-20 study (for GI: overall 35.6% with 5.7% Grade 3-4 in CA184024 and overall 29.8% with 7.6% Grade 3-4 MDX010-20; for skin 42.9% overall with 3.2% Grade 3-4 in CA184024 and overall 42.7% overall with 1.5% Grade 3-4 in MDX010-20). As could be expected, in comparison to the MDX010-20 study a higher proportion of grade 3-4 irAEs was reported in CA184024 after DTIC +ipilimumab treatment (56.3% in CA184024 vs 20.6% in the MDX010-20 study).

Serious adverse event/deaths/other significant events

Diarrhoea and colitis were consistently the most common treatment-related serious adverse events (SAEs) reported in the clinical database for patients receiving ipilimumab across studies and doses. In patients receiving ipilimumab 3 mg/kg monotherapy, the frequency of treatment-related SAEs was 16.8% in MDX010-20 and 17.1% in the pooled 3 mg/kg group.

In the MDX010-20 study, treatment-related SAEs were reported in 16.8%, 12.6% and 3.8% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100 and gp100 monotherapy groups, respectively. The most common treatment-related SAEs reported in the ipilimumab monotherapy and ipilimumab plus gp100 groups were primarily irAEs, most commonly GI irAEs of colitis (5.3% and 3.4%, respectively) and diarrhoea (3.8% and 3.4%, respectively), both of which were not reported as treatment-related SAEs in the gp100 monotherapy group.

For studies using a 10 mg/kg dose, the most common treatment-related SAE, were likewise diarrhoea (11.4%) and colitis (7.1%). Treatment related SAEs reported under the SOCs of investigations (4.0%) and hepatobiliary disorders (3.1%) were also common in the 10 mg/kg ipilimumab studies.

Table 14 – Treatment-related SAEs Reported in at Least 2 Subjects in Any Group During the Induction Phase -Treated Subjects

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER OF SUBJECTS (%) MDX010-20 3 MG/KG IPI N = 131	MDX010-20 3 MG/KG IPI+ GP100 N = 380	MDX010-20 GP100 N = 132	CA184004/022 POOLED 3 MG/KG IPI N = 111	CA184004/ 007/008/022 POOLED 10 MG/KG IPI N = 325	CA184042 10 MG/KG IPI N = 28
ANY DRUG RELATED SERIOUS ADVERSE EVENT	22 (16.8)	48 (12.6)	5 (3.8)	19 (17.1)	95 (29.2)	7 (25.0)
GASTROINTESTINAL DISORDERS	10 (7.6)	24 (6.3)	2 (1.5)	10 (9.0)	48 (14.8)	4 (14.3)
COLITIS	7 (5.3)	13 (3.4)	0	5 (4.5)	23 (7.1)	3 (10.7)
DIARRHOEA	5 (3.8)	13 (3.4)	0	5 (4.5)	37 (11.4)	3 (10.7)
ABDOMINAL PAIN	1 (0.8)	0	0	1 (0.9)	6 (1.8)	1 (3.6)
VOMITING	1 (0.8)	0	1 (0.8)	1 (0.9)	7 (2.2)	0
ENTEROCOLITIS	0	0	0	0	2 (0.6)	0
INTESTINAL PERFORATION	0	2 (0.5)	0	0	0	0
LARGE INTESTINE PERFORATION	0	2 (0.5)	0	1 (0.9)	0	0
NAUSEA	0	0	1 (0.8)	0	2 (0.6)	0
ENDOCRINE DISORDERS	5 (3.8)	4 (1.1)	0	3 (2.7)	12 (3.7)	1 (3.6)
HYPOPHYSITIS	2 (1.5)	1 (0.3)	0	1 (0.9)	4 (1.2)	0
HYPOPITUITARISM	2 (1.5)	3 (0.8)	0	3 (2.7)	5 (1.5)	0
HYPOTHYROIDISM	0	1 (0.3)	0	0	2 (0.6)	0

SYSTEM ORGAN CLASS PREFERRED TERM	NUMBER OF SUBJECTS (%) MDX010-20 3 MG/KG IPI N = 131	MDX010-20 3 MG/KG IPI+ GP100 N = 380	MDX010-20 GP100 N = 132	CA184004/022 POOLED 3 MG/KG IPI N = 111	CA184004/ 007/008/022 POOLED 10 MG/KG IPI N = 325	CA184042 10 MG/KG IPI N = 28
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS	3 (2.3)	8 (2.1)	0	5 (4.5)	12 (3.7)	1 (3.6)
ASTHENIA	1 (0.8)	1 (0.3)	0	1 (0.9)	2 (0.6)	0
FATIGUE	1 (0.8)	0	0	1 (0.9)	3 (0.9)	0
PYREXIA	0	4 (1.1)	0	3 (2.7)	6 (1.8)	1 (3.6)
RENAL AND URINARY DISORDERS	3 (2.3)	0	0	0	3 (0.9)	0
RENAL FAILURE	2 (1.5)	0	0	0	0	0
HAEMATURIA	0	0	0	0	2 (0.6)	0
VASCULAR DISORDERS	3 (2.3)	0	1 (0.8)	0	2 (0.6)	0
HYPOTENSION	2 (1.5)	0	0	0	0	0
BLOOD AND LYMPHATIC SYSTEM DISORDERS	1 (0.8)	3 (0.8)	0	0	5 (1.5)	0
ANAEMIA	0	1 (0.3)	0	0	4 (1.2)	0
HEPATOBILIARY DISORDERS	1 (0.8)	1 (0.3)	0	0	10 (3.1)	0
AUTOIMMUNE HEPATITIS	0	0	0	0	5 (1.5)	0
HEPATITIS	0	1 (0.3)	0	0	2 (0.6)	0
JAUNDICE	0	0	0	0	2 (0.6)	0
INVESTIGATIONS	1 (0.8)	0	1 (0.8)	0	13 (4.0)	0
ALANINE AMINOTRANSFERASE INCREASED	0	0	0	0	7 (2.2)	0
ASPARTATE AMINOTRANSFERASE INCREASED	0	0	0	0	8 (2.5)	0
METABOLISM AND NUTRITION DISORDERS	1 (0.8)	2 (0.5)	1 (0.8)	2 (1.8)	10 (3.1)	2 (7.1)
DEHYDRATION	0	2 (0.5)	1 (0.8)	1 (0.9)	7 (2.2)	2 (7.1)
RESPIRATORY, THORACIC AND MEDIASTINAL DISORDERS	1 (0.8)	3 (0.8)	0	0	3 (0.9)	0
PNEUMONITIS	0	1 (0.3)	0	0	2 (0.6)	0

Deaths

Across studies and doses, ~ 20% to 25% of patients died during the induction phase, most (> 90%) due to disease progression or other causes considered unrelated to study drug. Treatment-related deaths were defined as treatment-related AEs with an outcome of death and were summarized for the entire study duration (including the induction phase, re-induction/ maintenance phases, and more than 70 days after last dose). The rates of treatment-related deaths for the entire study duration ranged from ~ 2% to 3% across all groups. No treatment-related deaths were reported in the re-induction or maintenance phases.

In MDX010-20, treatment-related deaths (for the entire study duration) were reported in 3.1%, 2.1%, and 1.5% of patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy

groups, respectively. In the ipilimumab groups, 1.5% and 1.3% of patients experienced a treatment-related death in association with an irAE. The rate of deaths during the induction phase as well as treatment-related deaths for the entire study duration was similar between the 3 mg/kg and 10 mg/kg groups.

Overall, the rate of treatment-related deaths in patients who received 3 mg/kg ipilimumab monotherapy was 2.5% (6/242; 4/131 [3.1%] in the ipilimumab monotherapy group in MDX010-20 and 2/111 [1.8%] in the pooled 3 mg/kg group from the Phase 2 studies).

Table 15 – Deaths During the Induction Phase and All Treatment-related Deaths During the Entire Study Duration - Treated Subjects

	MDX010-20			Phase 2 Studies		
	3 mg/kg N = 131	3 mg/kg + gp100 N = 380	gp100 N = 132	Pooled 3 mg/kg N = 111	Pooled 10 mg/kg N = 325	CA184042 10 mg/kg N = 28
Deaths during the induction phase						
All Deaths	27 (20.6)	82 (21.6)	36 (27.3)	26 (23.4)	71 (21.8)	8 (28.6)
Unrelated[a]	25 (19.1)	75 (19.7)	34 (25.8)	24 (21.6)	65 (20.0)	7 (25.0)
Treatment-related[b]	2 (1.5)	7 (1.8)	2 (1.5)	2 (1.8)	6 (1.8)	1 (3.6)
Treatment-related death > 70 days after last dose[c]	1 (0.8)	0	0	0	1 (0.3)	0
All treatment-related deaths	3 (2.3)	7 (1.8)	2 (1.5)	2 (1.8)	7 (2.2)	1 (3.6)
Associated with an irAE[d]	1 (0.8)	5 (1.3)	0	1 (0.9)	6 (1.8)	0
Treatment-related deaths post-induction phase[b]						
Re-induction/maintenance[e]	0	0	0	0	0	0
Post-study AE[f]	1 (0.8)	1 (0.3)	0	0	2 (0.6)	0
Associated with an irAE[d]	1 (0.8)	0	0	0	1 (0.3)	0
Treatment-related deaths for entire study[b]						
All treatment-related deaths	4 (3.1)	8 (2.1)	2 (1.5)	2 (1.8)	9 (2.8)	1 (3.6)
Associated with an irAE[d]	2 (1.5)	5 (1.3)	0	1 (0.9)	7 (2.2)	0

[a] Primarily due to progressive disease (causes of death are summarized in SCS-A Appendix 2.203A).

[b] Treatment-related AEs with an outcome of death; all treatment-related Grade 5 AEs are presented in Tables 2.1.2B and 2.1.2C and summarized in SCS-A Appendix 2.14A.

[c] Deaths more than 70 days after the last induction dose associated with a treatment-related AE with an outcome of death reported during the induction phase.

[d] At least 1 AE with an outcome of death was an irAE

[e] Safety in the re-induction and maintenance phases is presented in Sections 5.9 and 5.10, respectively.

[f] Treatment-related AE more than 70 days after last dose with an outcome of death (SCS-A Appendices 2.1 and 2.2).

AE = adverse event; irAE = immune-related AE

No direct treatment related deaths were reported in the CA184024 study. In other phase 2 studies and in the ipilimumab+gp100 arm of the MDX010-20 study the percentage of treatment related death was +/- 2%.

Laboratory findings

Hematology

Across studies and doses, most patients had normal baseline white blood cell (WBC) levels, absolute neutrophil counts (ANC), and platelet counts (> 90% of patients assessed for each parameter); baseline abnormalities in hemoglobin were common in all groups (~ 35% to 50% of patients in each group).

In MDX010-20, most patients in each of the 3 treatment groups had normal on-study WBC, ANC, and platelet levels (> 90% of patients assessed for each parameter).

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 patients in each group; no Grade 3-4 abnormalities in WBC or platelets were reported in any group. In the pooled 3 mg/kg group, ≥ 90% of patients had normal on-study WBC, ANC, and platelet counts; Grade 3-4 abnormalities in WBC, ANC, and platelets were each reported in ~ 2% of patients.

On-study hemoglobin abnormalities were common (~ 50% of patients) and almost entirely Grade 1-2 in severity. In MDX010-20, Grade 3-4 hemoglobin abnormalities were reported in 0.8%, 1.7%, and 4.0% of patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively). All but 1 of these patients (in the gp100 monotherapy group) had an abnormal baseline hemoglobin level. In the pooled 3 mg/kg group, on-study hemoglobin abnormalities were reported for 61.0% of patients (Grade 3-4 in 4.8% of patients, all but 1 of these patients had an abnormal baseline hemoglobin value).

Most patients in the pooled 10 mg/kg group had normal on-study WBC, ANC, and platelet levels (92.2%, 94.2%, and 86.4% of patients, respectively). On-study abnormalities in WBC, ANC, and platelets were primarily Grade 1-2 in severity; Grade 3-4 abnormalities in WBC, ANC, and platelets were each reported in < 1% of patients in the pooled 10 mg/kg group.

Liver enzymes

Across studies and doses, most patients had normal LFTs at baseline, as assessed by baseline levels of ALT, AST, and total bilirubin (~ 90 to 95% of patients assessed for ALT and AST and ~ 97% of patients for total bilirubin). Baseline abnormalities in alkaline phosphatase (ALP) were reported in ~ 10 to 20% of patients.

With the 3 mg/kg dose, on-study abnormalities in ALT, AST, total bilirubin, and ALP were primarily Grade 1-2 in severity. In MDX010-20, Grade 3-4 abnormalities in ALT and AST were each reported in < 2% of patients and Grade 3-4 abnormalities in total bilirubin were reported in < 1% of patients. In the pooled 3 mg/kg group, Grade 3-4 abnormalities in ALT and AST were each reported in ~ 2% of patients. Grade 3 abnormalities in ALP were reported in 3.3%, 1.7%, and 0.8% of patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively, in MDX010-20 and 6.7% of patients in the pooled 3 mg/kg group; these abnormalities were mostly in patients with baseline abnormalities, including in all 4 of the patients in the ipilimumab monotherapy group and all 7 of the patients in the pooled 3 mg/kg group who had Grade 3 on-study abnormalities. One patient in the monotherapy group (M20-007-0059) died of hepatic failure associated with multi-organ failure.

In the pooled 10 mg/kg group, Grade 3-4 abnormalities in ALT, AST, and total bilirubin were reported in 7.5%, 7.2%, and 2.0% of patients, respectively. These rates are higher than with the 3 mg/kg dose and consistent with the higher rate of hepatic irAEs in the pooled 10 mg/kg group compared with

MDX010-20 and the pooled 3 mg/kg group. In CA184042, no Grade 3-4 abnormalities in AST or ALT were reported. Grade 3 abnormalities in ALP were reported in 3.0% of patients and 4.0% of patients in CA184042; no Grade 4 abnormalities were reported in either group.

Renal function tests

Most patients had normal kidney function at baseline, as assessed by baseline creatinine levels (~ 92 to 96% of patients assessed in each group in MDX010-20 and 88% and 93% of patients assessed in the pooled 3 mg/kg and 10 mg/kg groups, respectively).

In MDX010-20, most patients (~ 90%) in each of the 3 treatment groups had normal on-study creatinine levels (Table). On-study abnormalities in creatinine were primarily Grade 1 in severity; Grade 2 abnormalities were reported in ~ 2% of patients in each group. One (0.3%) Grade 3 abnormality was reported in a patient in the ipilimumab plus gp100 group.

In the pooled 10 mg/kg group, on-study abnormalities in creatinine levels were primarily Grade 1 in severity. Grade 2 abnormalities were reported in 3.6% of patients; 1 (0.3%) patient had a Grade 4 on-study abnormality (who had a normal value at baseline).

Pancreatic Enzymes

Most patients had normal pancreatic function at baseline, as assessed by serum lipase and amylase levels (~ 90% of patients assessed for lipase, 90% to 95% of patients assessed for amylase).

In MDX010-20, on-study lipase abnormalities were reported with similar frequency across the 3 groups (18.4%, 18.5%, and 19.7% of patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively) (Table). Grade 3-4 abnormalities were reported in 9.6%, 4.3%, and 5.1% of patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively (Table). In the pooled 3 mg/kg group, lipase abnormalities were reported in 20.8% of patients (Grade 3-4 in 8.5%). On-study abnormalities in amylase were primarily Grade 1-2 in severity. In MDX010-20, Grade 3-4 abnormalities in amylase were reported in 2.6% of patients in the gp100 monotherapy group compared with 0% and 0.9% of patients in the ipilimumab monotherapy and ipilimumab plus gp100 groups, respectively. In the pooled 3 mg/kg group, amylase abnormalities were primarily Grade 1-2; Grade 3-4 abnormalities were reported in 2.8% of patients. No cases of pancreatitis were reported in MDX010-20 or the pooled 3 mg/kg group.

In the pooled 10 mg/kg group, on-study lipase abnormalities were reported in 22.7% of patients; Grade 3-4 lipase abnormalities were reported in 6.5% of patients. On-study abnormalities in amylase were primarily Grade 1-2 in severity. Grade 3-4 amylase abnormalities were reported in 1.6% of patients. Pancreatitis was reported in 2 (0.6%) patients in the pooled 10 mg/kg group. Data for amylase and lipase were not collected for CA184042.

Safety in special populations

The safety profile of ipilimumab was similar in most subgroups analysed. Patients with medical histories of alcohol abuse, diverticulosis/diverticulitis or family histories of auto-immune disease were too few to permit proper analysis.

Treatment-related grade 3-5 AEs were less common in patients who had received immunotherapy prior to treatment with ipilimumab. This difference was observed in the 3 mg/kg groups, but not in the 10 mg/kg groups.

Differences between subgroups by tumour burden were expected. More AEs were reported in subgroups who received fewer doses. This is explained by these patients having met protocol-defined criteria for treatment modification for skipping or discontinuation due to irAEs. Death rate, due to

disease progression, was higher in patients who received only one dose. These patients typically discontinued treatment because of disease progression.

The phase 2 studies did not exclude HLA types other than HLA A2*0201. Analysis of irAEs over HLA types did not show a clear pattern. The pooled 3 mg/kg group shows no clear differences between HLA A2*0201 positive and negative patients, but based on the data from the 3 mg/kg and 10 mg/kg groups, influence of HLA type on the incidence of irAEs cannot be ruled out and needs to be studied further.

Safety related to drug-drug interactions and other interactions

Clinical pharmacology studies were not performed to evaluate the metabolism and the metabolic pathways of ipilimumab in humans, or to determine the potential for any drug-drug interactions of ipilimumab with other molecules.

Discontinuation due to adverse events

In MDX010-20, treatment related AEs leading to discontinuation of study therapy were reported in 9.9%, 6.8%, and 3.0% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively.

In Study CA184024, a very high number the patients treated with ipilimumab and DTIC discontinued study therapy during the initiation phase of the study due to drug toxicity (83 patients (33.6%) in the ipilimumab+DTIC group).

Post marketing experience

Not applicable.

2.6.1. Discussion on clinical safety

Safety data for the treatment of pretreated advanced melanoma with ipilimumab was gathered in clinical trials. Experience with treatment with ipilimumab 3mg/kg was combined with data from studies for which patients were treated with ipilimumab 10mg/kg. In the pivotal study, MDX010-20, ipilimumab 3mg/kg was compared with ipilimumab and gp100 tumour vaccine combination therapy and with gp100 monotherapy. Ipilimumab was not compared to a placebo or standard treatment in any of the smaller trials. Interpretation of the safety data is therefore more complex, since it cannot be ruled out that gp100 has an unfavourable safety profile that makes the data from the ipilimumab treated groups look better than it would in comparison with a placebo.

Treatment related AEs were common in all groups. In the gp100 group the incidence of treatment related AEs was 78.8%, which is comparable to the incidence of treatment-related AEs in the ipilimumab only group. Treatment-related SAEs and deaths were less common in the gp100 group than in the ipilimumab monotherapy arm, but the numbers are nevertheless considerable. A 1.5% risk of treatment-related death is not justified by the very limited therapeutic value of gp100.

The criteria for inclusion into the studies further limit the safety data. Patients with liver enzyme elevations, impaired renal function or a history of auto-immune disease were commonly excluded from the trials. In the pivotal study, only HLA A2*0201 positive patients were enrolled. The safety data base of 311 HLA A2 negative patients does not indicate a difference in irAEs for HLA A2 negative patients in comparison to HLA A2 positive patients.

Almost all patients experienced adverse events. Incidence of treatment-related AEs in the ipilimumab 3mg/kg group was high. Most SAEs were immune related, as can be expected based on the mechanism of action. The majority of immune-related AEs could be treated successfully. One patient developed grade 3 symptoms suggestive for human anti-human antibodies (HAHA).

There was 3.1% risk of treatment-related death associated with ipilimumab therapy, with half of these deaths occurring within the first month after treatment commenced. To address potential informative censoring in the analysis of OS, a conservative sensitivity analysis provided by the Applicant showed that, considering the treatment-related discontinuations and treatment-related deaths in the ipilimumab arm as deaths, this did not substantially change the result of OS analysis. Therefore, the CHMP considered that the gain in OS was not driven by possibly hidden treatment failure in the ipilimumab arm.

Elevated liver enzymes were reported and may reflect liver injury caused by the treatment. Levels of concomitant medication that is metabolized in the liver may be affected.

The characteristics of (ir)AEs reported for the CA184024 study are reasonably similar to the safety issues identified in the MDX010-20 study. The percentage of grade 3-4 AEs in the CA184024 study was higher than in the MDX010-20 study (37.2% in CA184024 vs 20.6% in the MDX010-20 study). Moreover, the number of patients discontinuing study therapy due to drug toxicity was much higher in the CA184024 study than in the MDX010-20 study (33.6% vs 9.9% respectively. However, the used ipilimumab doses in the CA184024 study is substantially higher than in the MDX010-20 study (10 mg/kg vs 3 mg/kg). The very high rate of discontinuation due to drug toxicity in the CA184024 study could be indicative for the lack of tolerability of 10 mg/kg dose ipilimumab in combination with DTIC.

Therefore, liver function tests and thyroid function tests should be evaluated at baseline and before each dose of YERVOY. In addition, any signs or symptoms of immune-related adverse reactions, including diarrhoea and colitis, must be assessed during treatment with YERVOY.

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.

Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies such as hypothyroidism), including those who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical trials. The CHMP was of the opinion that considering the supposed mechanism of action and the observed AE which were mainly immune related, additional safety concerns might be expected in these patients. Ipilimumab is a T cell potentiator that enables the immune response and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. Therefore, a warning has been included that ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening and used with caution in other patients with a history of autoimmune disease, after careful consideration of the potential risk-benefit on an individual basis. This population not studied has been included in the risk management plan and further data should continue to be collected.

2.6.2. Conclusions on the clinical safety

Treatment-related adverse events were common, leading to discontinuation in 9.9% of patients and to death in 3.1% in MDX010-20. Most SAEs were immune related, as can be expected based on the mechanism of action. The majority of immune-related AEs could be treated successfully. Extensive guidance for the management of irAE including the use of systemic corticosteroids has been included in the product information.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Table 16 – Summary of the risk management plan

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Important Identified Risks		
GI irARs (e.g.,. diarrhea, colitis, GI perforation)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label). Enhanced PV - Targeted questionnaire will be used for GI irARs resulting in severe complications such as GI perforation or colectomy. Enhanced PV- Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outline treatment modifications (discontinuation, dose omission) for toxicities, including GI irARs **SmPC Section 4. 4 Special warnings and Precautions for Use:** describes characteristics and recommended monitoring and management guideline. *Immune-Related Gastrointestinal Reactions*: describes characteristics and recommended monitoring and management guideline. **SmPC Section 4. 8 Undesirable effects** **Additional Risk Minimization Activities**: Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Hepatic irARs (e.g., hepatitis)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label). Enhanced PV - Targeted questionnaire will be used for hepatic irARs with severe	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outline treatment modifications (discontinuation, dose omission) for toxicities, including hepatic irARs. 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 × ULN or bilirubin levels > 3 × ULN at baseline.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
	outcome such as hepatic failure or death. Enhanced PV- Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 4 Special warnings and precautions for use** Immune-related hepatotoxicity Describes characteristics and recommended monitoring and management guideline. **SmPC Section 4. 8 Undesirable effects** **Additional Risk Minimization Activities:** Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Skin irARs (e.g., rash, pruritus)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label). Enhanced PV - Targeted questionnaire will be used for dermatologic irARs with severe outcome such as erythema multiforme, Stevens-Johnson syndrome, toxic epidermal necrolysis. Enhanced PV- Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outline treatment modifications (discontinuation, dose omission) for toxicities, including skin irARs **SmPC Section 4. 4 Special warnings and precautions for use** Describes characteristics and recommended monitoring and management guideline. **SmPC Section 4. 8 Undesirable effects** **Additional Risk Minimization Ac**tivities: Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Neurologic irARs (e.g., neuropathy)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label). Enhanced PV - Targeted questionnaire will be used for neurologic irARs with severe outcome such as Guillain-Barre syndrome or severe autoimmune neuropathy Enhanced PV- Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outline treatment modifications (discontinuation, dose omission) for toxicities, including neurologic irARs **SmPC Section 4. 4 Special warnings and precautions for use** Describes characteristics and recommended monitoring and management guideline. YERVOY is associated with serious immune-related neurological events.Fatal Guillain-Barré syndrome has been reported in clinical trials. 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 medicinal products 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 at the next scheduled dose. Doses omitted due to toxicity must not

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		be replaced. YERVOY must be permanently discontinued in patients with severe (Grade 3 or 4) sensory neuropathy suspected to be related to YERVOY. Patients must be treated according to institutional guidelines, and the administration of intravenous corticosteroids (e.g. 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. **SmPc Section 4. 8 - Undesirable effects** **Additional Risk Minimization Activities** Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Endocrine irARs (e.g., hypopituitarism, hypothyroidism, adrenal insufficiency)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label) Enhanced PV - Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outlines treatment modifications (discontinuation, dose omission) for toxicities, including endocrine irARs **SmPC Section 4. 4 Special warnings and precautions for use** Describes characteristics and recommended monitoring and management guideline. **SmPC Section 4. 8 Undesirable effects** **Additional Risk Minimization Activities**: Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Other irARs (e.g., pneumonitis, nephritis, non-infective myocarditis, pancreatitis, uveitis)	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label) Enhanced PV - Post-marketing prospective observational cohort study Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	**SmPC Section 4. 2 Posology and method of administration** Tables 1A and 1B outline treatment modifications (discontinuation, dose omission) for toxicities, including other significant irARs **SmPC Section 4. 4 Special warnings and precautions for use** Describes characteristics and recommended monitoring and management guideline. **Additional Risk Minimization Activities**: Additional communication tools will be distributed to HCPs to ensure that HCPs and their patients are made aware of signs, symptoms and risks associated with irARs and that HCPs have immediate access to treatment guidelines established to reduce serious complications.
Severe infusion reactions	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label)	**SmPC Section 4. 3 Contraindication** Hypersensitivity to the active substance or to any of the excipients **SmPC Section 4. 4 Special warnings and precautions for use** There were isolated cases 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

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
	Planned study: a randomized study to compare 3 vs 10mg/kg of ipilimumab on efficacy and safety in advanced melanoma	close monitoring. Premedications with anti-pyretic and anti-histamine may be considered. **SmPC Section 4. 8 Undesirable effects**
Important Potential Risks		
Immunogenicity	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label). To improve the specificity and sensitivity of the serum ECL assay to detect antibodies, which will be used for ongoing and future Phase 3 clinical studies. Analysis on immunogenicity will continue to be conducted in ongoing and future phase 3 clinical trials.	**SmPC Section 5.1 Pharmacodynamic Effects** 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.
Difference in efficacy in women ≥50 years	Subpopulation analyses will be conducted in future clinical trials	
Missing Information		
Paediatric data	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label) Benefit/risk of ipilimumab use in pediatric population will be evaluated according to PIP. Monitor ongoing pediatric study (CTEP7458/CA184070) Monitor studies in the PIP	**SmPC Section 4.2 Posology and method of administration** <u>Paediatric population</u> The safety and efficacy of YERVOY in children below 18 years of age have not been established. No data are available. YERVOY should not be used in the paediatric population.
Reproductive and lactation data	Routine PV activities (e.g., monitoring, evaluation, close follow up, and reporting of individual AE and literature reports as appropriate, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label) Ongoing nonclinical study on embryofetal development and pre- and postnatal development. Final results will be submitted by 1Q2012.	**SmPC Section 4.6 Fertility, pregnancy and lactation** <u>Pregnancy</u> There are no data on the use of ipilimumab in pregnant women. Final results of animal reproduction studies have not yet been reported. Human IgG1 crosses the placental barrier. The potential risk of treatment to the infant is unknown. YERVOY is not recommended during pregnancy or in women of childbearing potential not using effective contraception, unless the clinical benefit outweighs the potential risk. <u>Breastfeeding</u> It is unknown whether ipilimumab is secreted in human milk. Secretion of IgGs in human milk is generally limited and IgGs have a low oral bioavailability. Significant systemic exposure of the infant is not expected and no

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
		effects on the breastfed newborn/infant are anticipated. However, because of the potential for adverse reactions in nursing infants, a decision must be made whether to discontinue breast-feeding or to discontinue from YERVOY therapy taking into account the benefit of breast-feeding for the child and the benefit of YERVOY therapy for the woman. 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.
Data in ethnic groups	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label) Enhanced PV - safety data in ethnic groups will be collected in the Post-marketing prospective observational cohort study Monitor ongoing clinical studies	**SmPC Section 5.2 Pharmacokinetic properties** The effect of race was not examined as there was insufficient data in non-Caucasian ethnic groups.
Potential pharmacodynamic interaction with systemic immunosuppressants	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label)	**SmPC Section 4.5 Interaction with other medicinal products and other forms of interaction** *Other forms of drug interaction- corticosteroids* The use of systemic corticosteroids at baseline, before starting YERVOY, should be avoided because of their potential interference with the pharmacodynamic activity and efficacy of YERVOY. However, systemic corticosteroids or other immunosuppressants can be used after starting YERVOY to treat immune-related adverse reactions. The use of systemic corticosteroids after starting YERVOY treatment does not appear to impair the efficacy of YERVOY.
Severe hepatic impairment	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label)	**SmPC Section 4.2 Posology and method of administration** 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. **Section 5.2 Pharmacokinetic properties** No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.

Safety issue	Proposed pharmacovigilance activities	Proposed risk minimization activities
Severe renal impairment	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label)	**SmPC Section 4.2 Posology and method of administration** 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. **Section 5.2 Pharmacokinetic properties** No controlled studies have been conducted to evaluate the pharmacokinetics of ipilimumab in the paediatric population or in patients with hepatic or renal impairment.
Safety in patients with autoimmune disease	Routine PV activities (e.g., monitoring, evaluation, and reporting of individual AE and literature reports, periodic aggregate safety data analysis, signal detection via the Medical Surveillance Team, timely update of safety label)	**SmPC Section 4.4 Special warnings and precautions for use** Patients with a history of autoimmune disease (other than vitiligo and adequately controlled endocrine deficiencies, such as hypothyroidism), including those who require systemic immunosuppressive therapy for pre-existing active autoimmune disease or for organ transplantation graft maintenance, were not evaluated in clinical trials. Ipilimumab is a T-cell potentiator that enables the immune response (see section 5.1) and may interfere with immunosuppressive therapy, resulting in an exacerbation of the underlying disease or increased risk of graft rejection. YERVOY should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening and used with caution in other patients with a history of autoimmune disease after careful consideration of the potential risk-benefit on an individual basis.
Long-term safety	The proposed post-marketing study will follow the patients for a minimum of 3 years.	

The CHMP, having considered the data submitted in the MA application is of the opinion that the following risk minimisation activities are necessary for the safe and effective use of the medicinal product:

The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe Yervoy are provided with the following:

- Healthcare Professional FAQ Brochure
- Patient Information Brochures including Alert Cards

Key elements of the Healthcare Professional FAQ Brochure (Q&A format):

- Brief introduction to ipilimumab (indication and the purpose of this tool).
- List of important immune-related adverse reactions (irARs) and their symptoms, as outlined in section 4.4 of the Summary of Product Characteristics (SmPC):
    - Inflammation of the gastrointestinal tract, such as colitis, which can lead to bowel perforation
    - Inflammation of the liver, such as hepatitis, which can lead to liver failure
    - Inflammation of the skin that can lead to severe skin reaction (toxic epidermal necrolysis)
    - Inflammation of the nerves that can lead to neuropathy
    - Inflammation of the endocrine system including the adrenal, pituitary, or thyroid glands
    - Inflammation of the eyes
    - Other related irARs (e.g. pneumonitis, glomerulonephritis, multi-organ failure…)
    - Severe infusion reaction

- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and require early intervention, as outlined in the guidelines for the management of immune-related adverse reactions in section 4.4 of the SmPC.
- Importance of evaluating liver function tests (LFTs), TSH and signs/symptoms of irARs before each treatment.
- Follow-up of patients due to late onset (months after treatment) of irARs
- Reminder to distribute the Patient Information Brochure, and to educate patients/caregivers about symptoms of irARs and of the need to report them immediately to the physician.

Key elements for the Patient Information Brochure and Alert Card:

- Brief introduction to ipilimumab indication and the purpose of this tool.
- Information that ipilimumab can cause serious side effects in many parts of the body that can lead to death and need to be addressed immediately
- Request to inform the physician of all medical conditions before treatment.
- Description of the main symptoms of irARs and the importance of notifying their treating physician immediately if symptoms occur, persist or worsen.
    - Gastrointestinal: diarrhea, bloody stool, abdominal pain, nausea, or vomiting
    - Liver: yellowing of your skin or whites of your eyes
    - Skin: rash, blisters and/or peeling, mouth sores
    - Eye: blurred vision, vision changes, eye pain,
    - General: fever, headache, feeling tired, dizziness or fainting, dark urine, bleeding, weakness, numbness of legs, arms, or faces, changes in behavior, such as less sex drive, being irritable or forgetful
- The importance of not attempting to self-treat any symptoms without consulting their Healthcare professional first.
- Placeholder including the weblink of the Package Leaflet on the EMA website
- The importance of carrying the detachable wallet-sized Patient Alert Card at all times to show it at all medical visits to healthcare professionals other than the prescriber (e.g. emergency healthcare professionals). The Card reminds patients about key symptoms that need to be reported immediately to the physician/nurse. It also contains prompts to enter contact details of the physician and to alert other physicians that the patient is treated with ipilimumab.

The Marketing Authorisation Holder shall agree the format and content of the above material with the National Competent Authority prior to launch in the Member State.

The CHMP, having considered the data submitted, was of the opinion that the below pharmacovigilance activities in addition to the use of routine pharmacovigilance are needed to investigate further some of the safety concerns:

Description	Due date
The applicant commits to submit the final report for study DN120020 (Intravenous Study of Pre- and Post-natal Development in Cynomolgus Monkeys with a 6-month post-natal evaluation).	1Q2012
The applicant shall perform a randomized comparison study of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint.	Submission of protocol: 4Q2011 Submission of final report: 4Q2017
The applicant commits to continue analysing the efficacy and safety of ipilimumab in women over 50 years of age in ongoing and future clinical trials, particularly in the dose comparison study to be conducted.	For dose study, Submission of protocol: 4Q2011 Submission of final report: 4Q2017
The applicant commits to improve the specificity and sensitivity of the serum ECL assay to detect antibodies, which will be used for ongoing and future clinical studies.	1Q2012

Description	Due date
The applicant commits to conduct Study CA184143, a multinational prospective, observational study in patients with unresectable or metastatic melanoma.	Final protocol: Aug 2011 Annual interim results analysis reports from date of marketing authorisation Final study report: estimated 2017

User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

2.8. Benefit-Risk Balance

Benefits

- Beneficial effects

In the pivotal study MDX010-20, the efficacy of ipilimumab monotherapy and ipilimumab in combination with gp100, in comparison with gp100 monotherapy was investigated.

For ipilimumab monotherapy a median OS of 10.1 months (95% CI; 8.02-13.80) was reported whereas the OS for gp100 monotherapy was only 6.4 months (95% CI; 5.49-8.71). The median OS for ipilimumab plus gp100 was 10.0 months.

Long-term survival data indicates that 54 of the 403 patients in the ipilimumab plus gp100 group, 24 of the 137 patients in the ipilimumab monotherapy group, and 16 of the 136 patients in the gp100 monotherapy group, remain alive for a minimum of 2 years.

The observed OS benefit was consistent within most of the subgroups of patients analysed by the Applicant.

Also in the CA184024 study an OS benefit for patients treated with ipilimumab (DTIC+ipilimumab) was seen in comparison to patients treated with DTIC alone. The CHMP acknowledged the results of CA184024 as supportive for the efficacy results obtained in the MDX010-20 study.

- Uncertainty in the knowledge about the beneficial effects.

For women above 50 years of age, the data supporting an OS benefit of YERVOY treatment were limited: A HR close to 1 for this patient group was observed in MDX010-20 study and just above 1 in Study CA184024. As the subgroup analysis includes only small numbers of patients, no definitive conclusions can be drawn from these data. The efficacy and safety of ipilimumab in these patients will continue to be analysed in ongoing and future clinical trials, particularly in the dose comparison study to be conducted.

The number of patients with active brain metastases treated with ipilimumab is limited. Moreover, no efficacy data for patients with ocular melanoma are available.

In vitro data indicated that ipilimumab does not elicit CDC up to concentrations of 50 µg/ml. However, this is lower than the concentrations reached in human plasma after the 3mg/kg dose (Cmax ~85 µg/ml). The results of nonclinical pharmacodynamic studies indicated that the dose of 10 mg/kg is certainly an active level, but no dose-response was studied, and the dose inducing the maximum pharmacological effect is not known. Efficacy of the 3 mg/kg dose has been demonstrated in the pivotal study MDX010-20. Results of phase II studies suggest that a better efficacy might be expected for the 10 mg/kg dose, but also a higher toxicity is envisaged. However, results from the pivotal study with 3 mg/kg dose cannot be directly compared to those obtained from supportive studies conducted using the 10 mg/kg dose. A randomised comparison of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint is warranted.

Risks

- Unfavourable effects

The suggested working mechanism of ipilimumab is that by blocking CTLA-4, ipilimumab potentiates T-cell activation and proliferation. It has been hypothesised that an increased immune activity indirectly impact the tumour cells, however the increased activity of the immune system also contributes to the appearances of immune related AEs .

Throughout the clinical program in advanced melanoma, the vast majority (>96%) of patients with metastatic melanoma experienced AE of any grade during the induction phase, including in the gp100 monotherapy group as well as all ipilimumab treatment groups. Most common safety events of any grade reported in patients receiving ipilimumab were those affecting the GI tract and skin. These AEs are classified as irAEs and include diarrhoea, pruritus and rash, each were more commonly reported in the ipilimumab groups than in the gp100 group. In addition, the incidences of colitis and endocrine insufficiency were higher in the ipilimumab groups compared to the incidence in the gp100 group.

Diarrhoea and colitis were consistently the most common treatment-related SAEs reported in the clinical database for patients receiving ipilimumab across studies and doses.

In the MDX010-20 study, treatment-related SAEs were reported in 16.8%, 12.6% and 3.8% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100 and gp100 monotherapy groups, respectively.

Treatment-related death was reported for all treatment groups in the MDX010-20 study. Treatment-related deaths (for the entire study duration) were reported in 3.1%, 2.1%, and 1.5% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively. No treatment related deaths were reported in the CA184024 study. The percentage of treatment related death is about 2% in the submitted phase 2 study.

In MDX010-20, treatment-related AEs leading to discontinuation of study therapy were reported in 9.9%, 6.8%, and 3.0% of the patients in the ipilimumab monotherapy, ipilimumab plus gp100, and gp100 monotherapy groups, respectively. Treatment-related adverse events leading to discontinuation were reported in 33.6% for the CA184024 study.

The safety results of the CA184024 confirm the safety issues indentified in the MDX010-20 study. he characteristics of irAEs reported for the CA184024 study are reasonably similar to the safety issues identified in the MDX010-20 study.

Extensive guidance for the management of irAE including the use of systemic corticosteroids is included in the product information. The development or maintenance of clinical activity following ipilimumab treatment was similar with or without the use of systemic corticosteroids.

- Uncertainty in the knowledge about the unfavourable effects

No efficacy and safety data for patients with a history of any autoimmune disease other than vitiligo or adequately controlled endocrine deficiencies are available from the submitted clinical studies. Considering the supposed mechanism of action and the observed AEs which were mainly immune related, additional safety concerns might be expected in these patients. Therefore, a warning has been included that ipilimumab should be avoided in patients with severe active autoimmune disease where further immune activation is potentially imminently life threatening and used with caution in other patients with a history of autoimmune disease, after careful consideration of the potential risk-benefit on an individual basis. This population that was not studied has been included in the risk management plan and further data should continue to be collected.

Benefit-risk balance

- Importance of favourable and unfavourable effects

An improvement of overall survival was reported in the pivotal study in adult patients with advanced previously treated melanoma receiving ipilimumab monotherapy. Overall survival is an important objective in this population because of the very short long-term prognosis.

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

- Benefit-risk balance

Extensive guidance for the management of irAEs including the use of systemic corticosteroids has been included in the product information.

The CHMP considered that efficacy of 3 mg/kg ipilimumab treatment for patients with previously treated advanced melanoma patients, was demonstrated. The OS benefit is clinically relevant and compensates for the irAEs found.

The severity and the number reported AEs constitute a need for an ongoing (post approval) search for sub-groups of patients for whom ipilimumab treatment will appear to work out more favourably, and for those in which it is less beneficial (possibly women above 50 years of age, patients with primary CNS or ocular melanoma). This is in particular important for sub-groups who are especially at risk to experience (severe) AEs, for instance patients with autoimmune disease.

While the benefit-risk balance associated with the 3 mg/kg ipilimumab dosing is considered clearly positive, to gain a better understanding of the effect of dose of ipilimumab and benefits and risks, a further randomised study comparing of 3 mg/kg versus 10 mg/kg evaluating efficacy and safety in advanced melanoma with a survival endpoint is considered necessary.

2.8.1. Discussion on the benefit-risk balance

The overall quality of the drug product has been demonstrated. The product is controlled by adequate test methods and specifications. Although the testing of clearance of host cell proteins (HCP) is

sufficiently controlled by a generic CHO HCP assay, this generic assay is not considered the most suitable for its purpose based on the difficulties to fully demonstrate its sensitivity and accuracy. With this respect, the applicant is asked to continue the development and validation of a process-specific HCP assay.

The efficacy of ipilimumab in the treatment of advanced melanoma has been shown. Because a clinical relevant OS benefit is observed, the CHMP was of the opinion that the overall risk/benefit balance of Yervoy is positive for the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy.

2.8.2. Risk management plan

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns
- the following additional risk minimisation activities were required:
    - The Marketing Authorisation Holder shall ensure that all physicians who are expected to prescribe Yervoy are provided with a Healthcare Professional FAQ Brochure and Patient Information Brochures including Alert Cards in accordance with the key elements described in the conditions or restrictions with regard to the safe and effective use of the medicinal product.

2.9. Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus that the risk-benefit balance of Yervoy in the treatment of advanced (unresectable or metastatic) melanoma in adults who have received prior therapy was favourable and therefore recommended the granting of the marketing authorisation.